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5.01
1,2,3-Triazoles

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5.01.1 Introduction

The present chapter is devoted to 1,2,3-triazole and benzotriazole and their various derivatives. Triazolines (4,5-dihydro-1H-1,2,3-triazoles) are discussed in Section 5.01.6. Tautomeric forms of the parent molecules and atom numbering are given in Figure 1.

Figure 1 Tautomeric forms and atom numbering for 1,2,3-triazole and benzotriazole.

In CHEC(1984) <1984CHEC(5)669>, Chapter 4.11 on ‘Triazoles and their Benzo Derivatives’ (64 pages) covered the literature through 1982 and was strongly aligned to the monocyclic 1,2,3-triazoles with the considerable emphasis on ring-reduced derivatives. In CHEC-II(1996) <1996CHEC-II(4)1>, the corresponding 126-page chapter covered the literature from 1982–94, when the position had already changed significantly with the realization of the utility of benzotriazole as a synthetic auxiliary.
The present chapter is heavily biased toward benzotriazole as a consequence of numerous synthetic methods developed with the help of this molecule. It has been impossible to cover the field in a comprehensive manner in the pages available. We refer readers to the following reviews that have appeared during the last ten years:

(1) ‘Properties and Synthetic Utility of Substituted Benzotriazoles’ \(<1998CRV409>\) – this review covers the literature in a comprehensive manner through 1996;
(2) ‘Benzotriazole-Based Reagents for Efficient Organic Synthesis’ \(<1998ALD33>\) – another review of some of the synthetic applications;
(3) ‘Benzannulations’ \(<1999T8263>\) – specifically deals with benzotriazole mediated benzannulations;
(4) ‘Michael Additions of Benzotriazole-Stabilized Carbanions’ \(<1998CCC599>\);
(5) ‘The Generation and Reactions of Non-stabilized $\alpha$-Aminocarbanions’ \(<1998T2647>\) – includes significant amount of benzotriazole chemistry;
(6) ‘Designing Efficient Routes to Poly-functionality’ \(<2000PAC1597>\) – deals with benzotriazole derivatives;
(7) ‘The Preparation of Mono-, 1,1-Di-, trans-1,2-Di- and Tri-Substituted Ethylenes by Benzotriazole Methodology’ \(<2001SL458>\);
(8) ‘Benzotriazole an Ideal Synthetic Auxiliary’ \(<2003CEJ4587>\) – gives some highlights,
(9) ‘Benzotriazole-Mediated Amino-, Amido-, and Alkylthio-Alkylation’ \(<2005T2555>\); and
(10) ‘Benzotriazoles as Advantages N-, C-, S-, and O-Acylating Agents’ \(<2005SL1656>\).

### 5.01.2 Theoretical methods

Experimental dipole moments and acidities of azoles, including 1,2,3-triazole, show linear correlations with their π-electron excess calculated by the semiempirical AM1 method \(<2003CHE71>\). Experimental dipole moments of azoles agree well with those calculated by the DFT program ALLCHEM \(<2003PCA4172>\). Calculated dipole moments $\mu$ (in units of Debye,D) of a few selected azoles are listed below:

- Pyrrole: 1.93
- Pyrazole: 2.33
- Imidazole: 3.84
- 1H-1,2,3-triazole: 4.55
- 2H-1,2,3-triazole: 0.12
- 1H-1,2,4-triazole: 2.93
- 4H-1,2,4-triazole: 5.81

$Ab\ initio$ optimized geometries at B3LYP/6-311+G levels suggest that aromatic stabilization of $2H$-1,2,3-triazole is the highest of all azoles \(<2003T1657>\). Some values (in units of kcal mol$^{-1}$) are given below for comparison:

- Pyrrole: 18.04
- Pyrazole: 20.46
- Imidazole: 16.18
- 1H-1,2,3-triazole: 20.21
- 2H-1,2,3-triazole: 22.21
- 4H-1,2,4-triazole: 12.19
- 1H-tetrazole: 14.13

Bond dissociation energies for several heterocyclic systems calculated by two $ab\ initio$ methods, CBS-Q, G3 and G3B3, show similar values \(<2003JPO883>\). The G3B3 data for three selected azoles are as follows:

- Pyrrole: $N(1)$-H = 95.2 (kcal mol$^{-1}$)
  - C(2)-H: 119.7
  - C(3)-H: 119.2

- Pyrazole: $N(1)$-H = 109.2
  - C(3)-H: 117.8
  - C(4)-H: 121.0
  - C(5)-H: 119.9

- 1H-1,2,3-triazole: $N(1)$-H = 109.5
  - C(4)-H: 121.5
  - C(5)-H: 122.7
Potassium cation affinities of several azoles and other compounds in the gas phase were calculated by hybrid density functional theory [B3-LYP with 6-311 + G(3df, 2p) basis set] <2003CEJ3383>. There is a striking difference in binding energies of 1H- and 2H-1,2,3-triazoles. Some of the collected data are as follows:

| Compound                  | Energy (kJ mol\(^{-1}\)) |
|---------------------------|--------------------------|
| Pyrrole                   | 77.1                     |
| Pyrazole                  | 90.5                     |
| 1-methylpyrazole          | 94.5                     |
| 3-methylpyrazole          | 92.8                     |
| 1,4-dimethylpyrazole      | 100.0                    |
| 1,3,5-trimethylpyrazole   | 103.4                    |
| Imidazole                 | 111.1                    |
| 1H-1,2,3-triazole         | 118.6                    |
| 2H-1,2,3-triazole         | 64.5                     |
| 1H-tetrazole              | 109.7                    |
| 2H-tetrazole              | 88.5                     |

Monte Carlo calculations of interactions of 1H-benzotriazole with water reveal significant electronic polarization of the heterocycle. The dipole moment is increased by 2.89 D for the ground state and 2.75 D for the excited state to the total values of 6.89 and 6.40 D, respectively. Direct measurements of dipole moments in water are not possible, but these numerical results are supported by experimental solvatochromic blue shift of the \(\pi \rightarrow \pi^*\) transition <2003IJQ572>.

Theoretical calculations at the B3LYP/6-31G* and B3LYP/6-311++G** levels concluded that 2-(hydroxymethyl)-benzotriazole 2 is slightly more stable than 1-(hydroxymethyl)benzotriazole 1. The energy difference of 0.22 kcal mol\(^{-1}\) suggests that both isomers should be almost equally abundant; however, in solid state and in solutions, only isomer 1 is observed. One of the possible explanations of this phenomenon is formation of strong intermolecular hydrogen bonding between the OH group and N-3 in condensed phase of derivative 1. Less basic nitrogen atoms in derivative 2 do not provide such stabilization <2004JHC285>.

Atomic charges of anions 3 and 4 have been evaluated at the HF/6-31G* level using several partitioning schemes. The data obtained from the natural population analysis (NPA) method are listed below. The electron-withdrawing power of the CN groups is clearly demonstrated by the total charge of the ring change from \(-1.34\) to \(-0.84\) <2003SSI1129>.

| Compound | Charge (e) |
|----------|------------|
| 3        | \(-0.41\)  |
| 4        | \(-0.31\)  |
| 3        | \(-0.18\)  |
| 4        | \(-0.12\)  |
| 3        | \(-0.17\)  |
| 4        | \(-0.05\)  |
| \(\Sigma\) | \(-1.34\)  |
| \(\Sigma\) | \(-0.84\)  |
5.01.3  Experimental Structural Methods

5.01.3.1  X-Ray Crystal Structure

X-Ray crystallographic data for several basic derivatives of $1H$-1,2,3-triazole and benzotriazole are included in CHEC(1984) and CHEC-II(1996). Hundreds of new $1H$-1,2,3-triazole structures have been analyzed since; some crystallographic data for representative examples (structures 5–12) are collected in Table 1.

Table 1  Selected bond lengths (in Å) for 1,2,3-triazole derivatives 5–12

| Compound | $N(1)$–$N(2)$ | $N(2)$–$N(3)$ | $N(3)$–$C(4)$ | $N(1)$–$C(5)$ | $C(4)$–$C(5)$ | Other | Reference |
|----------|----------------|----------------|----------------|----------------|----------------|--------|-----------|
| 5        | 1.359          | 1.293          | 1.359          | 1.351          | 1.373          | 1.486: $N(1)$–$C_1$ | 2004NN521 |
| 6        | 1.354          | 1.303          | 1.361          | 1.351          | 1.372          | 1.442: $N(1)$–$C_1$, 1.493: $C(4)$–$C_1$ | 2005H(65)1035 |
| 7        | 1.342          | 1.309          | 1.365          | 1.344          | 1.342          | 1.484: $N(1)$–$C_1$, 1.503: $C(4)$–$C_1$ | 2002JFC(116)81 |
| 8        | 1.341          | 1.333          | 1.329          | 1.339          | 1.399          | 1.422: $N(2)$–$C_1$, 1.490: $C(4)$–$C_1$ | 2002BMC963 |
| 9        | 1.324          | 1.358          | 1.338          | 1.340          | 1.417          | 1.416: $N(2)$–$C_1$, 1.356: $C(4)$–$N_1$ | 2006ARK(xv)53 |
| 10       | 1.334          | 1.321          | 1.351          | 1.334          | 1.368          | 1.477: $C(4)$–$C_1$, 1.749: $C(5)$–$S$ | 2001CHE470 |
| 11       | 1.332          | 1.331          | 1.352          | 1.351          | 1.400          | 2.090: $N(2)$–$Ru$ | 2003OM3107 |
| 12       | 1.316          | 1.329          | 1.317          | 1.348          | 1.400          | 0.858: $N(1)$–$H$, 1.746: $C(5)$–$S$ | 2004POL1981 |
As can be seen in Table 1, for N-1 substituted triazoles (structures 5–7), the N(1)–N(2) bonds (1.342–1.359 Å) are significantly longer than the N(2)–N(3) bonds (1.293–1.309 Å), reflecting more single- and more double-bond character, respectively. An electron-withdrawing substituent at C-4 (compound 5 vs. 6) shortens slightly the N(2)–N(3) bond and stretches the N(1)–C(α) bond indicating that such derivatives should dissociate more easily. In 2-substituted triazole 8, both N–N bonds are approximately equal. However, when two substituents of different electronic properties are attached, as in compound 9, the N–N bonds differ substantially, with that closer to an electron-withdrawing substituent being shortened and that closer to an electron donor being elongated. This observation can be rationalized by contribution of resonance forms involving the amino and carbonyl groups at C-4 and C-5, respectively. For the same reason, the C(4)–C(5) bond in derivative 9 is the longest one in the series suggesting diminished aromatic character for this molecule.

Because substituents of the ring may have different effects on the individual bonds, it is informative to compare averages of the five ring bond lengths. In this aspect, the average bond of the triazole system in compound 9 (1.355 Å) is the longest in the series 5–12 supporting the low aromatic character of this molecule. For comparison, the average bond length in molecule 8 is 1.348 Å. Triazole anion structure 10 reveals relatively short bonds with an average bond length of 1.341 Å. The triazole ring in ruthenium complex 11, with average bond length of 1.353 Å, exhibits similar character to that of molecule 9 due in part to its resonance involving the carbonyl group at C-4. In the relatively simple and electron-rich molecule 12, the average N–N bond (1.322 Å) and N–C bonds (1.332 Å) are the shortest in the whole series.

Table 2 lists bond lengths for the heterocyclic ring of the benzotriazole systems in derivatives 13–21. In comparison with 1,2,3-triazoles, N-1 substituted benzotriazoles have significantly longer N(1)–N(2) bonds (average 1.364 Å vs. 1.352 Å) and somewhat longer N(2)–N(3) bonds (average 1.307 Å vs. 1.301 Å). In general, the C–N bonds and C–C bonds in the heterocyclic ring of benzotriazole derivatives are also slightly longer than the corresponding bonds in 1,2,3-triazoles. This causes the average heterocyclic ring bond in the whole series of benzotriazole derivatives 13–21 (1.361 Å) to be significantly longer than that in 1,2,3-triazole derivatives 5–12 (1.346 Å), reflecting the diminished aromatic character and therefore the higher reactivity of the benzotriazole system.

| Compound | N(1)–N(2) | N(2)–N(3) | N(3)–C(3a) | N(1)–C(7a) | C(3a)–C(7a) | Other Reference |
|----------|-----------|-----------|------------|------------|-------------|----------------|
| 13       | 1.368     | 1.296     | 1.367      | 1.361      | 1.391       | 1.440^4          |
| 14       | 1.349     | 1.309     | 1.373      | 1.365      | 1.404       | 1.468^4          |
| 15       | 1.377     | 1.310     | 1.383      | 1.371      | 1.410       | 1.434^4          |
| 16       | 1.373     | 1.307     | 1.380      | 1.367      | 1.407       | 1.471^a          |
| 17       | 1.369     | 1.299     | 1.374      | 1.367      | 1.388       | 2003ANS973       |
| 18       | 1.344     | 1.326     | 1.381      | 1.343      | 1.376       | 1.457^a          |
| 19       | 1.368     | 1.302     | 1.380      | 1.377      | 1.391       | 1.431^a          |
| 20       | 1.336     | 1.355     | 1.354      | 1.356      | 1.381       | 1.413^b          |
| 21       | 1.351     | 1.296     | 1.374      | 1.363      | 1.411       | 1.477^a, 1.455^c |

^aN(1)–Cα.
^bN(2)–Nα.
^cN(2)–Cα’.
5.01.3.2 $^1$H NMR Spectroscopy

Due to rapid proton exchange between forms 22, 23, and 24 (Scheme 1), benzotriazole exhibits at room temperature just two C–H signals, each for two protons, in its $^1$H NMR spectra. However, when the temperature is lowered, the signals broaden and finally split into four separate resonances of the four individual C–H protons. The results of such study for an acetone solution of benzotriazole are given in Table 3. The situation is additionally complicated by formation of adducts 25 and 26, which at $-90^\circ$C contribute 25% and 5%, respectively, to the total molecular population.

![Scheme 1](image)

| Compound | Temperature | $H-4$ | $H-5$ | $H-6$ | $H-7$ |
|----------|-------------|-------|-------|-------|-------|
| 22–24    | 21 °C       | 8.00  | 7.44  | 7.44  | 8.00  |
| 22–24    | $-85^\circ$C | 8.11  | 7.48  | 7.48  | 8.05  |
| 25       | 21 °C       | 8.20  | 7.36  | 7.47  | 8.06  |
| 25       | $-85^\circ$C | 8.28  | 7.45  | 7.56  | 8.11  |
To illustrate the $^1$H NMR assignment of benzotriazole derivatives, spectral data for three benzotriazol-1-yl derivatives of tetrahydropyran, 27–29, are presented in Table 4 <2001CJC1655>. Chemical shifts (in ppm) for the ring protons as well as the $\alpha$-hydrogen atoms of the attached substituents in triazole derivatives 30 <2004TL6129>, 31 <2002BMC947>, 32 <2005JOC815>, 33 <2006T8115>, 34 <2006SC951>, 35 <2006OL3227>, 36 <2006OL3227>, 36 <2005JA15998>, and 38 <2005JA15998> are also shown below together with the structures.

### Table 4

$^1$H NMR chemical shifts (ppm), multiplicity and coupling constants (Hz) for benzotriazol-1-yl derivatives 27–29

| Compound | $H-4$ | $H-5$ | $H-6$ | $H-7$ | $H-\alpha$ |
|----------|-------|-------|-------|-------|-----------|
| 27       | 8.05 dt (8.2, 0.9) | 7.37 ddd (8.2, 6.9, 0.9) | 7.48 ddd (8.4, 6.9, 0.9) | 7.74 dt (8.4, 0.9) | 6.02 dd (8.3, 3.0) |
| 28       | 8.07 dt (8.2, 0.9) | 7.38 ddd (8.2, 6.9, 0.9) | 7.50 ddd (8.2, 6.9, 0.9) | 7.73 dt (8.2, 0.9) | 6.41 dd (10.7, 2.7) |
| 29       | 8.08 dt (8.3, 0.9) | 7.39 ddd (8.2, 7.0, 0.9) | 7.48 ddd (8.2, 7.0, 0.9) | 7.67 dt (8.3, 0.9) | 5.87 d (7.5) |

1,2,3-Triazoles
5.01.3.3 $^{13}$C NMR Spectroscopy

To illustrate signal assignments in $^{13}$C NMR spectra of the benzotriazol-1-yl system, chemical shifts for five $\alpha$-(benzotriazol-1-yl)tetrahydrofurans (structures 39–43) \(^<2003JPO158>\) and three corresponding tetrahydropyrans (structures 27–29) \(^<2001CJC1655>\) are listed in Table 5. Selected $^{13}$C NMR spectral data for triazolyl nucleoside analogs 44–50 \(^<2003SPL461>\) are collected in Table 6.

**Table 5** $^{13}$C NMR chemical shifts (in ppm) for the benzotriazol-1-yl and $\alpha$-carbon atoms in the spectra of derivatives 27–29 and 39–43 taken in CDCl$_3$

| Compound | C-\(\alpha\) | C-4 | C-5 | C-6 | C-7 | C-7\(a\) | C-3\(a\) |
|----------|-------------|-----|-----|-----|-----|---------|---------|
| 27       | 85.5        | 119.6 | 124.0 | 127.1 | 110.7 | 132.1 | 146.3 |
| 28       | 80.2        | 120.0 | 124.1 | 127.5 | 110.6 | 132.2 | 146.1 |
| 29       | 87.9        | 120.2 | 124.3 | 127.9 | 110.1 | 132.2 | 146.6 |
| 39       | 87.9        | 119.8 | 124.1 | 127.4 | 110.4 | 132.8 | 146.2 |
| 40       | 88.8        | 119.8 | 124.0 | 127.6 | 110.3 | 133.4 | 145.4 |
| 41       | 93.6        | 119.9 | 124.4 | 128.1 | 109.9 | 132.7 | 145.9 |
| 42       | 88.3        | 119.5 | 123.8 | 126.9 | 110.1 | 133.2 | 145.1 |
| 43       | 90.6        | 119.7 | 124.1 | 127.4 | 110.6 | 132.9 | 146.2 |

**Table 6** Chemical shifts (ppm) for selected carbon atoms of derivatives 44–50 in their $^{13}$C NMR spectra taken in DMSO-d$_6$

| Compound | C-4 | C-5 | C-1\(\alpha\) | C-4\(\alpha\) | C-5\(\alpha\) |
|----------|-----|-----|--------------|--------------|--------------|
| 44       | 143.1 | 140.0 | 87.9 | 180.0 | 180.0 |
| 45       | 138.9 | 132.2 | 86.2 | 163.1 | 158.0 |
| 46       | 138.5 | 133.0 | 86.4 | 161.2 | 156.9 |
| 47       | 138.7 | 132.0 | 86.4 | 160.7 | 156.2 |
| 48       | 138.7 | 132.3 | 86.5 | 160.7 | 156.5 |
| 49       | 138.7 | 132.1 | 86.2 | 160.8 | 156.4 |
| 50       | 144.3 | 135.3 | 85.2 | 163.5 | 176.7 |

5.01.3.4 $^{15}$N NMR Spectroscopy

In the previous issue of *Comprehensive Heterocyclic Chemistry* \(^<1996CHEC-II(4)>\), the $^{15}$NMR spectra of 1,2,3-triazoles and benzotriazoles are extensively discussed, but 1,2,3-triazolines are only briefly mentioned. To clarify the picture, data for typical 4,5-dihydro-1H-1,2,3-triazoles (51–61) \(^<2002J(P2)126>\) are collected in Table 7. For the ring nitrogen atoms, the highest field resonance is always assigned to N-1. To distinguish positions of N-2 and N-3 resonances, which sometimes come close to each other, isotopic labeling at N-1 and N-2 is used.
The data presented indicate that change of a N-1 substituent from aliphatic to aromatic causes moderate downfield shifts of the N-1 and N-3 resonances and a strong upfield shift of the N-2 resonance. This feature can be explained by the resonance effect of the aromatic ring. Electron-withdrawing substituents at C-4 shift strongly upfield the N-3 signals but do not significantly change the N-1 and N-2 resonances. Substituents at C-5 shift significantly upfield the N-1 resonances. An sp² C-5 atom shifts the N-3 resonance dramatically downfield, especially when a heteroatom is attached (structures 58–60).

### 5.01.4 Thermodynamic Aspects

#### 5.01.4.1 Ring-Chain Equilibriums

Mixed malondiamide 62 on reaction with benzenesulfonyl azide and sodium ethoxide in ethanol is converted into open-chain diazo-derivative 64, which readily cyclizes to triazoles 63 and 65 (Scheme 2). Rapid equilibration in solution prevents separation of individual components of the reaction mixture. NMR studies of the equilibrium between products 63, 64, and 65, carried out in DMSO-d₆, are summarized in Table 8. It is evident from the collected data that the equilibrium depends strongly on the substituent R. Electron-withdrawing substituents on the phenyl ring destabilize structure 63 but stabilize form 65. Ortho-substituents on the aromatic ring, both electron-donating and electron-withdrawing, strongly destabilize triazoles 63, but they stabilize open-chain form 64. The benzyl derivative exists almost exclusively in the triazole form 63 <2003CHE168>.

| Table 7 | ¹⁵N Chemical shifts in ppm for 4,5-dihydro-1H-1,2,3-triazoles 51–61 taken in CDCl₃ with nitromethane as external reference (δ = 0 ppm) |
| Compound | N-1 | N-2 | N-3 | Other nitrogens |
| 51 | −195.5 | 54.6 | −31.4 | |
| 52 | −182.8 | 35.0 | −29.5 | |
| 53 | −195.5 | 52.8 | −56.2 | −127.1 (CN) |
| 54 | −182.5 | 37.6 | −50.7 | −286.4 (NEt₂) |
| 55 | −175.4 | 34.6 | −30.4 | |
| 56 | −168.3 | 32.7 | −17.6 | −12.7 (NO₂) |
| 57 | −176.9 | 35.8 | −46.8 | |
| 58 | −179.7 | 32.4 | −6.9 | |
| 59 | −172.9 | 36.4 | 3.5 | −160.4 (NMe) |
| 60 | −163.1 | 44.0 | 32.8 | |
| 61 | −173.9 | 33.5 | −27.5 | |
5.01.4.2 Mononuclear Complexes

The strong coordination of benzotriazole and its derivatives to metal ions makes them attractive ligands. Thus, slow concentration of an aqueous solution of benzotriazole and zinc perchlorate results in formation of colorless prism crystals of composition \( \text{Zn}[\text{BtH}_4(\text{H}_2\text{O})_2](\text{ClO}_4)_2 \), where \( \text{BtH} = \text{benzotriazole} \). X-Ray crystal structure analysis shows that the crystals belong to monoclinic \( C_2/c \) space group, with lattice parameters \( a = 13.838 \) Å, \( b = 13.374 \) Å, and \( c = 16.944 \) Å, \( \beta = 103.206^\circ \), \( V = 3053.1 \) Å\(^3\), \( Z = 4 \), \( R_I = 0.0411 \). The zinc ion is coordinated by four nitrogen atoms from four benzotriazole molecules and two oxygen atoms from water molecules to form an octahedral coordination polyhedron of complex 66. Detailed analysis of the X-ray data indicates that the complex consists of two pairs of identically bonded benzotriazolyl systems located on the opposite sides of the central atom with the Zn–N bond lengths of 2.119 and 2.223 Å, respectively. The Zn–O bond length is 2.157 Å. The difference in Zn–N bond lengths is attributed to strong hydrogen bonding of two of the benzotriazolyl substituents with the perchlorate anions that decreases electron density on the N-3 atoms and weakens their bonding with the Zn ion. A similar complex, structure 67, is obtained from copper (II) perchlorate with the Cu–N bond lengths of 2.009 and 2.090 Å, and the Cu–O bond length of 2.393 Å. The much longer Cu–O bond of complex 67 in comparison with the Zn–O bond in complex 66 is attributed to strong Jahn–Teller effect in the copper complex <2002ICC453>.

### Table 8 Ratio between compounds 63–65 in DMSO-d\(_6\) solutions

| Substituent R | 63 (%) | 64 (%) | 65 (%) |
|--------------|--------|--------|--------|
| Ph           | 35     | 35     | 30     |
| 4-MeOC\(_6\)H\(_4\) | 42     | 42     | 16     |
| 4-BrC\(_6\)H\(_4\) | 25     | 40     | 35     |
| 3-(NO\(_2\))C\(_6\)H\(_4\) | 0.8    | 0.2    | 99     |
| 2-MeOC\(_6\)H\(_4\) | <0.1   | 58     | 42     |
| 2,4,6-Cl\(_3\)C\(_6\)H\(_2\) | <0.1   | 90     | 10     |
| PhCH\(_2\)   | 99.6   | 0.2    | 0.2    |
Concentration of an ethanolic solution of dimethylglyoxime, cobalt(II) chloride and benzotriazole results in deposition of crystalline complex 68. The product is stable at room temperature; however, it slowly decomposes upon heating. Thermal analysis reveals that the compound releases first the chloride atom and 50% of the benzotriazole content to form a new complex that is stable to 225 °C. Probably in this new form, the benzotriazole moiety coordinates two cobalt ions simultaneously. Further heating to 350 °C removes the benzotriazolyl moieties completely <2003JPY699>. The first step of decomposition can be summarized as follows: 

$$[\text{Co(dmgH)}_2(\text{BtH})\text{Cl}] \rightarrow [\text{Co(dmgH)}_2(\text{Bt})_{0.5}]$$

where dmgH = dimethylglyoxime anion, BtH = benzotriazole.

A reaction of 2-(benzotriazol-1-yl)pyridine with copper(II) nitrate, carried out in methanol, provides complex 69. The product crystallizes in monoclinic space group $P2_1/n$. The copper atom lies in the crystallographic center of inversion, and it is coordinated to two chelating ligands and two methanol molecules. In structures 66–68 discussed above, the benzotriazolyl N-3 atom is involved in bonding. By contrast, in structure 69, the benzotriazolyl N-2 atom is used to coordinate to the copper ion, with the bond length of 2.047 Å. The bond length of pyridyl-N-Cu is 2.034 Å. In analogy to structure 67, the axial Cu–O bonds in complex 69 are elongated (2.298 Å) <2003JCD992>.

The ester derived from (benzotriazol-1-yl)methanol and ferrocenecarboxylic acid reacts in dichloromethane with cobalt(II) iodide to provide complex 70 in quantitative yield, which recrystallizes from dichloromethane/hexane to give green air-stable crystals. The X-ray structure analysis reveals that the cobalt center is coordinated to two iodine atoms and the N-3 atoms of two benzotriazole ligands. The angles N–Co–N, N–Co–I, and I–Co–I of 103.5°, 109.0° (average), and 116.2°, respectively, are close to the ideal tetrahedral angle. Some deviation from the tetrahedral geometry is indicated by the relatively large I–Co–I and relatively small N–Co–N angles; this is presumably caused by strong repulsion between the iodide anions. The bond lengths, Co–N 2.033 and 2.044 Å and Co–I 2.551 and 2.569 Å, are typical for this type of complexes <2002JOM(658)251>.
5.01.4.3 Di-, Tri-, and Polynuclear Complexes

(Benzotriazol-1-yl)methyl 2,5-thiophenedicarboxylate reacts with \([\text{RhCl(CO)}_2]_2\) in toluene at room temperature to give quantitatively rhodium(i) complex as an air-stable yellow solid. The dimeric nature of the molecule is clearly indicated by its ESI molecular peak at \(m/z = 1220\). Complex 71 catalyzes methyl iodide promoted carbonylation of methanol to give acetic acid and methyl acetate with much higher catalytic activities than the classical rhodium catalysts. Treatment with carbon monoxide and methyl iodide converts compound 71 into complex 72 in high yield (Equation 1). In a single-crystal X-ray analysis, complex 72 turns out to be a macrocycle containing two dinuclear iodo-bridged Rh(III) units. The four rhodium atoms have distorted octahedral geometries. The four Rh–N bonds are almost equal in length (2.091, 2.102, 2.128, and 2.139 Å). The Rh–C bond lengths are 1.840–1.867 Å. The bond lengths for each of the Rh₂I₆ units (2.605–2.692 Å) are typical for that type of structures. In contrast to Rh(I) macrocycle 71, Rh(III) complex 72 does not catalyze the carbonylation of methanol.<2001EJ3005>.

Cisplatin is one of the most frequently used anticancer agents despite several drawbacks including acquired drug resistance and serious side effects. To overcome these problems, an intensive search is going on to find safer alternatives. In one such approach, dinuclear Pt(II) complex 73 is obtained as dinitrate salt from a reaction of \([\text{cis-Pt(NH}_3)_2(\mu-OH)_2](\text{NO}_2)_2\) with 4-phenyl-1,2,3-triazole. According to X-ray structure determination, the coordination of the Pt atoms is square planar with the Pt–N(ammine) distances slightly longer (2.015–2.044 Å) than the Pt–N(triazole) distances (1.985–1.996 Å). The Pt–O bond lengths are 2.027 and 2.028 Å. A weak intramolecular hydrogen bond is observed between one of the ammine groups as donor and the triazole N-3 atom as acceptor.<2002JA4738>.

Compound 73 and its simpler analog without any substituent on the triazole ring exhibit higher cytotoxicity to L1210 murine leukemia cells than cisplatin. To explain the effect of its action on DNA, a reaction of complex 73 with 9-ethylguanine, as a model nucleobase, was studied using NMR. In the first step, the hydroxyl bridge is broken and 9-ethylguanine is attached to one of the platinum centers to give intermediate 74. In the following step, the freed diamminohydroxyplatinum group migrates to N-3 of the triazole ring to provide thermodynamically more stable intermediate 75. Finally, a reaction with another molecule of 9-ethylguanine provides final adduct 76 (Scheme 3)<2002JA4738>.

Reaction of Ni(NO₃)₂·6H₂O with 1-hydroxybenzotriazole (BtOH) and NH₃ in DMF provides trinuclear complex \([\text{Ni}_3(\text{BtO})_6(\text{NH}_3)_6]\) 77. Variation of the solvent and the BtOH/Ni(II) ratio afford the same complex, in various solvated forms, as the only product isolated. According to the X-ray analysis, the central Ni atom, Ni-2, in the trinuclear molecule is joined to each of the other two Ni atoms, Ni-1 and Ni-3, by three bridging BtO⁻ ligands. Each BtO⁻ ion is coordinated to Ni-2 via the N-3 atom of the benzotriazole ring and to one of the terminal Ni atoms via N-2. The ammonia ligands complete the six-coordination pattern at each of the terminal Ni atoms. The metal centers have slightly distorted octahedral geometries. The molecule is almost linear, with the Ni(1)–Ni(2)–Ni(3) bond angle of 177.9°. The Ni–N(ammine) bond distances (2.074–2.123 Å) are very close to the Ni–N(Bt) bond lengths (2.087–2.160 Å) <2002TMC377>.
Heating of a suspension of powdered manganese in a DMF solution of 1-hydroxybenzotriazole and ammonium thiocyanate in air results in formation of a polymeric complex 78 of general formula \([\text{Mn}_3(\text{BrO})_2(\text{NCS})_4(\text{DMF})_8]_n\). In this reaction zero-valent manganese is oxidized by oxygen from the air to Mn(II). Composition of this complex does not depend on the reagent ratio indicating that complex 78 is a thermodynamic product. According to X-ray analysis, complex 78 consists of dinuclear subunits of two Mn(II) atoms bridged by two oxygen atoms from BrO\(^-\) ligands, forming a planar four-membered ring \([-\text{Mn}(1)-\text{O}-\text{Mn}(2)-\text{O}–]\). The octahedral coordination of each of these manganese atoms is completed by three oxygen atoms from DMF molecules and one nitrogen atom from the NCS\(^-\) anion.

Scheme 3

1,2,3-Triazoles
The dinuclear subunits in polymer 78 are connected via mononuclear subunits containing atoms Mn(3) coordinated by N-3 atoms of two anions derived from 1-hydroxybenzotriazole. The octahedral coordination of the Mn(3) atom is completed by two oxygen atoms from DMF molecules and two nitrogen atoms from NCS\(^-\) anions. The Mn(1)-O(BtO) bond lengths are 2.186 and 2.206 Å, which is a little more than the Mn(1)-O(DMF) bond lengths of 2.176 Å. The Mn(3)-N(BtO) bonds (2.262 and 2.277 Å) are also longer than the Mn(3)-N(NCS) bonds (2.199 and 2.218 Å) <2002EJ12488>.

Addition of a methanolic solution of 1-methylbenzotriazole (BtMe) to an aqueous solution of Fe(II)(ClO\(_4\))\(_2\)\(\times\)H\(_2\)O and sodium dicyanamide (Nadca) results in slow deposition of crystalline complex [Fe(BtMe)\(_2\)(dca)\(_2\)]. X-Ray analysis reveals that the obtained complex (structure 79) consists of one-dimensional linear chains, in which the Fe(II) centers are bridged by the dicyanamide anions. The coordination sphere at each Fe(II) center is completed by two 1-methylbenzotriazole ligands occupying the axial positions. Coordination geometry around the Fe(II) atom is distorted octahedral with the Fe-N(dca) bond length of 2.136 Å and the Fe–N(BtMe) bond length of 2.208 Å. Similar linear polymeric complexes are obtained from Mn(II) and Cu(II) salts <2006POL360>.

A similar complex 80 is also produced in a reaction of cobalt(II) nitrate with potassium tricyanomethanide (Ktcm) and benzotriazole (BtH). According to the X-ray data for this complex, the CoN\(_6\) octahedron is only slightly distorted, having the N–Co–N’ angles in the range of 88.37–91.16°. The equatorial Co–N(tcm) distances (2.106 and 2.110 Å) are
slightly shorter than the axial Co–N(Bt) bonds (2.149 Å). The polymeric one-dimensional chains are cross-linked by hydrogen bonding between the benzotriazole NH atoms and the uncoordinated CN groups of the bridging ligands in the adjacent chains <2004AXC250>.

5.01.5 Reactivity of Fully Conjugated Rings

5.01.5.1 Nucleophilic Aliphatic Substitution

Alkylation reactions of 1,2,3-triazole and benzotriazole are exhaustively discussed in CHEC(1984) and CHEC-II(1996). The electrophilic reagents, usually alkyl halides, sulfates or sulfonates, attack N-1 or N-2 atoms of the ring producing mixtures of the corresponding 1-alkyl- and 2-alkyl triazoles <1984CHEC(5)669, 1996CHEC-II(4)1>. Some progress in this field provides finding of direct alkylation of benzotriazole with alcohols in the presence of triphenylphosphine and NBS <1997SC1613>. Presumably, the first step is formation of a reactive intermediate 81 that is attacked later by benzotriazole in the S_N2 fashion to give derivative 82 (Scheme 4). The reaction is regioselective and provides exclusively 1-alkyl-, 1-(arylmethyl)-, 1-(2-alken-1-yl)-, and 1-(2-alkyn-1-yl)benzotriazoles, respectively. Secondary alcohols give the corresponding alkyl derivatives in low yields, while tertiary alcohols do not alkylate benzotriazole under these conditions.

Scheme 4

In aqueous micellar medium using cetyltrimethylammonium bromide as a surfactant, benzotriazole is alkylated regioselectively at N-1 with n-propyl and n-butyl bromides, but activated alkylating agents (benzyl chloride, allyl bromide, phenacyl chloride, etc.) produce mixtures of benzotriazol-1-yl and -2-yl isomers in ratios varying from 55:45 to 80:20, respectively <2001BCJ2133>. Alkylation of benzotriazole with bis(2-chloroethyl) ether under these conditions provides a mixture of derivatives 83–85 with isolated yields of 13%, 32% and 22%, respectively (Equation 2). Use of ionic liquids as media for alkylation of benzotriazole provides generally higher regioselectivity; however, the trend is opposite to that under micellar conditions with phenacyl bromide and similar compounds providing exclusively benzotriazol-1-yl derivatives and n-alkyl halides giving mixtures of benzotriazol-1-yl and -2-yl derivatives in a ratio of 15:1 <2004H(63)1077>.
Microwave irradiation can facilitate alkylation of benzotriazole. Thus, compound 86 is cleanly prepared in 95% yield upon irradiation of a solution of benzotriazole and the corresponding benzyl bromide in DMF for 40 s <2006BML999>. Very often microwave-assisted alkylation of benzotriazole works best when no solvent is used; for example, derivative 87 is prepared this way in 94% yield <2003T865>. Phase-transfer catalysis can also be used to increase the yield and improve regioselectivity of the alkylation process as it is illustrated by preparation of compound 88 in 72% yield in the presence of a pyridinophane <2006S654>. In another example, a reaction of benzotriazole with ethyl chloroacetate and K₂CO₃ in ethyl acetate is catalyzed by polyethylene glycol (PEG 400) to give a mixture of ethyl (benzotriazol-1-yl)acetate 89 (56%) and its benzotriazol-2-yl isomer (15%) <2002SRI265>.

Adamantylation of benzotriazole represents a special case because direct substitution in adamantanyl halides by an SN₂ mechanism is impossible, and an SN₁ mechanism is improbable. In this case, reactive cation 91 is generated by oxidative cleavage of the C-I bond in 1-iodoadamantane 90. Benzotriazole added to the reaction mixture binds cations 91 to afford a mixture of benzotriazol-1-yl 92 and -2-yl 93 derivatives in a ratio of 26:74 and the total yield of 67% (Scheme 5) <2001RJO1762>.

Alkylation of 1,2,3-triazole with N-(2-bromoethyl)phthalimide in the presence of Cs₂CO₃ followed by cleavage of the phthalyl moiety with hydrazine provides 1-(2-aminoethyl)-1,2,3-triazole 94 in 51% yield <2003JME1116>. A reaction of 4-nitro-1,2,3-triazole with propargyl bromide in the presence of KOH gives a mixture of isomeric 1-propargyl-1,2,3-triazoles 95 and 96 in the equimolar ratio <2003RJO1792>. However, in acidic media, when N-1
and N-3 positions are protonated, 2-substituted derivatives of 1,2,3-triazole are formed regioselectively. Thus, isopropyl alcohol reacts with 1,2,3-triazole in 95% sulfuric acid to provide 2-isopropyl-1,2,3-triazole in 80% yield <2002JHC1111>.

Alkylation of benzotriazole with (chloromethyl)trimethoxysilane 99 provides a mixture of its derivatives 98 and 100 in a ratio of 1:3. In a reaction with tris-(2-hydroxyethyl)amine, compound 100 is converted to derivative 101 in nearly quantitative yield. Compound 98 reacts with tris-(2-hydroxyethyl)amine similarly (Scheme 6) <2003ARK(xiii)125, 2003CHE1639>.

When positive charge of the reaction center is stabilized by an adjacent atom, even the acetoxy anion can be a good leaving group. Such a situation is typical in derivatives of sugars. Thus, heating of an equimolar mixture of benzotriazole and tetraacetylycerose at 150°C for 15 min results in formation of products 102 (63%) and 103 (3%) <2002NN73>. Due to strong electron-donating abilities of the ferrocene system, ferrocenyl methyl carbinol reacts eagerly with benzotriazole in the presence of 45% fluoroboric acid to give 1-(α-ferrocenylyethy)benzotriazole 104 in 93% yield <2004JOM(689)2473>. Catalyzed by ytterbium triflate, (phenoxymethyl)oxirane reacts with benzotriazole to afford derivative 105 in 71% yield <2003SC2989>. 1,5-Dioxaspiro[3,2]hexane with remarkably strained molecules reacts directly with benzotriazole without any catalyst to give oxetane derivative 106 as the main product in 41% isolated yield. The preference for N-2 substitution in product 106 seems to result from steric hindrance at the reaction center. However, under basic conditions, the same reagent gives product 107 (isolated yield 27%) as a result of a regular SN2 attack on the oxirane methylene carbon atom <2003JOC1480>.

5.1.5.2 Nucleophilic Attack on Aromatic Rings

The anion derived from benzotriazole attacks electron-deficient aromatic rings of pyrylium salts 108 in position para to oxygen to give 4H-pyran 109 in high yields. Positions ortho in salts 108 are blocked by aryl groups (R1 = R4 = Ar) to avoid reactions there <1999JPR152>. Derivatives 109 have been found to be very useful in the synthesis of corresponding 4-alkyl pyrylium salts 111, via 4-alkyl-4-(benzotriazole-1-yl)-4H-pyran 110 (Scheme 8). Benzo[b]pyrylium <1997JOC8198, 1998EJO2623> and xanthylum <1997JOC8198> salts react similarly. Derivatives similar to adducts 109 were also obtained from nitrogen (N-methylacridinium) and sulfur (thioxanthylum) cationic heterocyclic systems <1999JHC927>. When R1 = R4 = H, the anions derived from pyrans 109 may also rearrange to 1,2-diaryl-2,4-cyclopentadien-1-ols 112 <1999JPR152>.

Scheme 6

BtNa = sodium benzotriazolide
Scheme 7

Scheme 8
Upon microwave (µw) irradiation, benzotriazole and its derivatives react readily with 2-chloropyridine to afford products 113-115 in 87%, 72%, and 70% yield, respectively (Scheme 9). 2-Chloroquinoline reacts similarly. 2-Bromopyridine and 2-bromoquinoline give generally lower yields in these reactions <2006OL415>.

Scheme 9

Microwave-induced reaction of 5-acetamidobenzotriazole 116 with 4-chloroquinoline gives a mixture of products 117 (43%), 118 (30%), and 119 (10%) (Equation 3). Interestingly, the product ratio does not depend on the solvent used (toluene, DMF, NMP) <2006T1895>.

Catalyzed by a copper–diamine complex, benzotriazole reacts well even with nonactivated aromatic iodides. The case is illustrated in Scheme 10 by formation of 1-phenylbenzotriazole 120 in 90% yield. The acetyl group as an electron-withdrawing substituent in para position has surprisingly negative effect on the product yield as derivative 121 is isolated in only 63% yield. Potassium phosphate is used as a base. The reactions are highly regioselective with the benzotriazol-1-yl to benzotriazol-2-yl isomer ratio higher than 25:1 <2004JOC5578>.

Scheme 10

Nucleophilic substitution of a nitro group by benzotriazole or triazole in strongly electron-deficient aromatic systems can also be easily achieved. Thus, heating of an equivalent mixture of 1,3,5-trinitrobenzene with benzotriazole and K₂CO₃ in NMP at 80 °C for 4 h affords products 122 and 123 in a ratio of 2:3 with 96% total yield. A similar reaction of 1,3,5-trinitrobenzene with 1,2,3-triazole gives a mixture of derivatives 124 and 125 in a molar ratio of 1:9. Surprisingly, only N-2 substitution is observed when 2-(3,5-dinitrophenyl)benzotriazole 123 is heated with benzotriazole and K₂CO₃ to give product 126 in 92% yield. Substitution of the last nitro group is also possible, but the reaction is much slower. Insoluble in most common solvents, 1,3,5-tribenzotriazolylbenzene 127 is isolated in analytically pure form in 62% yield. It can be concluded that electron-withdrawing abilities of benzotriazolyl substituents are comparable to those of a nitro group to activate aromatic rings for nucleophilic substitution (Scheme 11) <2004RCB588>. 
5.01.5.3 Addition to Multiple Bonds

Under strongly acidic conditions (10% molar equivalent of TsOH), benzotriazole adds to unactivated alkenes to afford a mixture of 1-alkyl- and 2-alkylbenzotriazoles. Because protonation of the double bond with formation of the corresponding carbocation is the first step in these additions, Markovnikov’s rule is followed, and derivatives with a benzotriazolyl substituent at the terminal carbon atom are not observed. Three examples of such additions are depicted in Scheme 12. Thus, in a reaction with styrene, benzotriazol-1-yl 128 and -2-yl 129 are formed in a ratio of 6.5:1 and total yield of 46%. In a reaction with 4-phenylbutene, derivatives 130 and 131 are obtained in a ratio of 1.9:1 and total yield of 65%. Normal terminal alkenes give the corresponding benzotriazol-1-yl and benzotriazol-2-yl derivatives as well, but the total yields are significantly lower (25% from 1-octene and 29% from 1-decene). Increasing the amount of TsOH from 10 to 100 mol% improves slightly the overall yield, but it also results in more complex mixtures of the products due to rearrangements of the original carbocations. Cyclohexene does not react with benzotriazole at 80°C; however, at 120°C, a mixture of derivatives 132 and 133 is obtained in a ratio of 1.1:1 and total isolated yield of 56% <1995J(P2)1645>.
Michael addition of benzotriazole to electron-deficient double bonds is described in CHEC-II(1996) <1996CHEC-II(4)1>. One of the innovations in this field is running the reaction of benzotriazole with chalcone in a micellar medium to afford a mixture of derivatives 134 and 135 in the molar ratio of 4:1 and total yield of 75% (Scheme 13) <2003CL1064>. Even more important innovation is running such reactions enantioselectively with application of optically active bases as catalysts. Thus, addition of benzotriazole to α,β-unsaturated ketones derived from acetone in the presence of catalyst B produces mixtures of products 136 and 137 in ratios varied from 3:1 to 2:1 with total yields in the range of 53–75% and high enantioselectivity (70–98% ¼ ee) <2005AGE2393>. Addition of benzotriazole to 1-nitro-1-alkenes proceeds enantioselectively in the presence of catalyst C to provide exclusively benzotriazol-1-yl derivatives 138 in the average yield of 77% and high ee (64–94%) <2006OL1391>.

When the electron-deficient alkene contains a good leaving group X at the double bond, addition of benzotriazole may be followed by elimination of X (or HX) with restoration of the double bond. The total effect is a nucleophilic substitution of group X by benzotriazolide anion. Four examples of such reactions are gathered in Scheme 14. Thus, benzotriazolyl nitronyl nitroxide 139 must result from addition of the benzotriazolide anion to C-2 of 2-bromo-4,4,5,5-tetramethyl-4,5-dihydro-1H-imidazole-3-oxide-1-oxyl followed by elimination of Br/C0 <2004T99>. Sometimes, the intermediate adducts are stable enough to be isolated and characterized. Such is the case of adduct 140 that is obtained from a low temperature reaction of benzotriazole with methyl 2-(trifluoroacetyl)vinyl sulfone. At slightly elevated temperature, adduct 140 eliminates spontaneously methanesulfonic acid to give product 141 <2003RCB1791>. Addition of a benzotriazolide anion to carbon α of (E)-(2-phenylvinyl)phenyldiodonium tetrafluoroborate results in unstable benzyl anion 143 that rapidly eliminates iodobenzene to afford (E)-1-(2-phenylvinyl)benzotriazole 142 <2002JCM388>. Heating a mixture of benzotriazole, 2-chloro-1,1,1-trifluoroethane, KOH and DMSO at 80°C for 8 h leads to (E)-1-(2-chloro-1-fluorovinyl)benzotriazole 145. The proposed mechanism for this reaction involves elimination of HF from the starting material and trapping of the evolved 2-chloro-1,1-difluoroethene by benzotriazolide anion to form intermediate anion 144 that spontaneously eliminates F/C0 to give product 145 <2002T4077>.

Application of catalysts allows sometimes executing this addition/elimination process even with alkenes without any electron-deficient substituent attached. Such case is illustrated by an example in Scheme 15. In the presence of mercury-(II) acetate and trifluoroacetic acid, 1,2,3-triazoles 146 react with vinyl acetate at 70°C to give vinyl derivatives 148 in good yields (70–88%) <2002RJO1056>. Adducts 147 are presumed to be intermediates in this process.

In the presence of triphenylphosphine as a catalyst, benzotriazole adds readily to activated allenes. Its reaction with ethyl 2,3-butadienoate produces a mixture of adducts 149 (54%) and 150 (20%). Both derivatives form exclusively as (E)-isomers <2006T3710>. In a reaction of benzotriazole with dibenzoylacetylene and
triphenylphosphine (used in the equimolar amount), a mixture of compounds 151 (40%) and 152 (45%) is obtained (Scheme 16). Neither open-chain benzotriazol-2-yl analog of 151 nor benzotriazol-1-yl analog of furan derivative 152 is detected. It seems to be the steric hindrance in reaction intermediates solely responsible for that distinction. To make the cyclization to a furan system possible, the molecule 151 must first assume (E)-configuration, and than bring the carbonyl groups to close proximity. Switching between (Z-) and (E)-configurations in compound 151 seems to be relatively easy by addition of another molecule of benzotriazole to the double bond followed by its elimination, but rotation of the α-benzoyl group would impose much strain on the molecule due to steric repulsion between its phenyl and the benzotriazolyl benzenoid ring. The less bulky benzotriazol-2-yl substituent in the original adduct of benzotriazole to the triple bond allows for such transformations without high energetic barriers.

## 5.01.5.4 Complexes with Borane

1-Benzylbenzotriazole 153 reacts rapidly with borane to form complex 154 in quantitative yield. Complex 154 and its analogs derived from 1-alkylbenzotriazoles are inert to water and air at room temperature and easy to handle solids. Treatment with BuLi followed by iodomethane converts complex 154 into its α-methylated product 155. In the case of a sterically hindered and less acidic substituent (compound 157), the corresponding complex with BH₃ 158 undergoes lithiation in position 4 to afford compound 159. Refluxing in ethanol removes the borane group from N-3 to restore the benzotriazole system (products 156 and 160) (Scheme 17) <1998OPP325>.
5.01.5.5 N-Oxides

Oxidation of 1-alkylbenzotriazoles 161 with dimethyldioxirane leads to the corresponding oxides 162, generally in high yield (Equation 4); however, in comparison with pyridine, the reaction is much slower. Electron-deficient substituents R make the oxidation process more difficult and the yields of products 162 are compromised (e.g., 40% for R = CN). 1-Benzoylbenzotriazole is not oxidized by this reagent. n-Butyllithium lithiates oxides 162 predominantly in position 7. Refluxing in acetic anhydride converts oxides 162 into starting 1-alkylbenzotriazoles. 2-Alkylbenzotriazoles 163 react differently with dimethyldioxirane; instead of the nitrogen, carbon atoms of the benzene ring are attacked to give dioxiranes 164 (Equation 5).
Scheme 16

\[
\begin{align*}
\text{153} & \xrightarrow{\text{BH}_3\cdot\text{THF}} \text{154} & \xrightarrow{\text{i, Bu}^\text{Li}} \text{155} & \xrightarrow{\text{EtOH, reflux}} \text{156} \\
\text{157} & \xrightarrow{\text{BH}_3\cdot\text{THF}} \text{158} & \xrightarrow{\text{i, Bu}^\text{Li}} \text{159} & \xrightarrow{\text{EtOH, reflux}} \text{160}
\end{align*}
\]

Scheme 17

\[
\begin{align*}
\text{161} \xrightarrow{\text{O-O}} \text{162} \\
\text{163} \xrightarrow{\text{O-O}} \text{164}
\end{align*}
\]
5.01.5.6 Triazolium Aminides

Aza analogs of N-oxides, aminides, are reactive 1-3-dipoles. In an example given in Scheme 18, 1,2,3-triazolium-1-aminides undergo cycloaddition to esters of propiolic acid to give unstable adducts that under the reaction conditions, reflux in acetone, rearrange to fused pyrrolo[2,3-\textit{d}]-1,2,3-triazolines (mesomeric forms and). Prolonged heating causes cleavage of the C–N bond (between C–3a and N-4) in and rearrangement of the obtained betaines to more stable 2,5-dihydro-1,2,3-triazines. This relatively complex process produces triazines in moderate yields (35–52%) \( \text{<2006TL1721, 2006JOC5679>}. \)

![Scheme 18](image)

**Scheme 18**

Benzyne generated in situ by diazotization of anthranilic acid adds readily to aminides to provide cycloadducts. Introduction of a nitro group into para position of the phenyl ring on the nitrogen terminus of the 1,3-dipole \( (X^2=\text{NO}_2) \) stabilizes the system and results in higher yields of product (70% vs. 50% for \( X^2=\text{H} \)). Electron-deficient imines react also with aminides, but the yields of isolated adducts are relatively low (10–26%) \( \text{<2003ARK(vii)110>}. \)

![Scheme 19](image)

**Scheme 19**
5.01.5.7 Thermolysis of Benzotriazole and Triazole Derivatives

Thermolysis of benzotriazole derivatives involves cleavage of the heterocyclic ring with extrusion of a molecule of nitrogen and formation of a diradical. If the substituent at N-1 of benzotriazole is suitable for trapping radicals, cyclization to a new heterocyclic system is usually the main route for quenching the diradical. Thus, gas-phase thermolysis of 1-arylxybenzotriazoles proceeds via diradical. The most favorable next step is formation of a bond between the carbonyl oxygen and the ortho carbon atom resulting in benzoazoxole. In another route, a bond forms between the ortho carbon atoms from both rings to give phenanthradinone derivative (Scheme 20). Distribution of the products is not affected much by substituents X supporting radical mechanism of the reactions.

The picture can be generalized. If the substituent is attached to benzotriazolyl N-1 by an sp² hybridized carbon atom, the produced diradical is relatively stable, and a product resulting from simple cyclization predominates, like in an example given in Scheme 20. Three additional examples of such reactions are shown in Equations (6)–(8). Thus, gas-phase thermolysis of hydrazones (R = Me or Ph, Ar = Ph or para substituted Ph) produces benzimidazoles as the main products in 27–50% yields. Minor side products result mostly from cleavage of other bonds in the molecule not involving benzotriazole, and no products resulting from direct radical trapping by the carbonyl group are detected. For a preparative purpose, it is more convenient to carry out pyrolysis of benzotriazole derivatives in high boiling solvents. This way, 8H-quinol[4,3,2-kl]acridine is obtained by refluxing a solution of 9-(1H-1,2,3-benzotriazol-1-yl)acridine in diphenyl ether. Similar thermal conversions of 9-(5'-substituted-1',2',3'-triazol-1'-yl)acridines generate corresponding 7H-pyrido[4,3,2-kl]acridines. Base catalysis may help the thermolysis, as it is illustrated by conversion of 5'-[(benzotriazol-1-yl)-spiro[cyclohexane-1,2']H-imidazo[4,5-b]pyridine into the corresponding fused benzimidazole derivative occurring in refluxing toluene.

Scheme 20

![Scheme 20](image.png)

Equations (6)–(8)
In other cases, extrusion of N\textsubscript{2} creates higher energy diradicals that are suitable for more complex rearrangements. Such situation is represented in Scheme 21 by gas-phase thermolysis of ketones 184. Diradical 185 created in the first step of this process undergoes a series of transformations that ends on stable molecule of indole 186 <2004JPO267>. Flash vacuum pyrolysis of naphthalenethiol 187 at 750°C causes elimination of benzotriazole with formation of \textit{2H}-naphtho[1,2-\textit{b}]thiete 188. Under the conditions applied, the liberated benzotriazole extrude a molecule of nitrogen end undergoes subsequent ring contraction to thermally more stable cyclopentadienecarbonitriles 189 and 190 (Equation 9) <1998JHC1505>.

\textbf{Scheme 21}

\textbf{5.01.5.8 Ionic and Radical Ring Opening with Loss of Nitrogen}

The presence of an electron-donating group adjacent to the benzotriazol-1-yl system renders the triazole ring susceptible to opening at elevated temperatures. Thus, upon heating to reflux in toluene, enamines 191 undergo ring scission between the N-1 and N-2 atoms to form betaines 192. The consecutive loss of a molecule of nitrogen followed by cyclization and rearrangement leads to quinazolines 193 (Scheme 22) <1995JOC246>.

\textbf{Scheme 22}
Anions obtained by lithiation of 1-(α-alkoxyalkyl)benzotriazoles 194 undergo ring cleavage followed by extrusion of nitrogen to give ortho-iminophenyl anions 195. These anions can be trapped by various electrophiles to provide practical synthetic methods for several heterocyclic systems 196-199 (Scheme 23) <1995JOC7625>.

Scheme 23

Dianion 201, generated by treatment of alcohol 200 with 2 molar equivalents of Bu"Li at −78 °C, undergoes ring opening with extrusion of N\textsubscript{2} and formation of new anion 202. Cyclization to oxirane 203 and hydrogen shift creates anion 204 that is hydrolyzed during work-up to aniline derivative 205 (Scheme 24) <1998H(48)187>.

Scheme 24

Anions 207, derived from 1-(diarylmethyl)benzotriazoles 206, can be oxidized with mild oxidants to relatively stable triaryl radicals 208. One of the possible reactions of radicals 208 is ring opening to give radicals 209. Elimination of nitrogen from 209 produces unstable species 210 that undergo intramolecular cyclization to phenanthridines 211 (Scheme 25) <1996JHC607, 1998JOC1467>. When substituents X and Y are identical, products 211
are obtained with average yield of 50%. When X and Y are different but of similar electronic character, mixtures of two isomeric phenanthridines are formed. Polycyclic phenanthridines are formed in these reactions when tricyclic analogs of 206 derived from acridine, xanthene, or thioxanthene are used as starting materials. Another possible reaction of radicals 208 is their dimerization resulting from combining one radical with another in position para of the aromatic ring (when X = H).

\[ \text{Scheme 25} \]

### 5.01.5.9 Intramolecular Electrophilic Attack on N-2

Treatment of 1-(α-ethoxyalkyl)benzotriazoles 212 with n-butyllithium and dimethyloctylsilyl chloride followed by acidic hydrolysis of the intermediates gives a mixture of pyrazoles 215 and 217 (Scheme 26). The probable reaction
pathway involves allylic anion 213 which undergoes cycloaddition to N-2 of the benzotriazole system assisted by simultaneous reaction of N-3 with the silyl chloride to give intermediate 214. Acidic cleavage of the bond between N-2 and N-3 leads to (2-aminophenyl)pyrazole 217. Under acidic conditions, derivative 217 rearranges slowly to pyrazole[5,1-b]benzimidazole system 215, via intermediate 216 \(<1996KGS775>\).

Treated with trifluoroacetic anhydride, sulfoxides 218 undergo conversion to triazapentalenes 219 with high yields. The process must involve acylation of the sulfoxide oxygen atom and generation of a carbocation that attacks the N-2 atom of benzotriazole. Hydrogenation over Raney nickel cleaves the C–S and one of the N–N bonds to generate ortho-substituted anilines 220 (Scheme 27) \(<2002EJO493>\).

\[
\text{Ar}=\text{Ph, 4-FC}_{6}H_{4} \text{ or 4-MeOC}_{6}H_{4} \\
R^{1}=\text{Me, Bu}^{1}, \text{Ph, 4-MeC}_{6}H_{4} \text{ or 2,5-Me}_{2}C_{6}H_{3} \\
R^{2}=\text{Pr}^{\alpha}, \text{Ph, or 4-MeC}_{6}H_{4}
\]

Scheme 27

Addition of benzotriazole to 1-phenyl-2-aroylacetylenes gives \(\alpha,\beta\)-unsaturated ketones 221 in high yields. By treatment with dimethylsulfonium ylide, ketones 221 are converted to epoxides 222, Opening of the oxirane ring and electrophilic attack of the obtained tertiary carbocation on N-2 of the benzotriazole system leads to betaines 223 that consecutively eliminate formaldehyde to give triazapentalenes 224 (Scheme 28) \(<2004ARK(iii)109>\).

\[
\text{Ar}=\text{4-MeC}_{6}H_{4}, \text{4-MeOC}_{6}H_{4}, \text{4-ClC}_{6}H_{4} \text{ or 2-thienyl}
\]

Scheme 28

### 5.01.6 Reactivity of Nonconjugated Rings

#### 5.01.6.1 Conversion of Triazolines to Triazoles

**5.01.6.1.1 Retro Diels–Alder reaction**

A convenient synthetic method for 1,2,3-triazoles unsubstituted at C-4 and C-5 utilizes a reaction of azides with norbornadiene, for example, Scheme 29 \(<2004JOC1081>\). The process is performed in refluxing dioxane. In the first step, norbornadiene undergoes 1,3-dipolar cycloaddition to glucose-derived azide 225 to give triazoline 226. The following retro Diels–Alder reaction results in the elimination of cyclopentadiene to furnish triazole derivative 227 in 79% yield.
Diethyl azidomethanephosphonate 228 reacts with norbornadiene at room temperature to give triazoline 229 in 86% yield. When heated at 60°C, derivative 229 decomposes with elimination of cyclopentadiene to provide (1,2,3-triazol-1-yl)methanephosphonate 230 in 74% yield. However, when it is left at room temperature for an extended period of time, triazoline 229 undergoes slow conversion to aziridine 231 with elimination of nitrogen (Scheme 30) <1995H(40)543>.

Scheme 29

Diethyl azidomethanephosphonate 228 reacts with norbornadiene at room temperature to give triazoline 229 in 86% yield. When heated at 60°C, derivative 229 decomposes with elimination of cyclopentadiene to provide (1,2,3-triazol-1-yl)methanephosphonate 230 in 74% yield. However, when it is left at room temperature for an extended period of time, triazoline 229 undergoes slow conversion to aziridine 231 with elimination of nitrogen (Scheme 30) <1995H(40)543>.

Scheme 30

5.01.6.1.2 Elimination of amines

1,3-Dipolar cycloaddition of 2-morpholino-1,3-diene 232 to azides provides triazolines 233 (Scheme 31). Triazolines 233a and 233b, derived from 4-(ethoxycarbonyl)- and 4-nitro-phenyl azides, respectively, are stable under the reaction conditions (benzene, 40°C); they can be isolated in good yields and fully characterized. However, phenyl derivative 233c is less stable and spontaneously eliminates morpholine to give triazole 234c. To eliminate morpholine from triazolines 233a and 233b, they are heated to reflux in aqueous acetic acid. Strong electron-withdrawing effect of the tosyl group in triazoline 233d promotes cleavage of the ring with elimination of diazomethane to furnish α,β-unsaturated carboximidamide 235. 1,5-Substitution of the triazole ring in derivatives 234 is confirmed by NMR studies <2005HCA1813>.

Less reactive (Z)-ethyl 3-fluoroalkyl-3-pyrrolidinoacrylates 236 require prolonged heating with azides to afford triazoles 238 in good yields (66–97%). The reactions give the best results when mixtures of reagents are heated neat, without any solvent added. Intermediate triazolines 237 do not survive under such conditions and spontaneously eliminate pyrrolidine to form triazoles 238. The reactions are proved to be strictly regioselective with the ethoxycarbonyl group always located at C-4 of the triazole system (Scheme 32) <2003T4395>.
Scheme 33 illustrates the difference in reactivity between triazolines obtained from cyclohexanone and cyclopentanone enamines. Thus, the reactions of azidophosphonates \(239\) with cyclohexanone enamines produce unstable aminotriazolines \(240\) that cannot be isolated due to their spontaneous elimination of amines to provide triazoles \(241\). Contrary to that, triazolines \(242\), derived from cyclopentanone enamines, are isolated in good yield (76–88%) and cannot be converted to the corresponding triazoles even by thermolysis \(<1995H(40)543>\). Probably, introduction of a double bond between two five-membered rings would involve too much molecular strain.
5.01.6.1.3 Elimination of alcohols or water

2-Ethoxyvinyl trifluoromethyl ketone 243 reacts slowly at elevated temperature with aryl and benzyl azides to provide triazoles 245 in good yield (51–88%). The reactions, carried out neat, are completed usually in 2–3 d(days). However, a longer reaction time (6 d) is required for 2-methylphenyl azide due to its steric hindrance. 5-Ethoxytriazolines 244, the expected intermediates in this process, readily eliminate ethanol under the reaction conditions and cannot be isolated (Scheme 34) <2002JFC(116)81>.

![Scheme 34](image)

In reactions with azides, ketones are directly converted to 5-hydroxytriazolines. Ketone enolate 247, generated by treatment of norbornanone 246 with LDA at 0 °C, adds readily to azides to provide hydroxytriazolines 248 in 67–93% yield. Interestingly, 1-azido-3-iodopropane subjected to the reaction with enolate 247 gives tetracyclic triazoline derivative 251 in 94% yield. The reaction starts from an electrophilic attack of the azide on the ketone α-carbon atom. The following nucleophilic attack on the carbonyl group in intermediate 249 results in triazoline 250. The process is completed by nucleophilic substitution of the iodine atom to form the tetrahydrooxazine ring of product 251 (Scheme 35) <2004JOC1720>.

![Scheme 35](image)

In contrast to the triazolines from Scheme 35, 5-hydroxytriazolines obtained from regular, unstrained ketones are unstable, eliminating rapidly water to furnish the corresponding triazoles. In an example given in Scheme 36, azide 252 reacts readily with cyclohexanone enolate to provide triazole 254 in 95% yield. Triazoline intermediate 253, formed in the first step of this reaction, is very unstable and cannot be isolated. The case of open-chain ketones is illustrated by a reaction of azide 252 with diethyl ketone. Again, intermediate 5-hydroxytriazoline 255 decomposes rapidly to give, in part, triazole 256. However, a more complex process involving elimination of nitrogen and rearrangement to amide 257 competes with the main reaction, making this synthesis less attractive <2004JOC1720>.
5.01.6.1.4 Oxidation
When a solution of phenacyl halide 258 and excess tosyl hydrazide in methanol is heated to reflux, 1-(tosylamido)-4-aryltriazole 261 is formed. The reaction proceeds presumably via dihydrazide derivative 259 that subsequently undergoes intramolecular cyclocondensation to triazoline 260. In the following step, the triazoline must be oxidized to the final triazole product 261. Mechanism of the oxidation is not quite clear, but the probable oxidant is the starting phenacyl halide, as a half of it is converted to the corresponding acetophenone tosylhydrazone that is isolated as the main side product of the reaction (Scheme 37) <2004H(63)1175>.

5.01.6.2 Elimination of N₂
Cycloaddition reactions of dimethyl benzylidenemalonate 262 with azides provide triazolines 263. All compounds 263, except one with \( R = \text{Ph} \), are stable in xylene at 110°C. The phenyl derivative eliminates molecular nitrogen to give dimethyl 1,3-diphenylaziridine-2,2-dicarboxylate 264. At elevated temperature, the aziridine system is not
quite stable and may partially exist as open ylide form 265. Thioketones added to the reaction mixture trap species 265 to provide tetrahydrothiazoles. Two examples of such reactions – with thiobenzophenone to give thiazolidine 266 and with adamantanthione to furnish derivative 267 – are presented in Scheme 38 (2002HCA2056, 2002HCA2644).

Acyl azides 268, derived from furan, thiophene and selenophene, add slowly at room temperature to the strained double bond of 5-methylenebicyclo[2.2.1]hept-2-ene. Two regioisomeric triazolines, 269 and 270, which form in the first step, are unstable and decompose with elimination of nitrogen to provide aziridine derivatives 271. Products 271 are isolated in good yield (73–85%). It is worthy to note that not only the terminal, unstrained double bond in the starting material, 5-methylenebicyclo[2.2.1]hept-2-ene, is unaffected, but also the typical dipolarophiles like esters of crotonic, propiolic and but-2-ynoic acids do not react with azides 268 under these conditions (Scheme 39) (2002J(P1)1420).

1-(Azidomethyl)benzotriazole 272 reacts with N-methylmaleinimide in refluxing toluene to give, after 3 h, exclusively triazoline derivative 273, together with the unreacted starting materials. Prolonged heating of the starting materials results in formation of more triazoline 273; however, products of its decomposition to derivatives 274 and 275 are also present. Refluxing of a solution of triazoline 273 in toluene for 24 h leads to a mixture of aziridine 274 and its opened isomer 275 in 4:1 ratio (Scheme 40) (1996JHC335).

Triazolines 277 are isolated in high yield (87–94%) when the reactions of glucal 276 with azides are carried out in refluxing trimethyl or triethyl orthoformate. In all other solvents, triazolines 277 undergo immediate conversion to triazoles 278. It is believed that the orthoformates act as nonbasic acid-scavenging solvents. Irradiated with UV light in acetone, triazolines 277 are smoothly converted to aziridines 279. Without isolation, aziridines 279 are treated with nucleophiles in the presence of a Lewis acid to provide aminoglycosides 280 in high yield (Scheme 41) (2004JA8356).

Fluoroalkanesulfonyl azides 281 add readily to vinyl ethers to provide triazolines 282 in good yield (67–84%). At room temperature, slow decomposition of the products is observed with evolution of nitrogen and formation of piperazine derivatives 284. No other products are observed. Formation of piperazines 284 must involve cleavage of the triazoline ring with formation of zwitterionic intermediates 283 (Scheme 42) (2004JFC(125)445).
Scheme 39

Scheme 40

Scheme 41
Reactions of fluoroalkanesulfonyl azides \( \text{287} \) with tetrahydropyran proceed fast in dichloromethane at room temperature. Evolution of nitrogen is observed together with formation of \( N\)-(fluoroalkanesulfonyl)-2-tetrahydropyranoimines \( \text{289} \). The reactions are believed to involve 1,3-dipolar cycloaddition of tetrahydropyran to azides \( \text{287} \) with formation of relatively unstable triazolines \( \text{286} \). Opening of the triazoline ring results in zwitterionic structure \( \text{285} \) that is losing molecular nitrogen and rearranges to final product \( \text{289} \) by 1,2-hydrogen shift (\text{2003JFC(120)65}\rangle. In a similar manner, reactions of azides \( \text{287} \) with dihydropyridines lead to \( N\)-alkanesulfonylimines \( \text{290} \), via labile triazolines \( \text{288} \) (\text{Scheme 43} \langle2000JFC(106)133\rangle).

\[ \text{R}^F = C\text{F}_{9}, \text{Me}_2\text{CHOCHF}_2, \text{CICF}_2\text{CF}_2\text{OCF}_2\text{CF}_2 \text{or ICF}_2\text{CF}_2\text{OCF}_2\text{CF}_2 \]
\[ \text{R} = \text{Et or Me}_2\text{CHCH}_2 \]

\text{Scheme 42}

\text{Scheme 43}

5.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

5.01.7.1 Reactions of the Benzenoid Ring of Benzotriazole

Tetrachlorobenzotriazole \( \text{291} \) is readily prepared in 87% yield by heating a solution of benzotriazole in a mixture of hydrochloric and nitric acids (\text{1955JA5105}\rangle). 5,6-Dibromobenzotriazole \( \text{292} \) is prepared in 62% yield by treatment of benzotriazole with bromine and silver sulfate in concentrated sulfuric acid (\text{2004BMC2617}\rangle). Under more forcing conditions, when the reaction is run in refluxing nitric acid, 4,5,6,7-tetrabromobenzotriazole \( \text{293} \) is formed.
(Scheme 44) <1957JA4395>. 1-Ethylbenzotriazole 295 <1984CHEC(5)669, 1996CHEC-II(4)1> is chlorinated by refluxing in a mixture of concentrated hydrochloric and nitric acids to give 1-ethyl-4,5,6,7-tetrachlorobenzotriazole 294 in 81% yield <1957JA4395>. A reaction of derivative 295 with bromine in refluxing concentrated nitric acid provides 1-ethyl-4,5,6,7-tetrabromobenzotriazole 296 in 68% yield <1957JA4395>.

**Scheme 44**

Coupling of 5-aminobenzotriazole 297 with a diazonium salt derived from 4-methoxyaniline generates diazo derivative 298. Conversion of the amino group into maleinimide produces dye 299 (Scheme 45). Diels–Alder cycloadditions of dye 299 to diene tagged nucleotides allows for their efficient labeling <2002CC2100>.

**Scheme 45**

Benzotriazole and its 2-alkyl derivatives 300 undergo [2+2] cycloaddition to maleimide when irradiated with UV light at λ>290 nm to give photoadducts 301 (Equation 10). In all cases, only exo diastereomers are formed. Since 1-alkylbenzotriazoles are completely unreactive under such conditions, unsubstituted benzotriazole must react as its
2-H tautomer. This remarkable difference in reactivity originates from a greater differentiation in bond lengths in the benzenoid ring of 2-substituted benzotriazoles in comparison with their benzotriazol-1-yl analogs. Bonds C(4)–C(5) in derivatives 300 are relatively short (1.377 Å); this renders them more double bond character and makes more susceptible to [2+2] cycloadditions <2002OL1487>.

![Reaction Scheme](image)

\[
\text{R}^1 = \text{H}, \text{Me} \text{ or PhCH}_2 \\
\text{R}^2 = \text{H}, \text{Me}, \text{Et or Bu}^1
\]

5.01.7.2 Organometallic Derivatives and Their Reactions with Electrophiles

1-Benzylxoytriazole 302 is lithiated exclusively at C-5. Treatment of lithio derivative 303 with electrophiles provides an easy access to 5-substituted triazoles 304, which are obtained in 67–97% yield (Scheme 46) <1997JOC9177>. Tetrabutyltin derivative 306 becomes a convenient intermediate in the synthesis of ketones 305 (yield 59–93%) <1998S1181>. Organozinc intermediate 307 is suitable for palladium coupling with aryl iodides to provide products 308 in 71–87% yield. Apart of derivatives 308 with phenyl substituents that listed in Scheme 46, 5-aryltriazoles derived from pyridine, thiophene, and pyrazole are also prepared this way.

![Scheme 46](image)

\[E^+ = \text{Me, DMF, ClCO}_2\text{Me, ClCONMe}_2, \text{C}_2\text{Cl}_6, \text{Br}_2, \text{I}_2, \text{or Me}_2\text{S}_2\]
\[R = \text{Me, n-C}_1\text{H}_{23}, \text{Bu}^1, \text{Ph}\]
\[X = \text{H, 2-F, 2-NH}_2, 4-OH, 4-\text{OMe, 4-NO}_2\]
5.01.7.3 Iodo Derivatives

5-Iodo-1,2,3-triazoles 310 are found to be versatile starting materials for derivatization of the triazole ring with \( \text{sp}^2 \) and \( \text{sp} \) carbon substituents. In Suzuki coupling with areneboronic acids, 5-aryltriazoles 309 are obtained in 64–98% yield. The reaction is catalyzed by palladium dichloride–triphosphine complex and proceeds well in the presence of KOH as a base. In reactions with alkeneboronic acids, 5-(alken-1-yl)-1,2,3-triazoles 311 are generated in 59–95% yield. In a Heck reaction with methyl vinyl ketone, 5-iodotriazoles 310 are converted to unsaturated ketones 312 in 87–98% yield. Acrolein gives aldehyde 312 (R\(^4\) = H) in only 62% yield, but the yields of products 312 obtained from a reaction of iodide 310 with methyl acrylate (R\(^4\) = OMe) are much higher (92–98%). Acrylonitrile reacts well; however, mixtures of (E)- and (Z)-isomers of nitriles 313 are obtained. Heck coupling of iodide 310 with styrene is much slower, but product 314 is obtained as a single (E)-isomer in 92% yield. In a Sonogashira reaction, 5-iodotriazoles 310 are coupled with alkynes to provide derivatives 315 in 71–99% yield (Scheme 47).

![Scheme 47](image)

5.01.7.4 Carboxylic Acids and Their Derivatives

Esters of 1,2,3-triazolecarboxylic acids are the most common derivatives of triazole (Section 5.01.9); therefore, their conversions to other, more useful, functionalities are of great importance. In an example given in Scheme 48, 4-triazolecarbocyclic ester 317, obtained from a reaction of \( \beta \)-ketoester 316 with 4-chloro-2-nitrophenyl azide, is hydrolyzed to free acid 318 (82% yield) by 4% KOH. Heated to reflux in DMF for 3 h, acid 318 undergoes decarboxylation to triazole derivative 319 with 81% isolated yield.

Acid chloride 321, obtained in 85% yield by refluxing a solution of carboxylic acid 320 in thionyl chloride, is converted to azide 322 in 86% yield by treatment with sodium azide in pentane. Reactions of azide 322 with amines of low nucleophilicity in refluxing DMF provide ureas 323 in 24–90% yield via Curtius rearrangement. In these reactions, 3-bromo- and 4-bromoaniline give also the corresponding amides, which are formed by simple substitution of the N\(_2\) group in azide 322 with amines, as the side products. Secondary amines and primary amines with more nucleophilic NH\(_2\) groups (e.g., \( p \)-anisidine and \( t \)-butylamine) provide exclusively the corresponding amides (Scheme 49).

![Scheme 49](image)
Ester 324 is hydrolyzed to acid 325 by refluxing in 10% NaOH. In a reaction with thionyl chloride, acid 325 is converted to acid chloride 326, which is isolated as a solid in 96% yield and consecutively converted into amide 327 in 85% yield. Treatment of amide 327 with LDA extracts a proton from the methyl group. The generated anion is trapped by added benzonitrile. Subsequent cyclocondensation of the obtained imine anion with the amide group provides derivative 328 in 62% isolated yield (Scheme 50) <2003EJM983>.

In an example given in Scheme 51, tricyclic system 331 is generated by cyclocondensation between the ethoxycarbonyl group at C-5 of the triazole ring and the amino group of the substituent at N-1. The process that starts from catalytic reduction of the nitro group in derivative 329 does not stop at amine 330, but the subsequent spontaneous cyclocondensation leads directly to product 331 that is isolated in 60% yield <2002EJM565>.

Ethyl 5-chloromethyl-1,2,3-triazole-4-carboxylate 332, obtained by cyclocondensation of 3-amino-4-azidofurazan with ethyl 4-chloroacetoacetate, is converted to pyrrolidine derivative 333 in 97% yield. Heating at reflux with 1 N HCl deprotects the carboxylic group. The obtained acid 334 is treated with carbonyldiimidazole followed by pyridine-4-carboxylic acid amidrazone to provide product 335 in 25% yield. Compound 335 is a potent inhibitor of glycogen synthase kinase-3 (GSK-3) (Scheme 52) <2003JME3333>.

Scheme 48

Scheme 49

R = α-naphthyl, β-naphthyl, 3-BrC₆H₄, 4-BrC₆H₄ or 2,5-Cl₂C₆H₃
5.01.7.5 Carbaldehydes

Cyclocondensation of diazomalonaldehyde 336 with 4-fluoroaniline carried out in methanol-acetic acid provides 1-(4-fluorophenyl)-1,2,3-triazole-1-carbaldehyde 337 in 78% yield. Oxidation with MnO$_2$ in the presence of sodium cyanide in methanol converts aldehyde 337 into methyl ester 338 with 79% yield. Hydrazide 339 (84% yield) is obtained in a reaction of ester 338 with hydrazine. Product 339 reacts with various aromatic aldehydes to give hydrazones possessing interesting antiplatelet activity (Scheme 53) <2003BMC2051>. 

Scheme 50

Scheme 51

Scheme 52
5.01.7.6 Amines

1,2,3-Triazoles substituted with an amino group at C-5 are readily available from cycloaddition of nitriles to azides. They have become convenient intermediates in synthesis of biologically active compounds. In an example given in Scheme 54, cycloaddition of anions derived from cyanoacetamides \(340\) to benzyl azide provides 5-amino-1,2,3-triazole derivatives \(341\) in 75–91% yield. Catalyzed by phosphorus oxychloride, amines \(341\) undergo cyclocondensation with DMF under mild conditions (40°C) to give amidines \(342\). At higher temperature (80°C), cyclocondensation occurs with elimination of dimethylamine to form 1,2,3-triazolo[4,5-d]pyrimidin-5-ones \(343\), which are isolated in 71–85% yield. However, lower yield (30%) is obtained for \(R = 2\)-MeOC\(_6\)H\(_4\). For \(R = H\), simple heating of the corresponding amine \(341\) with formamide at 210°C provides derivative \(343\) in good yield <2003RCB1770>.

![Scheme 54](image)

In a synthesis similar to that depicted in Scheme 54, aminoesters \(344\) dissolved in DMF are treated with POCl\(_3\) and heated at 50–60°C for 2 h. The simple work-up procedure involves pouring into ice-water, neutralization with NaOH and separation of the precipitate by filtration to afford amidines \(345\) in 66–86% yield (Equation 11). Some of the obtained amidines exhibit selective antibacterial activity <2003SC3969>.

\[
\text{Equation 11}
\]

\(X = H, p\)-Me, \(p\)-MeO, \(p\)-EtO, \(p\)-MeCO, \(p\)-NO\(_2\), \(p\)-Cl, 
\(m\)-F, \(m\)-Cl, \(m\)-Br, \(m\)-CF\(_3\), or \(m\)-NO\(_2\)
1,3-Dipolar cycloaddition of 2-cyanoacetamide to 2-azido-4-(hydroxymethyl)-cyclopentanol 346, carried out in ethanol in the presence of sodium ethoxide, provides regioselectively 5-amino-1,2,3-triazole derivative 347 in 52% yield. In the following step, the hydroxy groups are protected by acetylation with acetic anhydride to give diester 348 in 75% yield. Surprisingly, the amino group is not nucleophilic enough to be acetylated under such conditions. Diazotization (isoamyl nitrite) and substitution with iodide (diiodomethane) converts amine 348 into 5-ido derivative 349 that is isolated in 55% yield. By coupling with terminal alkynes under modified Sonogashira conditions, iodide 349 is converted to alkynes 350 in 52–77% yield. Treated with 40% aqueous dimethylamine in ethanol at 80 °C in sealed tubes, amido groups in derivatives 350 undergo intramolecular cycloaddition to alkynes resulting in formation of pyridine rings. In the same step, the hydroxy groups are deprotected to provide 6-substituted 1,2,3-triazolo[4,5-\textit{c}]pyridin-4-ones 351 in 51–72% yield (Scheme 55).<2005T11744>.

When a solution of azide 352 and nitrile RCH2CN in ethanol is treated with sodium ethoxide, the anion derived from nitrile undergoes 1,3-dipolar cycloaddition to azide 353. Generated anion 354 tautomerizes to more stable aromatic form 355. Nucleophilic attack of the triazoloamine anion on the ethoxycarbonyl group in intermediate 355 results in elimination of an ethoxy anion and ring closure to give pyrrolo[3,4-\textit{e}]1,2,3-triazolo[1,5-\textit{a}]pyrimidin-5-one 356 in high yield. Heating of compound 356 (R = Ph) in DMSO in the presence of traces of water results in its hydrolysis to aminoacid 357. Under the reaction conditions, 5-aminotriazole system 357 undergoes Dimroth rearrangement to more stable derivative 358. Spontaneous cyclocondensation between the carboxylic group and the triazole ring in 358 leads to 6-methyl-3,5,7-triphenyl-4,6-dihydro-8H-pyrrolo[3,4-\textit{e}]1,2,3-triazolo[1,5-\textit{a}]pyrimidin-8-one 359 that is isolated in almost quantitative yield (Scheme 56).<2000JHC747> . Similar transformations are reported for ethyl 1-benzyl-3-azido-4-phenylpyrrolocarboxylic acid <2002T9723>.

Ethyl 3-azido-1-methyl-1H-indole-2-carboxylate 361 is prepared in 70% yield by diazotization of amine 360 followed by substitution of the created diazonium group with sodium azide. In cycloadditions with nitrile anions, azide 361 forms triazole intermediates 362. However, under the reaction conditions, cyclocondensation of the amino and ethoxycarbonyl groups in 362 results in formation of an additional ring. This domino process provides efficiently 4H-indolo[2,3-\textit{e}]1,2,3-triazolo[1,5-\textit{a}]pyrimidines 363 in 70–80% yield (Scheme 57).<2006TL2187>.

Scheme 55

![Scheme 55](image-url)
Scheme 56

Scheme 57
In a similar tandem reaction, ethyl 2-azido-1-methyl-1H-indole-3-carboxylate 364 is converted to indolo[3,2-e]1,2,3-triazolo[1,5-a]pyrimidin-5-ones 366 via triazole intermediates 365 that are not separated (Scheme 58). Products 366 are obtained in 80-90% yield as potential intercalates of DNA <2003H(60)2669>.

Azide 367 is prepared from 4-sec-butyl-2-nitroaniline in 76% yield by its diazotization followed by treatment with sodium azide. In a 1,3-dipolar cycloaddition with cyanoacetamide, azide 367 is converted to triazole 368 that without separation is directly subjected to Dimroth rearrangement to give derivative 369 in 46% yield. Reduction of the nitro group provides ortho-phenylenediamine 371 in 91% yield <2000EJM715>. Cyclocondensation of diamine 371 with phosgene furnishes benzimidazol-2-one 370 in 39% yield, whereas its reaction with sodium nitrite in 18% HCl leads to benzotriazole derivative 372, which is isolated in 66% yield (Scheme 59). Products 370 and 372 exhibit potassium channel activating ability <2001FA841>.

Scheme 58

Scheme 59
Amino groups on the benzenoid ring of benzotriazole behave similarly to those of typical aromatic amines. 4-Aminobenzotriazole 373 is readily diazotized to provide diazonium chloride 374. In couplings with phenols or aromatic amines, diazonium derivative 374 is converted to the corresponding azo dyes. Three examples of such reactions providing dyes 375 (67%), 376 (84%) and 377 (64% yield) are shown in Scheme 60 <2002AN838>. Dyes of this type are used for labeling of nucleotides <2003TL1339>.

Scheme 60

5.01.8 Reactivity of Substituents Attached to Ring Nitrogens

Functional groups can be attached to the ring nitrogen atoms in position 1 or 2 of unsubstituted or symmetrically substituted aromatic rings of 1,2,3-triazoles and benzotriazoles giving rise to distinctive regioisomers 378 and 379, respectively. In most cases, isomers 378 form kinetically in predominant amounts. In some instances, there is a rapid equilibrium between isomers 378 and 379 in solution <1996CHEC-II(4)1>. For many reactions, there is no different outcome if pure isomers 378, 379 or their mixtures are employed. For these reasons and clarity of the treatment, in the following paragraphs, only triazol-1-yl and benzotriazol-1-yl 378 isomers are depicted in schemes, even if the corresponding triazol-2-yl 379 isomers are also present in the mixtures. If the chemistry of isomers 378 and 379 differs remarkably, they are treated separately.

5.01.8.1 Ring N-C(sp³)-R, R = C(sp³), or H

Upon treatment with n-butyllithium at −78 °C, 1-methylbenzotriazole 380 is lithiated on the methyl group to give 1-(lithiomethyl)benzotriazole 381. Rapid addition of a carboxylic ester to the solution provides α-(benzotriazol-1-yl)alkyl ketone 382 in high yield (Scheme 61) <1997JOC4142>. This easy access to ketones 382 and their reactivity makes them valuable intermediates in several syntheses. Their chemistry is discussed separately in Section 5.01.8.4.
When treated with Bu\textsuperscript{t}Li, 1-(3-chloropropyl)benzotriazole 383, obtained from a reaction of benzotriazole with 1-bromo-3-chloropropane and NaOH, undergoes cyclization to 1-cyclopropylbenzotriazole 384 <1998JOC6710>. Further lithiation followed by treatment with ketones provides alcohols 385 (Scheme 62). Upon heating at 60 °C with low valent titanium <1998JOC6704>, alcohols 385 are converted into interesting cyclopropylidene derivatives 386. 1-(3-Chloro-2-methylpropyl)benzotriazole gives analogous products with a methyl group on the cyclopropane ring <1998JOC6710>.

Perhaps due to oxidizing quinoid type electronic structure of benzotriazol-2-yl derivatives, some of their properties are completely different from those of isomeric benzotriazol-1-yl derivatives. Thus, anions derived from 2-alkylbenzotriazoles 388 are rapidly converted to appropriate radicals that undergo coupling to form dimers as mixtures of racemic 289 and meso 390 forms <1996LA745>. When the reaction mixture is kept for an extended period of time at −78 °C, (Z)- 391 and (E)- 392 alkenes are formed. When benzophenone is added to the reaction mixture, alcohols 387 are obtained in good yields; however, benzaldehyde does not react under these conditions (Scheme 63).

Scheme 61

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When treated with Bu\textsuperscript{t}Li, 1-(3-chloropropyl)benzotriazole 383, obtained from a reaction of benzotriazole with 1-bromo-3-chloropropane and NaOH, undergoes cyclization to 1-cyclopropylbenzotriazole 384 <1998JOC6710>. Further lithiation followed by treatment with ketones provides alcohols 385 (Scheme 62). Upon heating at 60 °C with low valent titanium <1998JOC6704>, alcohols 385 are converted into interesting cyclopropylidene derivatives 386. 1-(3-Chloro-2-methylpropyl)benzotriazole gives analogous products with a methyl group on the cyclopropane ring <1998JOC6710>.

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Scheme 62

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Perhaps due to oxidizing quinoid type electronic structure of benzotriazol-2-yl derivatives, some of their properties are completely different from those of isomeric benzotriazol-1-yl derivatives. Thus, anions derived from 2-alkylbenzotriazoles 388 are rapidly converted to appropriate radicals that undergo coupling to form dimers as mixtures of racemic 289 and meso 390 forms <1996LA745>. When the reaction mixture is kept for an extended period of time at −78 °C, (Z)- 391 and (E)- 392 alkenes are formed. When benzophenone is added to the reaction mixture, alcohols 387 are obtained in good yields; however, benzaldehyde does not react under these conditions (Scheme 63).
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Scheme 63

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Perhaps due to oxidizing quinoid type electronic structure of benzotriazol-2-yl derivatives, some of their properties are completely different from those of isomeric benzotriazol-1-yl derivatives. Thus, anions derived from 2-alkylbenzotriazoles 388 are rapidly converted to appropriate radicals that undergo coupling to form dimers as mixtures of racemic 289 and meso 390 forms <1996LA745>. When the reaction mixture is kept for an extended period of time at −78 °C, (Z)- 391 and (E)- 392 alkenes are formed. When benzophenone is added to the reaction mixture, alcohols 387 are obtained in good yields; however, benzaldehyde does not react under these conditions (Scheme 63).
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In a direct comparison of the reactivity of 1-alkyl- and 2-alkylbenzotriazoles, compound 393 was lithiated in the presence of benzophenone with 1 equiv of LDA to give a mixture of alcohol 394 and dimer 395 (Equation 12) <1996LA745>. No reaction was detected at the carbon adjacent to the benzotriazol-1-yl moiety. When benzaldehyde was used instead of benzophenone, only dimer 395 was obtained. This suggests that α-benzotriazol-2-yl carbon radical reactions are much faster than those of α-benzotriazol-1-yl) carbanions.

\[
\begin{align*}
\text{Ph}_2\text{C} &= \text{O} \\
\text{LDA} &
\end{align*}
\]

(12)

\[\text{393} \rightarrow \text{394} + \text{395}\]

5.01.8.2 Ring \(\text{N} - \text{C}(\text{sp}^3) - \text{C} - \text{C}\)

5.01.8.2.1 Ring \(\text{N} - \text{C}(\text{sp}^3) - \text{Ar}\). No reaction on Ar

Easy synthesis of (benzotriazol-1-yl)methylenes and –heteroarenes, and their reactivity, makes them convenient starting materials for further transformations. Benzotriazole assisted side-chain elaboration of alkylarenes can be illustrated by reactions carried out on 2-(benzotriazol-1-yl)methyl-5-methylthiophene 396 (Scheme 64). Starting material 396 can be readily obtained by refluxing a solution of 1-(hydroxymethyl)benzotriazole, 2-methylthiophene and a catalytic amount of TsOH in dioxane. α-Deprotonation of derivative 396 with \(\text{Bu}^\text{a}\text{Li}\) followed by treatment with an electrophile leads to product 397. Phenyl isocyanate, phenyl isothiocyanate, benzaldehyde, alkyl iodides, benzyl bromide, and cyclohexanone have been used as electrophiles. Upon treatment with nucleophiles, the benzotriazole moiety in compounds 397 can be substituted to give products 398. To replace the benzotriazolyl group with hydrogen, derivatives 397 are treated with zinc in refluxing acetic acid <1997JOC6215>. Similar benzotriazole-assisted side-chain transformations are reported for benzene <1997JOC721>, pyrrole <1996JOC1624, 1996TL5641>, and indole <1995JOC3401, 1995SC539, 1996JOC7558>.

\[
\begin{align*}
\text{396} &\xrightarrow{i, \text{Bu}^\text{a}\text{Li}} \text{397} &\xrightarrow{\text{ii, E}^+} \text{398}
\end{align*}
\]

\(\text{E}^+ = \text{R}, \text{PhCH}_2\text{Br}, \text{PhCH}=\text{O}, \text{PhN}=\text{C}=\text{O}, \text{PhN}=\text{C}=\text{S}, \text{and cyclohexanone}\)

Scheme 64

An additional stabilization of the negative charge provided by the adjacent aryl group in aryllithiomethyl intermediates 400 makes 1-(arylthiomethyl)benzotriazoles 399 attractive starting materials for many syntheses. Thus, reaction of anions 400 with esters of carboxylic acids leads to α-(benzotriazole-1-yl) ketones 401, which can be easily reduced to carbinols 402.
In another approach, adducts \(402\) are produced directly by addition of anions \(400\) to carbonyl groups of aldehydes or ketones <1997JOC238, 1998JOC6704>. Low valent titanium, generated by reduction of TiCl\(_3\) with lithium or Zn–Cu couple metals, converts carbinols \(402\) into olefins \(403\) (Scheme 65). The reaction sequence depicted in Scheme 65 allows introduction of a variety of substituents \(R^1\): for example, chiral allylamines are produced from aminoacids, or dienes are formed stereoselectively from \(\alpha,\beta\)-unsaturated aldehydes or ketones. Reaction of lithio derivatives \(400\) with tosylhydrazones of aldehydes leads directly to (E)-stilbenes in a stereospecific manner <1999JOC3332>. Reaction of anions \(400\) with chloromethyltrimethylsilane provides very useful intermediates \(404\) <1997JA9321>. Consecutive \(\alpha\)-lithiation followed by addition to a carbonyl group of an aldehyde leads to alkoxide \(405\). During heating, anions \(405\) undergo an intramolecular rearrangement with elimination of benzotriazole to produce silylated allyl alcohols \(406\) (Scheme 66) <1998JOC9978>. This approach provides a general method for the synthesis of allyl alcohols substituted with an aryl or heteroaryl group in the \(\beta\) position.
Additions of lithiated silyl derivatives 404 to α,β-unsaturated compounds bearing electron-withdrawing substituents X provide silyl derivatives 407 with high 1,4-regioselectivity. Elimination of trimethylsilyl and benzotriazolyl groups facilitated by heating with CsF leads to γ,δ-unsaturated ketones, nitriles, sulfones, nitroalkanes, or amides 408 <1998JOC9987>. Formylation of intermediates 404 produces masked acroleins 409 that provide easy access to 2-substituted allyl alcohols 410. Imines obtained from condensation of aldehydes 409 with amines can be similarly converted to the corresponding allylamines <1999JOC6080>.

Additions of anions 400 to carbonyl groups of aldehydes or ketones produce anions 411 that upon treatment with ZnBr2 eliminate benzotriazole at elevated temperature and rearrange to ketones 412 (Scheme 67) <1996JOC7571>. This insertion of carbons carrying aryl or heteroaryl substituents provides a convenient method for one-carbon chain extension or ring expansion for aldehydes and ketones. The reaction is characterized by significant regioselectivity; of two groups R1 and R2, preferences for the migration are in the order: H > aryl > alkyl and tert-alkyl > sec-alkyl > n-alkyl.

\[ R^1 \text{C} R^2 \quad \overset{400}{\rightleftharpoons} \quad \text{ZnBr}_2 \quad \overset{411}{\rightarrow} \quad \text{Zn}^+ R^1 \text{C} R^2 \]

Scheme 67

Substitution of one of the α-hydrogens in 1-(arylmethyl)benzotriazole 399 with an alkyl bearing an aromatic ring opens new frontiers. When the distance is right, an intramolecular electrophilic attack of α-carbon on an ortho atom of the aromatic ring is possible. Examples of such annihilation reactions are given in Scheme 68. Thus, treatment of derivative 414, obtained by alkylation of intermediate 400 with (2-bromoethyl)benzene, with zinc bromide results in formation of indane 413. Alternatively, intermediate 414 can be first alkylated to product 415 and then annulated to 1,1-disubstituted indane 416. For effective annulation, the link between the aromatic ring and α-carbon must consist of two or three atoms. Heteroatoms are also accepted, as exemplified by phenoxy derivatives 417–420. Heterocyclic aromatic rings can be used as well; for example, annulated products 424 and 425 are obtained from 1-(3-chloropropyl)-3-methylindole 422 via intermediate 421 or its methylated analog 423, respectively <1998JOC3445>. Similar annihilation reactions involving thiophene are also described <1997JOC6215>.

Two sequential lithiations and treatments with different bifunctional electrophiles make possible one-pot syntheses of relatively complex molecules. Thus, in the [1+2+2] annulation depicted in Scheme 69, alkylation of 1-benzylbenzotriazole 399 with 2-bromoacetalddehyde diethyl acetal to give intermediate 426 is followed by alkylation with N-benzylidenecetamide to produce derivative 427. Following treatment with formic acid causes cyclization to ethoxypyrrolidine 428 that subsequently eliminates ethanol and benzotriazole to give pyrrole 429 <1997JHC1379>.

Anions derived from treatment of (diarylmethyl)benzotriazoles 430 with Bu"Li are readily trapped by bromoacetophenone to produce ketones 431. Increased acidity of the hydrogens in β-position, with respect to the benzotriazolyl moiety, renders derivatives 431 susceptible to elimination of benzotriazole to give diarylvinyl ketones 432 (Scheme 70). Both benzotriazol-1-yl and -2-yl derivatives, and their mixtures, can be employed in these reactions <1998JOC3450>. Treatment of (diarylmethyl)benzotriazoles 430 with metallic lithium and electrophiles results in substitution of benzotriazole with formation of derivatives 436. The yields are generally good, and a variety of electrophiles can be employed. Some unusual outcome of these reactions can tentatively be explained by a single-electron transfer (SET) from lithium to starting compounds 430 to give radical anions 433 which eliminate benzotriazole to form relatively stable radicals 434. Following reduction with metallic lithium (another SET) converts radicals 434 into anions 435 that are finally trapped by electrophiles to give products 436 <1997JOC4116>. 

\[ \text{Scheme 69} \]

1,2,3-Triazoles
Scheme 68

Scheme 69

[399]
5.01.8.2.2 Ring N–C(sp³)-Ar. Reactions on Ar

Lithiated 1-(arylmethyl)benzotriazoles 400 (Ar = phenyl, tolyl, or anisyl) readily undergo Michael additions to α,β-unsaturated aldehydes or ketones 437 to give γ-carbonyl-alkyl derivatives 438. Upon treatment with acids, the carbonyl group of intermediate 438 is activated for an electrophilic attack on the ortho carbon of the ring to produce tetrahydronaphthalene derivative 439 which eliminates consecutively water and benzotriazole to give the naphthalene 440 (Scheme 71) <1997JOC721>. Substitution of one of the α protons in compound 400 with an alkyl group allows the introduction of substituents to C-4 of naphthalene. Analogous reactions of 1-[(1-methylindol-3-yl)methyl]benzotriazole lead to corresponding carbazoles <1996JOC7558>. Similar [3+3] benzannulation reactions are occur for furans <1997JOC8205>, indolizines <2000JOC8059>, pyrroles <1996TL5641, 1997JOC4148>, thiazoles <2000JOC8059>, and thiophenes <1997JOC6215>; several examples of which can be found in review articles <1999T8263, 1998CCC599>.

Derivatives 400 containing electron-rich aromatic rings undergo readily [3+2] cycloaddition with styrenes. Two examples of such reactions are presented in Scheme 72. Thus, alkylation of an anion derived from benzylbenzotriazole 441 gives derivative 442. Following treatment with ZnBr₂ cleaves the bond with benzotriazole to generate the corresponding benzyl cation which is then trapped by styrene to give a new cation that finally cyclizes on to the aromatic ring at its ortho position to furnish indan 443 <1997SC2467>. A similar process converts 1-methyl-3-[benzotriazole-1-yl]methyl]indole 444 into tricyclic system 446, via intermediate 445 <1996JOC7558>. 
Treatment of anions derived from 2-(diphenylmethyl)benzotriazole 447 with iodine generates relatively stable radicals 448 which undergo spontaneous dimerization to adducts 449 (Scheme 73).<ref>1998JOC9992</ref>. When one of the phenyl rings in starting material 447 is substituted in the para position, similar dimerization occurs readily, but it
is prevented by substitution of both para positions. Contrary to the behavior of an analogous adduct obtained by dimerization of triphenylmethyl radicals \(<1925CRV91, 1968TL249>\), adduct 449 does not dissociate back to radicals 448, indicating different characters of these two species. Treated with bases, adduct 449 eliminates one benzotriazole to give highly conjugated system 450, red in color. Acidic hydrolysis converts adduct 449 into carbinol 451. Radicals similar to 448 can be also generated from 1-(diarylmethyl)benzotriazoles, but they are less stable undergoing easily ring opening with extrusion of nitrogen \(<1998JOC1467>\).

5.01.8.2.3 Ring N–C(sp<sup>3</sup>)-C–C, nonaromatic

N-Allylbenzotriazoles (452 and its benzotriazol-2-yl analog) behave somewhat similarly to N-benzylbenzotriazoles. Anions derived from compounds 452 upon treatment with n-butyllithium undergo alkylation exclusively at the position 2 to the benzotriazole moiety to give products 453 (Scheme 74). The lithiation and alkylation steps can be repeated to produce dialkylated derivatives 454, possibly with two different alkyl groups. Although only benzotriazol-1-yl compounds are shown in Scheme 74, in this case, both benzotriazol-1-yl and benzotriazol-2-yl derivatives have similar reactivity and their mixtures can be used effectively in the reactions next mentioned without separation \(<1998TL363>\). Treatment of compounds 453 and 454 with metallic lithium in the presence of aldehydes or ketones cleaves the bonds with benzotriazole creating allylic anions that are trapped by the carbonyl groups to produce carbinols 455 and 456, respectively, in high yields.

In the presence of a palladium catalyst, the benzotriazole moiety in derivatives 452, 453 (and also in compound 454) can be substituted with amines to give allylamines 457 (Scheme 75) \(<1998JOC5232>\). Sulfonamides can also be N-allylated this way when triphenyl phosphite is used in place of triphenylphosphine as a complexing catalyst agent \(<2000JOC8063>\). Palladium-catalyzed reactions of derivatives 453 and 454 with enamines lead to \(\gamma,\delta\)-unsaturated ketones \(<1999JOC7625>\). Lithiated allylbenzotriazoles 452 and 453 react with aldehydes and ketones to form alcohols 458 \(<2000JOC8063>\). Following treatment with amines and the catalyst converts alcohols 458 into unsaturated aminoaocohols 459.

The reaction of allylbenzotriazoles with amines can also be carried out intramolecularly. Thus, alkylation of derivatives 452 or 453 with 1-bromo-3-chloropropane gives chloropropyl derivative 460. Subsequent substitution of the chlorine atom with an alkylamino group is easily accomplished by heating a solution of derivative 460 and amine R<sup>3</sup>NH<sub>2</sub> in DMF. Intramolecular substitution of the benzotriazole moiety by the amino group in amines 461 occurs at room temperature in the presence of a palladium catalyst to furnish 2-vinylpyrrolidines 462 (Scheme 75) \(<1999JOC6066>\). Similarly, alkylation of derivatives 452 and 453 with 1-bromo-4-chlorobutane and the following transformations lead to 2-vinylpiperidines \(<1999JOC6066>\).
Reaction of lithiated allylbenzotriazole 452 with chloromethyltrimethylsilane yields silyl derivative 464 which can be further alkylated to give compound 465 (Scheme 76) \(<1999\text{JOC}1888\>). Upon heating, product 465 is readily converted to diene 466 via vicinal elimination of benzotriazolyl and silyl substituents. Additions of lithiated silyl derivative 464 to carbonyl groups of aldehydes lead to alcohols 463 which readily eliminate benzotriazole and silane to furnish 2-(1-hydroxyalkyl)butadienes 466 (R<sub>1</sub> = 1-hydroxyalkyl).

Additions of lithiated N-allylbenzotriazoles 452 and 453 add readily to the C=T= bond of Schiff bases derived from aromatic or heteroaromatic aldehydes and amines to give amines 467. In the presence of a palladium catalyst and copper(II) oxidizing agent, amines 467 are smoothly converted to pyroles 468 (Scheme 77) \(<2000\text{JOC}8074\>). Addition of lithiated allylbenzotriazoles 453 to the C=N bond of isothiocyanates leads to thioamides 470. Catalyzed by ZnBr<sub>2</sub>, thioamides 470 undergo cyclization to aminothiophenes 469 \(<2001\text{JOC}2850\>). When the nucleophilic attack of the sulfur atom on the allylic system is blocked by methylation as in compound 471, the nitrogen atom takes the leading role and 2-(methylthio)pyrroles 472 are formed instead.

When an additional leaving group is present at the allylic system, conversion of N-allylbenzotriazoles to five-membered heterocyclic rings is facilitated. Thus, α-ethoxy derivative 473 undergoes smooth rearrangement promoted by ZnBr<sub>2</sub> to give (γ-ethoxyallyl)benzotriazole 474. After lithiation, the obtained anion is trapped by a Schiff base to give anion 475. Catalyzed by ZnBr<sub>2</sub>, intermediate 475 undergoes cyclization with elimination of benzotriazole and ethanol to furnish 1,2-diarylpvrole 476 (Scheme 78) \(<1995\text{S}1315\>). Alkylation of (γ-ethoxyallyl)benzotriazole 474 occurs exclusively at the carbon α producing derivatives 478, which, in their lithiated forms, add readily to the carbonyl group of aldehydes. Obtained anions 479 are rapidly converted to 2,3-disubstituted furans 480 upon treatment with ZnBr<sub>2</sub> \(<1995\text{S}1315\>). Treatment with ZnBr<sub>2</sub> and water converts ethoxyallyl derivatives 478 into α,β-unsaturated aldehydes 477.
The morpholin-4-yl substituent in \( \gamma \)-position behaves similarly to the ethoxy group. Compound 481 is easily prepared by double addition of benzotriazole to acrolein followed by elimination of one of the benzotriazolyl moieties induced by treatment with NaH. Lithiation of derivative 481 followed by addition to a Schiff base results in formation of diarylpyrrole 476. Lithiated product 481 is alkylated exclusively at the carbon \( \alpha \), in relation to the benzotriazolyl substituent, giving intermediate 482. Subsequent treatment with a Grignard reagent leads to enamine 483 (Scheme 79) \(<1995\text{TL}343>\).

A phenyl substituent at the \( \gamma \)-carbon atom is a much weaker electron donor in comparison with the discussed above ethoxy and morpholin-4-yl groups. Nevertheless, 1-(\( \gamma \)-phenylallyl)benzotriazole 484 is still lithiated exclusively at the carbon \( \alpha \) as it is evident from its reaction with aldehydes and ketones leading to dienes 486, resulting from
elimination of benzotriazole and water from intermediate carbinols \textbf{485} \textsuperscript{<1997JOC238>}. However, the strongly electron-withdrawing phenylsulfonyl group at the $\gamma$-carbon shifts the equilibrium from form \textbf{487} to form \textbf{488}, which upon its alkylation gives sole product \textbf{489} (Scheme 79) \textsuperscript{<1998JHC173>}. 

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node (A) at (0,0) {\textbf{476}};
\node (B) at (2,0) {\text{\textit{i, Bu}^n\text{Li}}};
\node (C) at (4,0) {\textit{ii, Ar}^1\text{CH}=\text{NAr}^2};
\node (D) at (0,-2) {\textbf{481}};
\node (E) at (2,-2) {\text{i, Bu}^n\text{Li}};
\node (F) at (4,-2) {\textit{ii, R}^1\text{X}};
\node (G) at (6,-2) {\textbf{482}};
\node (H) at (8,-2) {\textbf{R}^2\text{MgX}};
\node (I) at (10,-2) {\textbf{483}};
\node (J) at (0,-4) {\textbf{484}};
\node (K) at (2,-4) {\text{i, Bu}^n\text{Li}};
\node (L) at (4,-4) {\textit{ii, R}^1\text{R}^2\text{C}=\text{O}};
\node (M) at (6,-4) {\textbf{485}};
\node (N) at (8,-4) {\textbf{486}};
\node (O) at (10,-4) {\textbf{487}};
\node (P) at (12,-4) {\textbf{488}};
\node (Q) at (14,-4) {\text{i, base}};
\node (R) at (16,-4) {\textit{ii, RX}};
\node (S) at (18,-4) {\textbf{489}};
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 79}

\subsection{5.01.8.3 Ring N–C(sp$^3$)-C=N}

Hydrazones \textbf{490} are readily obtained from the corresponding ketones. Upon treatment with 6 molar equivalents of n-butyllithium, they are deprotonated to dianions which lose rapidly the tosyl moiety to form anions \textbf{491} that further eliminate spontaneously $\text{N}_2$ and benzotriazole to give alkynes \textbf{492} (Scheme 80). In the special case, when $R^1=\text{PhO}$ (compound \textbf{493}), organolithium reagents eliminate first the phenoxy group to give intermediates \textbf{494}. Addition of group $R^1$ to \textbf{494} followed by elimination of tosylate, nitrogen and benzotriazole provides alkynes \textbf{495}. Due to the stronger electron-donating influence of the phenylthio group in compound \textbf{496}, the benzotriazolyl moiety is eliminated preferentially leading to unstable sulfide \textbf{497}, which is converted by excess $\text{Bu}^n\text{Li}$ to acetylene \textbf{498} \textsuperscript{<1997JOC4142>}. Treated with only 3 molar equivalents of $\text{Bu}^n\text{Li}$, hydrazones \textbf{490} behave differently. Bond cleavage between N-1 and N-2 of the benzotriazole ring in the initial dianion \textbf{499} leads to dianion \textbf{500}. Following ring closure produces benzotriazine system \textbf{502}. The next step of the transformation sequence depends on substituent $R^1$. When $R^1$ is an aryl, the structure is stable enough to survive work-up as dihydrobenzotriazine \textbf{501}. When $R^1$ is an alkyl, the whole hydrazone group is eliminated producing benzotriazine \textbf{503} (Scheme 81) \textsuperscript{<1997SC3963>}. When phenoxy derivative \textbf{493} is subjected to such treatment, the dianion formed, analogous to \textbf{500}, loses molecular nitrogen to give energetic dianion \textbf{504} that quickly undergoes cyclization/elimination to furnish indole \textbf{505}. 

\textbf{Scheme 80} 

\textbf{Scheme 81}
Scheme 80

1,2,3-Triazoles

Scheme 81
Treated with thionyl chloride, hydrazones \( R_1 = H, R_2 = \text{aryl} \) undergo cyclocondensation to thiadiazoles \( 506 \); whereas from aliphatic derivatives \( R_1 = H, R_2 = \text{alkyl} \), mixtures of thiadiazoles \( 507 \) and \( 508 \) are formed \(<2002H(58)311>\).

Oximes \( 509 \) can be converted to their tosylates \( 510 \), but use of a large excess of KOH converts them directly into \( 2H \)-azirines \( 511 \) (Scheme 82) \(<2003JOC9105>\). The benzotriazolyl moiety in azirines \( 511 \) can be substituted by nucleophiles (organomagnesium reagents, potassium phthalimides, and sodium thiophenoxide) to give disubstituted azirines \( 512 \).

### 5.01.8.4 Ring N–C(sp\(^3\))-C─O

There are several methods available that lead to \( \alpha \)-benzotriazolyl ketones \( 517 \) (Scheme 83). Thus, the anions derived from \( N \)-alkylbenzotriazoles \( 513 \) can be trapped by acid chlorides or esters \(<1998JOC3438, 1998H(48)1567>\). Alternatively, in reactions with aldehydes, \( N \)-alkylbenzotriazoles \( 513 \) are converted to \( \beta \)-benzotriazolyl alcohols \( 516 \) that are consecutively oxidized to ketones \( 517 \) \(<1996LA1235>\). Other approaches include substitution of halogens in \( \alpha \)-haloketones \( 514 \) by benzotriazole, \(<2000JHC167, 2002ARK(iii)46>\), reactions of esters of \( \alpha \)-benzotriazolylicarboxylic acids \( 515 \) with Grignard reagents \(<1997JOC4142>\), addition of benzotriazole to but-2-ene-1,4-diones \( 518 \) \(<1992PJC1633>\), and reactions of \( N \)-chlorobenzotriazole with trimethylsilyl derivatives of the corresponding ketones \(<1998JCM334>\). In an interesting modification of the above methods, benzotriazoleacetic acid \( 519 \) \(<1935LA113>\) is alkylated to produce carboxylic acids \( 520 \), which are then dilithiated and treated with acyl halides to give ketones \( 517 \), via unstable intermediates \( 521 \) \(<2004ARK(iii)22>\).

Removal of the benzotriazole moiety from ketones \( 517 \) can be accomplished in several modes. Thus, treatment of derivative \( 522 \) with lithium naphthalenide followed by methyl iodide provides ketone \( 523 \) in 51% yield (Scheme 84) \(<2002ARK(iii)46>\). Upon treatment with butyllithium, anions derived from \( 1-( \text{aryl methyl}) \)-benzotriazoles \( 524 \) can be trapped by esters of arylcarboxylic acids to give ketones \( 525 \) which are readily oxidized with molecular oxygen under mild conditions to give diaryl 1,2-diketones \( 526 \) in good yields. This provides a convenient synthetic method for unsymmetrical 1,2-diketones, especially valuable when \( \text{Ar}_1 \) and \( \text{Ar}_2 \) are heterocyclic systems \(<2005JOC3271>\). When trimethylsilyl derivatives \( 527 \) are treated with TFA in dichloromethane, both the trimethylsilyl and benzotriazolyl groups are eliminated to provide 1,2-diarylpropan-1-ones \( 528 \) in high yields \(<1998JOC9983>\). Heating of ketones \( 527 \) with CsF in DMF yields also propenones \( 528 \), but usually a rearrangement occurs and the corresponding chalcones are the main products \(<1998J(P2)2515>\). Samarium iodide induced removal of benzotriazole from ketones \( 529 \) works well with variety of groups \( R \) to provide ketones \( 530 \) in high yield under mild reaction conditions \(<1998H(48)1567>\).

\[ [3+3] \] Annulation reaction of (benzotriazol-1-yl)acetone \( 531 \) with chalcones provides an efficient route to 3,5-diarylphenols \( 538 \). The reaction is catalyzed by NaOH in ethanol. In the first step, Michael addition of ketone \( 531 \) to the \( \text{C}═\text{C} \) bond of a chalcone gives diketone \( 532 \). In the second step, condensation between the carbonyl
group at Ar\(^1\) with the methyl group gives cyclohexenone 533. In the following steps, benzotriazole is eliminated, and the obtained cyclohexadienone 534 rearranges to phenol 538 (Scheme 85). Diketones 536, obtained by Michael addition of (benzotriazol-1-yl)acetophenones 535 to chalcones, cannot undergo such cyclocondensation to form phenols, but they react readily with ammonium acetate to give pyridines 537.

5.01.8.5 Ring N–C(sp\(^3\))-C(sp)

Some chemistry of propargylbenzotriazole 539 and its applications in organic synthesis is already described in CHEC-II (1996) <1996CHEC-II(4)1>. Further development in this field led to very useful oxirane derivatives 540 <1995JOC638>. Primary amines in refluxing isopropanol cause opening of the oxirane ring with addition of the amine to form aminomethyals 541 that undergo spontaneous intramolecular cyclocondensation to give pyrroles 543 (Scheme 86). The benzotriazolyl moiety in 542 can be directly substituted with nucleophiles or the molecule can be first lithiated at its \(\alpha\)-carbon then treated with electrophiles and finally the benzotriazolyl group be removed to provide further classes of substituted pyrroles <1996JOC1624>.

1-(2-Hydroxyethyl)pyrroles 543 obtained from reactions of oxiranes 540 with 2-aminoethanol are readily converted to 2,3-dihydro-1\(H\)-pyrrolo[1,2-a]pyrroles 544 <1997JOC4148>. Analogously, 1-(3-hydroxypropyl)pyrroles give homologous 5,6,7,8-tetrahydropyrrolo[1,2-a]pyridines. Easy manipulation with the benzotriazolyl moiety allows for convenient synthesis of a wide variety of fused [1,2-a]pyrroles. A similar chemistry of indoles is also described <1997JOC4148>.

Lithiated pyrrole derivative 542 undergoes Michael addition to \(\alpha,\beta\)-unsaturated aldehydes or ketones, and the obtained adducts readily undergo cyclization to indoles 545 in the presence of acids as catalysts <1996TL5641>. Similarly, lithiated 2-[(benzotriazol-1-yl)methyl]furans 546, obtained from oxiranes 540 by their cyclization promoted by Bu\(^{\ast}\)OK, react with \(\alpha,\beta\)-unsaturated aldehydes or ketones to provide benzofurans <1997JOC8205>. 1,3-Dipolar cycloaddition of propargylbenzotriazole 539 to nitrile oxides (R-C\(\equiv\)C-N\(\equiv\)O) gives oxazoles 547 in excellent yields <2000JHC1505>. Addition of lithiated propargylbenzotriazole 539 to aldehydes or ketones followed by methylation with iodomethane provides ethers 548. Treatment with metallic lithium and the same or different aldehydes or ketones R\(^{\prime}\)R\(^{\prime}\)C\(\equiv\)C==O converts ethers 548 into protected alkynediols 549 <1999TL253>. Introduction of an alkoxy group to the \(\alpha\)-carbon opens new possibilities regarding transformation and benzotriazole removal process from 1-propargylbenzotriazole. Thus, ether 550 <1995JOC7612> can be coupled with vinyl triflates or bromides to give enynyl products 551. Following alkylation at the carbon \(\alpha\) gives unstable derivatives 552 that are readily hydrolyzed to enynyl ketones 553. In another approach, alkynes 550 are coupled with aryl iodides, and the obtained ethers 554 are alkylated and hydrolyzed to ketones 555 (Scheme 87) <1997JOC8201>.
Michael addition of (benzotriazol-1-yl)acetonitrile 557 to \(\alpha,\beta\)-unsaturated ketones followed by heterocyclization provides new means for preparation of 2,4,5-trisubstituted pyridines. The reaction is catalyzed by bases. In the presence of secondary amines, a nucleophilic attack of amine on the CN group in adduct 556 initiates the cyclization to tetrahydropyridine 558 that subsequently eliminates water and benzotriazole to give pyridine 559. Analogously, in the presence of NaOH, pyridone 560 forms, via intermediate 561 (Scheme 88) \(<1997\text{JOC}6210\>.

![Scheme 88](image)

**5.01.8.6 Ring N–C(sp\(^3\))-N**

In solution, 1-(\(\alpha\)-aminoalkyl)benzotriazoles 562 are in equilibrium with iminium cation 563 and hence with their benzotriazole-2-yl isomers 564 (Scheme 89). Protonation or complexation of the benzotriazolyl moiety (e.g., Mg, Zn, B, Al reagents) facilitates the transformation. Intermediate iminium cations 563 can be trapped by nucleophiles providing synthetic pathways to various amines. Many such reactions are described in CHEC-II(1996) \(<1996\text{CHEC-II}(4)1\>\), and some newer results are compiled in reviews \(<2005\text{T}2555\>.

![Scheme 89](image)

For clarity, in the following schemes of this subsection, the benzotriazol-2-yl structures are often omitted when such derivatives are present in the reaction mixtures, and their chemistry is not different from that of the benzotriazol-1-yl derivatives. When there is a clear distinction in chemistry, the benzotriazol-2-yl isomers are treated separately.
5.01.8.6.1 Substitution of benzotriazole with nucleophiles

Since the publication of CHEC-II (1996), the range of nucleophiles used for substitution of the benzotriazolyl moiety in derivatives 562 and applied reaction conditions have been widely expanded. Thus, treatment of benzotriazolyl amines 562 with organozinc bromoacetate, provides conveniently amines 565 (Scheme 90)<1998T7167. This extends the scope of this reaction to substituents bearing groups sensitive to organomagnesium reagents previously used for this purpose <1996CHEC-II(4)1>. Reactions of intermediates 562 with alkynylmagnesium and alkynylmagnesium reagents carried out in toluene lead to allylamines 566 and propargylamines 567 in excellent yield <2002S199>. Less stable perfluoroalkylmagnesium reagents give amines 568 when the reactions are carried out at low temperature with additional activation of derivatives 562 with trifluoroboron etherate <1997TL7015>. Propargylamines 567 can be also conveniently prepared in reactions of compound 562 with dialkylidethylaluminumates <1999JOC488>. Treatment of benzotriazolyl derivatives 562 activated by addition of ZnBr2 with sodium salts of amides allows preparation of acylaminals 569 <1998S1421>. N-α-Aminoalkyl)benzotriazoles 562 react smoothly with silyl enolates in the presence of lanthanide catalysts to provide aminoketones 570 (R6 = Ph) or aminoesters 570 (R6 = alkoxy or phenoxy group) in practically quantitative yields <1996TL3731>. In the presence of aluminum chloride, the iminium cations derived from 1-[(dialkylamino)methyl]benzotriazoles 562 (R1 = H) add to the C-3 atom of allyltrimethylsilane, and the obtained adducts rearrange to aminosilanes 571 via a 1,5-hydride shift from group R2 to C-2 of the allyl system <1999OM4270>. Polymer-bound derivatives 562 provide a convenient tool for combinatorial synthesis of compound libraries <1999JCO173>.

Scheme 90
Addition of benzotriazole to enamines 572 derived from cyclic or acyclic dialkyl ketones gives \(\alpha\)-aminoalkylbenzotriazoles 573–574, in which the benzotriazole moiety can be easily substituted by an alkyl, aryl, alkenyl, or alkynyl group in reactions with appropriate organomagnesium or organolithium reagents to form corresponding tertiary amines 575 (Scheme 91). This approach extents the scope of tert-alkylation of secondary amines <2005JOC286>.

**Scheme 91**

Condensation of succinaldehyde (obtained by hydrolysis of 2,5-dimethoxyfuran) with benzotriazole and (\(\beta\))-2-phenylglycinol provides \((3S,5R,7aR)-5-(benzotriazole-1-yl)-3-phenyl[2,1-b]oxazolopyrrolidine\) 577 (Scheme 92). Oxazolopyrrolidine 577 is a convenient synthon for asymmetric syntheses of 2-substituted and 2,5-disubstituted pyrrolidines. Thus, in a reaction with allyltrimethylsilane, the benzotriazolyl moiety is substituted with an allyl group to provide derivative 576. Hydrogenation of product 576 cleaves the chiral auxiliary to give (2R)-2-propylpyrrolidine. Alternatively, reactions of intermediate 576 with Grignard reagents lead to chiral 2,5-disubstituted pyrrolidines <1999JOC1979>. Direct treatment with organomagnesium reagents converts oxazolopyrrolidine 577 into mixtures of *cis* 578 and *trans* 579 2,5-disubstituted pyrrolidines that can easily be separated by chromatography.

**Scheme 92**

Nu: = PhZnBr, P(OEt)_3, Me_2C=C(OMe)O’SiMe_3, CH_2=CR-O’SiMe_3, or CH_2=CR-CH_2SiMe_3.
Again, hydrogenation removes readily the chiral auxiliary from the nitrogen atom in intermediates 578 and 579. Similar treatment of the piperidine analog of compound 577, obtained by condensation of glutaraldehyde with benzotriazole and (S)-2-phenylglycinol leads to chiral 2,6-disubstituted piperidines <1998JOC6699>. Chiral (pyrrolidin-2-yl)-phosphonates are obtained from oxazolopyrrolidine 580 (prepared by condensation of 2,5-dimethoxytetrahydrofuran with benzotriazole and (R)-phenylglycinol) which reacts with triethyl phosphite to give intermediate 581 that is alkylated to produce derivatives 582 and finally deprotected by hydrogenation <2004TL5175>. Condensation of ethyl glyoxylate with (S)-2-phenylglycinol and formaldehyde gives N-[(benzotriazol-1-yl)methyl]oxazolidine 583 in which the benzotriazolyl moiety can be substituted with various nucleophiles in the presence of ZnBr2 to provide chiral N-substituted oxazolidines 584 <1999JCM162>.

Derivatives of optically active α-aminocarboxylic acids are also used successfully in reactions with aldehydes and benzotriazole. Condensation of esters of α-aminocarboxylic acids with formaldehyde and benzotriazole gives derivatives 585 in which the benzotriazolyl moiety can be substituted by nucleophiles to give various products 586 (Scheme 93) <2003JOC9088>. Amides 587 derived from α-aminocarboxylic acids undergo condensation with succinaldehyde and benzotriazole to give benzotriazolyl derivatives 588 from which the benzotriazolyl group can be readily removed by treatment with sodium borohydride to furnish optically active tetrahydro-1H-pyrrolo[1,2-a]-imidazol-2-ones 589 <2002JOC4951>. Analogous reactions with glutaraldehyde provide corresponding hexahydropyrrol-2(3H)-ones <2002JOC4951>. Diamines 590 obtained by reduction of amides 587 with lithium aluminium hydride undergo condensation with benzotriazole and two molecules of formaldehyde to give derivatives 591 in which the benzotriazolyl moiety is easily substituted by various nucleophiles to provide unsymmetrically substituted chiral imidazolidines 592 <2002JOC3109>.

![Scheme 93](image)

Similarly to imidazolines 591, derivatives 593, obtained by condensation of monosubstituted 1,3-propanediamines with formaldehyde and benzotriazole, react with organomagnesium reagents to give corresponding hexahydropyrimidines bearing two different substituents on the nitrogen atoms <2002JOC3115>. Analogously, condensation of
2-aminobenzylamine with formaldehyde and benzotriazole produces compound 594 in which the benzotriazolyl groups can be substituted by treatment with organomagnesium reagents or other strong nucleophiles. The conversion can be carried out stepwise with two different Grignard reagents, first substituting the more reactive benzotriazolyl group connected to the nitrogen atom in position 3 <2002JOC3115>. Treatment of benzotriazolyl derivatives 595, originating from glycine, with sodium hydride in refluxing THF results in esters of trans-2,3-piperazinedicarboxylic acid 596, although formation of aziridine systems could be anticipated <1996HCO1996>. The molecular structure of products 596 is confirmed by NMR and X-ray crystallographic data, but the mechanism of their formation is not yet clear.

The ylide obtained from (methyl)triphenylphosphonium bromide reacts with morpholine derivatives 597 to give phosphonium salts 598 which upon treatment with n-butyllithium are converted to new ylides 599. In a reaction with aldehydes, ylides 599 form N-(1,3-disubstituted allyl)-morpholines 602 (Scheme 94) <1996AQ138>. Another less common nucleophile that can be used for substitution of the benzotriazolyl moiety in N-(α-aminoalkyl)benzotriazoles is an adduct of N-benzylthiazolium salt to an aldehyde which reacts with compounds 597 to produce adducts 600. Under the reaction conditions, refluxing in acetonitrile, salts 600 decompose to liberate aminoketones 601 <1996H(42)273>.

Scheme 94
Due to the high strain energy of a three-membered ring, an interesting case is represented by benzotriazolyl-aziridines. Upon heating, the C–C bond of the aziridine ring in (benzotriazol-1-yl)aziridines 603 is cleaved to give azomethine ylides 604 that can be trapped by diethyl acetylenedicarboxylate to form unstable pyrroline intermediates which consecutively eliminate benzotriazole to furnish pyrroles 605 (Scheme 95). By contrast, in (benzotriazol-2-yl)aziridines 606, the C-N bond is cleaved, and the dipolar species 607 undergo [3+2] cycloaddition to acetylenedicarboxylate to form pyrrolines 608 that aromatize to pyrroles 609 by elimination of benzotriazole <1999JOC346>.

Scheme 95

1-[a-(Dialkylamino)benzyl]benzotriazoles 610, obtained by condensation of benzaldehydes with benzotriazole and dialkylamines, react with sodium phenoxides to produce 2-[a-(dialkylamino)benzyl]phenols 611 (Equation 13). Derivatives of heterocyclic aldehydes (Ar = pyridin-4-yl, pyridin-3-yl, or thiophen-2-yl) react similarly <1999JOC6071>. As a practical example of such approach may serve derivatization of 4,13-diaza-18-crown-6-ether that is first condensed with benzotriazole and formaldehyde, and then the benzotriazolyl moiety is substituted with 7-hydroxycoumarin <1996JOC7585>.

1-(Aminomethyl)benzotriazoles 612 react with electron-rich vinyl groups to give adducts 613 in which the link between the benzotriazolyl moiety and the amine nitrogen atom is extended by two atom units (Equation 14). The benzotriazolyl in its new position still can be substituted with various nucleophiles allowing rapid building of interesting molecules <1996JOC7585>.
5.01.8.6.2 Cyclocondensation

When a nucleophile is already attached to the molecule of \( N-(\alpha\text{-aminoalkyl})\text{benzotriazole} \) 562 (Scheme 89) as substituent \( R^2 \) or \( R^3 \), it may trap liberated iminium cation 563 with formation of a heterocyclic ring. The simplest case is represented by derivatives 562 with an electron-rich aromatic ring in a proper distance on one of the amino group substituents. Three examples of \([5+1]\) cyclocondensation of this type (the five-atom unit comes from phenethylamines and the one atom piece comes from formaldehyde) are shown in Scheme 96 <2001TA2427>. Thus, upon treatment with \( \text{AlCl}_3 \), an iminium cation generated from \( N,N\text{-bis[(benzotriazol-1-yl)methyl]}\text{phenethylamine} \) 614, by cleavage of one of the bonds with benzotriazole, attacks the phenyl ring in its ortho position to produce \( N\text{-[(benzotriazol-1-yl)methyl]}\text{tetrahydroisoquinoline} \) 615. The second benzotriazolyl group can be removed by regular substitution with nucleophiles as discussed above to give tetrahydroisoquinoline 616. Two additional
examples in Scheme 96 show that the cyclization is not affected by even relatively complex substituents on the carbon α of the phenethylamine system, and the stereochemistry can be carried from the starting amines (617, 620) through the benzotriazolyl intermediates (618, 621) to the final products (619, 622) <2001TA2427, 2002JOC8224>. Some of the nucleophiles used for substitution of benzotriazole in derivatives of type 615 are listed in Scheme 96, but many others can be successfully employed as well <2002S601>.

Electron-rich heterocyclic rings are also used in such cyclocondensations. Thus, 1-(2-aminoethyl)pyrazole reacts with formaldehyde and benzotriazole to give bicyclic system 623 <2002JOC8220>, and an analogous reaction of 1-(2-aminoethyl)-3-methylindole leads to tricyclic system 624 <2003JOC4938>. Seven-membered rings are also formed as a result of analogous [6+1] cyclocondensations. Compound 625 was obtained from a reaction of 3-phenoxyethylamine with formaldehyde and benzotriazole, and compound 626 was obtained from a similar reaction N-(2-aminoethyl)-N-methylaniline <2002[P1]592>. In all of these derivatives, the remaining benzotriazolyl moiety can be easily substituted with various nucleophiles.

Reactions with dialdehydes allow the introduction of two additional rings in one step. Thus, condensation of 1-(2-aminoethyl)pyrrole with glutaraldehyde and benzotriazole gives tricyclic intermediate 627 in which the benzotriazolyl moiety can be readily substituted with nucleophiles to give products 628 (Scheme 97) <2002JOC8220>. Condensation of ethyl ester of L-tryptophan with 2,5-dimethoxytetrahydrofuran and benzotriazole in acetic acid gives tetracyclic intermediate 629 which upon treatment with nucleophiles (silyl derivatives) is converted to products 630 <1999T3489>.

Scheme 97

\[ \text{BtH = benzotriazole} \]
\[ \text{Nu = NaBH}_4, \text{RMgX, NaCN, CH}_2=\text{CR-OSiMe}_3 \text{ or CH}_2=\text{CR-CH}_2\text{SiMe}_3 \]
Cyclocondensations of \(N\)-(benzotriazolylmethyl)anilines 631 with electron-rich unsaturated compounds of the type \(R^3\text{CH}=\text{CH}X\) lead to 1,2,3,4-tetrahydroquinolines 633 (Scheme 98). In the first step, an iminium cation generated by dissociation of derivative 631 attacks the double bond of compound \(R^3\text{CH}=\text{CH}X\) to generate cation 632. In the second step, an intramolecular electrophilic attack of cation 632 on the \(ortho\) atom of the aniline ring furnishes tetrahydroquinoline 633. Depending on the reaction conditions and nature of the group X, benzotriazol-1-yl (and benzotriazol-2-yl) or group X remains as the substituent in position 4 of tetrahydroquinoline 633. For compounds lacking good leaving group, like styrenes \(<1997\text{JHC1259}>\), alkenes \(<1999\text{JHC371}, 1997\text{JHC1259}>\), \(N\)-vinylamides \(<1995\text{JOC3993}, 1999\text{JHC755}>\) and 9-vinylcarbazole \(<1995\text{JOC3993}>\), it is the group X that remains. In the case of enolizable aldehydes \(<1995\text{JOC7631}>\) or vinyl ethers \(<1995\text{JOC2588}>\), the benzotriazolyl moiety is usually retained as a substituent at the C-4 atom of tetrahydroquinoline 633 allowing further derivatization by substitution of benzotriazole with nucleophiles. Comparison of this new synthetic method for 1,2,3,4-tetrahydroquinolines with more classical ones has been reviewed \(<1996\text{T15031}>\).

\[
\begin{align*}
\text{631} & \xrightarrow{\text{H}^+ \text{ or Lewis acid}} \text{632} & \xrightarrow{\text{Y = benzotriazol-1-yl, benzotriazol-2-yl, or X}} \text{633} \\
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 & \quad \text{N} & \quad \text{N} & \quad \text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 & \quad \text{Y} & \quad \text{R}^3 \\
\text{631} & \quad \text{632} & \quad \text{633} \\
\end{align*}
\]

Scheme 98

Derivatives of higher aldehydes (634, \(R^1 \neq H\)) allow introduction of an additional substituent into position 2 of tetrahydroquinolines making variation of the tetrahydroquinoline system very versatile \(<1995\text{JOC7631}>\). In \(N,N\text{-bis(benzotriazolylmethyl)}\)anilines 635, both benzotriazolylmethyl groups may be involved in the cyclocondensation process producing julolidines \(<1996\text{JOC3117}, 1999\text{JOC3328}>\). When the nitrogen atom supporting the benzotriazolylalkyl group is already incorporated into a ring, like in structure 636, an additional ring is added to the heterocyclic ring system \(<1998\text{S1487}, 1999\text{JHC473}>\). Use of alkynes instead of alkenes in the reaction depicted in Scheme 98 results in formation of 1,2-dihydroquinolines \(<1998\text{JHC467}>\). Derivatives of aminoheterocycles, like compound 637 \(<2004\text{T8839}>\) also undergo readily \([4+2]\) cyclocondensation with enol ethers and vinylamides.

\[
\begin{align*}
\text{634} & \quad \text{635} & \quad \text{636} & \quad \text{637} \\
\end{align*}
\]

\(N,N\text{-Bis(benzotriazolylmethyl)}\)amines 638 derived from benzyl or phenethylamines undergo cyclocondensation with allylsilanes catalyzed by SnCl\(_4\) to give 4-chloropiperidines 640 (Scheme 99) \(<1999\text{JOC3328}>\). This \([3+3]\) cyclocondensation is assumed to proceed in two steps via intermediate 639. \([3+4]\) cyclocondensation of derivatives 638, originating from various aromatic and aliphatic amines, with dilithiated benzamides leads to 2,4-benzodiazepin-1-ones 641 \(<2002\text{JOC8237}>\).
Compound 642, obtained by condensation of glyoxal with benzotriazole and morpholine undergoes interesting [2+3] cyclocondensation with 2-aminopyridine to give imidazo[1,2-a]pyridine 643 (Equation 15) \(<\text{2003JOC4935}\>). Similar derivatives of piperidine and pyrrolidine are also described. 2-Amino- and 6-aminopyrimidines react similarly to give imidazo[1,2-a]- and imidazo[1,2-c]pyrimidines, respectively.

Introduction of hydrazines opens new possibilities in the cyclocondensation pattern when both nitrogen atoms of hydrazines can be involved in the process. Thus, hydrazine derivative 644 reacts with electron-rich unsaturated compounds according to [3+2] cyclocondensation pattern to produce pyrazolidines 645 (Scheme 100).
Condensation of succinaldehyde with arylhydrazines and benzotriazole gives 1-aminopyrrolidines that upon treatment with organomagnesium reagents rearrange to 1,4,5,6-tetrahydropyridazines.

5.01.8.6.3 Reduction to α-amino radicals and α-amino anions

Treatment of N-(α-aminobenzyl)benzotriazoles with samarium diiodide generates radicals that undergo coupling to form vicinal diamines (Scheme 101). Formation of intermediate radicals at low temperature is confirmed by EPR. Short-living radicals are readily converted to more stable radicals by treatment with 2-methyl-2-nitrosopropane.

When one of the substituents on the amine nitrogen atom is ready to trap a radical formed by treatment of N-(α-aminoalkyl)benzotriazole with SmI₂, cyclization may occur. Such a situation is depicted in Scheme 102. Thus, (4-penten-1-yl)amine derivative is reduced to radical that is then rapidly trapped by the alkenyl group and...
converted to radical \( \text{654} \). The following reaction with excess \( \text{SmI}_2 \) gives samarium intermediate \( \text{655} \). During aqueous work-up, derivative \( \text{655} \) is hydrolyzed to 3-methylpiperidine \( \text{656} \) (\( E = H \)). Alternatively, treatment with electrophiles converts intermediate \( \text{655} \) to piperidines \( \text{656} \) with various substituents at C-3 \(<2000\text{J}(P2)1375>\). Similarly, \( \text{SmI}_2 \) converts \( \gamma,\delta \)-unsaturated amines \( \text{657} \) to pyrrolidines \( \text{658} \) with good yields \(<2002\text{T}6837>\).

\( \alpha \)-Aminocarbanions generated by treatment of \( N-(\alpha\text{-aminobenzyl})\)benzotriazoles \( \text{659} \) with \( \text{SmI}_2 \) (or \( \text{Li}/\text{Br} \)) can be readily trapped by aldehydes or ketones to provide \( \beta \)-aminoalcohols \( \text{660} \) (Scheme 103) \(<1997\text{JOC}4121>\). A similar reaction performed on \( N,N\text{-bis(benzotriazolylmethyl)} \)amines \( \text{662} \) results in formation of oxazolines \( \text{661} \), but the yields are low \(<1998\text{TL}6835>\). However, when styrenes are used to trap generated radicals (or anions), pyrrolidines \( \text{663} \) are obtained in good yields \(<1998\text{H}(48)2535>\).

\[ \begin{align*}
\text{R}^1 & \text{N} \quad \text{R}^2 \\
\text{R}^3 & \text{N} \quad \text{R}^4 \quad \text{R}^5 \\
\text{R}^6 & \text{H} \\
\text{R}^7 & \text{C}=\text{O} \\
\end{align*} \]

\[ \text{SmI}_2 \quad \text{or Li/LiBr} \]

\[ \begin{align*}
\text{R}^1 & \text{N} \quad \text{R}^2 \\
\text{R}^3 & \text{N} \quad \text{R}^4 \quad \text{R}^5 \\
\text{R}^6 & \text{OH} \\
\end{align*} \]

\[ \begin{align*}
\text{Ar} & \text{C}=\text{H} \\
\text{Ar} & \text{N} \quad \text{R} \\
\end{align*} \]

\[ \begin{align*}
\text{Ar} & \text{N} \quad \text{R} \\
\end{align*} \]

\[ \text{Scheme 103} \]

5.01.8.6.4 Derivatives of amides, thioamides, sulfonamides, and related compounds

Benzotriazolylalkyl amides \( \text{668} \) are easy to prepare by condensation of amides with aldehydes and benzotriazole. The chemistry of compounds \( \text{668} \) is to some extent similar to that of the corresponding amines discussed above; however, increased stability of derivatives \( \text{668} \) and higher stability of the products of their reactions bring additional synthetic possibilities. Thus, the reaction with organozinc reagents, usually prepared \textit{in situ} from zinc powder and alkyl bromides, leading to amides \( \text{664} \) is analogous to the reaction of the corresponding amines (Scheme 104) \(<1998\text{T}7167, 2000\text{TL}9691>\). By contrast, the reaction with sodium alkoxides producing \( N-(\alpha\text{-alkoxyalkyl)} \)amides \( \text{665} \) is unique to derivatives \( \text{668} \) \(<1995\text{JOC}4002, 2003\text{JOC}4338>\). Similarly to the amine analogs, allylation with allyltrimethylsilane converts compounds \( \text{668} \) to unsaturated amines \( \text{666} \) \(<1995\text{JOC}4002>\), but the reaction with enamines leading to ketoamides \( \text{667} \) \(<1999\text{JOC}7622>\) has little precedent among the corresponding derivatives of amines. Enol esters derived from ketones react as well, as it is illustrated by the example of acetone derivative \( \text{669} \) \(<1995\text{JOC}4002>\). Anions derived from \( t\)-butyl esters can also be used for substitution of benzotriazole to give \( \beta \)-amidoesters \( \text{670} \) \(<2002\text{JOC}4957>\). Enolizable aldehydes can be used for substitution of benzotriazole in derivatives \( \text{668} \) as well. Although the original product, \( \text{671} \), is unstable under the reaction conditions, in the case of \( R^1 \) being a reactive aromatic ring, subsequent cyclocondensation leads to a stable \( N\)-acylated 1-aminoindene \( \text{672} \) \(<2000\text{JOC}8066>\).

Condensation of 2,5-dimethoxy-2,5-dihydrofuran \( \text{673} \) with benzotriazole and an amine carried out in refluxing acetic acid produces 5-benzotriazolylpyrrolidin-2-one in good yield and with strong prevalence of benzotriazol-1-yl isomer \( \text{674} \) \(<2000\text{JOC}4364>\). Substitution of the benzotriazole moiety with nucleophiles gives 5-substituted 2-pyrrolidinones \( \text{675} \) (Scheme 105). When a reactive aromatic ring is attached to the nitrogen atom of 2-pyrrolidinone \( \text{674} \) by a two- or three-atom linker, the \( \text{ortho} \) carbon of the ring may serve as a nucleophile providing tricyclic systems \( \text{676} \) \(<2001\text{JOC}148> \) or \( \text{677} \) \(<2001\text{JOC}5590> \), respectively.
Formation of polycyclic systems is also possible when benzotriazole is attached to carbon 2 of the nitrogen substituent in the cyclic amide. As shown in Equation (16), cyclocondensation of 5-benzyloxazolidin-2-ones 678 promoted by TiCl₄ stereospecifically gives tricyclic system 679 that represents the core structure of many important natural products <1999TA255, 2004EJO3611>. In a specific case of 2-pyridyl derivatives 680, cyclocondensation with nitriles involves only the group attached to the amide nitrogen atom giving imidazo[1,5-α]pyridines 681 with the pyrrolidinone substituent in position 1 unchanged (Equation 17) <2001JOC2862>.
N-(Benzotriazol-1-yl)methyl derivatives of BOC-protected amines behave similarly to amides. Thus, treatment of an anion derived from compound 682 with methoxychalcone leads to 2-imidazolidinone 683 with the substituents at C-4 and C-5 oriented trans. Subsequent treatment with nucleophiles gives product 684 stereoselectively (Scheme 106) <2001JOC2858>. In the second reaction presented in Scheme 106, alkylation of compound 685 at the carbon α gives derivative 686 which upon treatment with TFA eliminates readily benzotriazole leading to 3-alkylidene-2,3-dihydro-1H-isoindolo-1-ones 687 <2002TL8055>.

Scheme 106

E = PhCH=N-C₆H₄-Ome-p
Nu: = PhMgBr/ZnCl₂, Allyl-SiMe₃,
    or CH₂=CPh-OSiMe₃,
R = alkyl or phenyl
The double anion, obtained from thioamide 688 upon its treatment with LDA or Bu\textsuperscript{+}Li, reacts with alkylating agents to give \( \alpha \)-alkyl derivatives 689 (E = alkyl) or with aldehydes to give \( \alpha \)-(1-hydroxyalkyl) derivatives 689 [E = RCH(OH)] (Scheme 107) <1995T8703>. The following substitution of benzotriazole with nucleophiles results in thioamides 690. This simple process allows introduction of two different groups to the carbon atom attached to the thioamide nitrogen. Use of only 1 molar equivalent of the base makes possible selective methylation of the sulfur atom to give thioamidate 691. The anion derived from compound 691 upon its treatment with sodium hydride adds readily to electron-poor double bonds to create unstable intermediate anion 692 that spontaneously eliminates benzotriazole and thiomethoxide to generate pyrrole 693 <1995T13271, 2000JOC8819>.

In the presence of ZnBr\textsubscript{2}, the benzotriazole moiety in dithiocarbamates 694 can be readily substituted by mercaptans or phosphites providing new access to derivatives 695 <2005ARK(ix)63>. Cyclic analogs of 694, 1,3-thiazolidine-2-thione and tetrahydro-\( 2H \)-1,3-thiazine-2-thione, react similarly. Substitution of the benzotriazolyl group in sulfonamide derivatives 696 with cyanides occurs under mild conditions in DMSO, alcohol or even water providing a good way for preparation of \( \Lambda \)-(\( \alpha \)-cyanoalkyl)sulfonamides <1997SC907>.

In the presence of Bu\textsuperscript{+}OK, (benzotriazole-1-yl)methyl isocyanide (BetMIC) 697 undergoes alkylation on the methylene group to give isocyanide 698. The anion derived from 698, upon its treatment with Bu\textsuperscript{+}OK, adds to the electron-deficient double bonds of \( \alpha \),\( \beta \)-unsaturated ketones, esters or nitriles to produce pyroles 699. A similar reaction of isocyanide 698 with Schiff bases provides imidazoles 700. In both cases, use of unsubstituted isonitriles 697 in the reactions leads to heterocycles 699 and 700 with \( R^1 = H \) (Scheme 108) <1997H(44)67>.

5.01.8.6.5 Imines and related compounds
In the presence of Bu\textsuperscript{+}OK, (benzotriazole-1-yl)methyl isocyanide (BetMIC) 697 undergoes alkylation on the methylene group to give isocyanide 698. The anion derived from 698, upon its treatment with Bu\textsuperscript{+}OK, adds to the electron-deficient double bonds of \( \alpha \),\( \beta \)-unsaturated ketones, esters or nitriles to produce pyroles 699. A similar reaction of isocyanide 698 with Schiff bases provides imidazoles 700. In both cases, use of unsubstituted isonitriles 697 in the reactions leads to heterocycles 699 and 700 with \( R^1 = H \) (Scheme 108) <1997H(44)67>.
The rich chemistry of parent iminophosphorane \( R_1 = H \), BetMIP, is described in CHEC-II(1996) and in a review article. Aza-Wittig reactions of iminophosphoranes with aldehydes provide imines. Treated with an excess of allylmagnesium reagent, imines are converted into \( N,N \)-bis(3-butenyl)amines, interesting intermediates for construction of heterocyclic systems (Scheme 109). Imines, particularly with \( R_1 = R_2 = \text{aryl} \), can be also conveniently prepared by direct condensation of aldehydes with benzotriazole and ammonia. Treatment of imine with \( n \)-butyllithium produces anion that adds readily to isothiocyanates to give intermediate anion. Loss of a benzotriazole anion followed by tautomerization leads to aminothiazole. This way, 5-aminothiazoles bearing aryl or heteroaryl substituents at C-2 and C-4 can be easily prepared in good yields.

Reaction of \( N \)-\{(benzotriazol-1-yl)methyl\}amide with \( \text{PCl}_5 \) gives chloroimine, which upon treatment with \( \text{Bu}^\text{1OK} \) is converted to nitrile ylide. Benzyl esters of \( \alpha,\beta \)-unsaturated acids used as dipolarophiles trap species to generate pyrroles (Scheme 110). When no trapping agent is added, the N-2 atom of benzotriazole act as a nucleophile, and tricyclic system is formed. Addition of benzyl bromide...
to the reaction mixture causes formation of a new tricyclic system that, according to the X-ray diffraction analysis, has structure 716 <2002JOC3118>. A reasonable explanation of this phenomenon is as follows. Benzylolation of species 711 creates cation 710 that, affected by excess Bu'OOK, loses its acidic benzylic proton to form betaine 713. Electron shift towards the positive charge causes breaking of the N–N bond. Freed 1,2,4-triazolyl group in intermediate 714 rotates to a more favorable position, and a bond between carbon atoms forms. Finally, oxidation of newly formed betaine 715, probably by atmospheric oxygen during work-up, results in stable heterocyclic system 716. Another possible mechanism, proposed by authors of the report <2002JOC3118>, starts from formation of the C–C bond by direct benzylation of nitrile ylide 709 that is followed by several rearrangements to produce final product 716.

Condensation of sulfoximine 717 with an aldehyde and benzotriazole produces N-[2-(benzotriazol-1-yl)alkyl]sulfoximine 718. Treatment with allyl silanes in the presence of BF₃ etherate or with organozinc reagents allows substitution of the benzotriazolyl moiety in compound 718 to produce variety of substituted sulfoximines 719 (Scheme 111) <2003ARK(xv)115>.

R¹ = Me or Ph  
R² = H or CO₂Et  
R³M = CH₂=CH₂SiMe₃, CH₂=CMe-CH₂SiMe₃, CH₂=CH-CH₂ZnCl, PhCH₂ZnCl, or PhZnCl

Scheme 111
5.01.8.6.6 Bis(heterocycle-N-yl)alkanes

One of the simplest molecules belonging to this category is that of bis(benzotriazol-1-yl)methane 720. Treated with an excess of Bu"Li, molecule 720 generates polyanion 721 which, when subjected to reactions with various electrophiles, gives C-α and/or C-7 substituted derivatives 722; an equimolar mixture of C-α, C-α, C-7 (722a) and C-α, C-7, C-7 (722b) trimethylated products forms in a reaction with iodomethane (Scheme 112). Under these conditions, reaction of 4-methylbenzonitrile with 721 gives enamine 723 in 70% yield.

Scheme 112

1,1-Bis(benzotriazol-1-yl)ethane treated with 2 molar equivalents of BuLi undergoes lithiation at C-α and C-7 to give intermediate 724 (Scheme 113). Consecutive treatment of the reaction mixture with iodomethane leads to dimethylated product 725a in high yield. In a reaction with iodoethane, apart of diethylated product 725b, mono-ethylated derivative 725c is also formed. Allyl iodide and benzyl bromide gives exclusively substitution at C-α (725d and 725e, respectively). Reaction with benzyldiene bromide leads to bromination at C-7 (725f). Reaction with p-tolyl isocyanate gives diamide 725g, and that with diethyl oxalate produces triazoloquinolone 726.

Scheme 113
Condensation of benzaldehydes with benzotriazole in the presence of thionyl chloride readily gives \(\alpha,\alpha\text{-bis}(\text{benzotriazol-1-yl})\)toluenes 727 that can be considered as 1,1-\(\text{gem}\)-dicarbanion equivalents. Thus, treatment of derivatives 727 with ketones and lithium metal suspended in THF at \(-78^\circ\text{C}\) generates substituted propylene glycols 728 (Equation 18) \(<1998\text{TL2289}>\).

\[
\begin{align*}
\text{727} & \quad + \quad \text{R}^2\text{R}^3\text{C}=\text{O} \quad \text{Li/LiBr} \quad \rightarrow \quad \text{728} \\
\text{R}^1=\text{H or Me;} \\
\text{R}^2\text{R}^3\text{C}=\text{O}=\text{cyclopentanone, cyclohexanone, 2-pentanone, 3-pentanone, or 4-heptanone}
\end{align*}
\]

In the presence of KOH, \(\text{tris}(\text{benzotriazol-1-yl})\)methane 729 reacts with nitrobenzenes to produce \(p\text{-[bis(\text{benzotriazol-1-yl})methyl]nitrobenzenes} 730 \text{ (Scheme 114)} \(<1996\text{TL347}>\). This vicarious nucleophilic substitution of hydrogen \(<1991\text{S103}>\) can be considered as a convenient way to \(p\text{-nitrobenzaldehydes} 731\). \(\text{Meta}\) and \(\text{para}\) substituted nitrobenzenes do not react with compound 729 under these conditions, probably due to steric reasons, but \(1\text{-nitronaphthalene} \)reacts producing a naphthalene analog of derivative 730.

\[
\begin{align*}
\text{729} & \quad + \quad \text{NO}_2 \quad \text{KOH} \quad \text{DMSO} \\
& \quad \rightarrow \quad \text{730} \\
& \quad \text{i, ZnBr}_2 \quad \text{ii, HCl/H}_2\text{O} \\
& \quad \rightarrow \quad \text{731} \\
\text{X=H, Cl, Br, or Ph}
\end{align*}
\]

\text{Scheme 114}

\(\text{N-[\text{(Benzotriazol-1-yl)methyl]azoles} 734\) are dialkylated with 1,4-dibromobutane to give 1,1-disubstituted cyclopentanes 733. 1,5-Dibromopentane reacts similarly producing cyclohexanes 735 (Scheme 115) \(<2002\text{JOC8230}>\). Two alternative methods are used for elimination of benzotriazole: treatment with \(\text{ZnBr}_2\) or with KOH. In some cases, acidic elimination works better, in others, basic elimination is preferred. Both methods convert cyclopentane derivatives 733 to 1-(cyclopenten-1-yl)azoles 732 and their cyclohexane analogs 735 to 1-(cyclohexen-1-yl)azoles 736. \(\alpha\text{-Protons in pyridinium salts} 737\) are acidic enough to be removed by weakly basic triethylamine. Obtained ylides 738 add to esters of 2-bromo-2-alkenecarboxylic acids or analogous benzonitriles to give intermediate betaines 739. A nucleophilic attack of the anionic site on C-2 of the pyridinium system followed by elimination of HBr leads to indolizines 740 (Scheme 116) \(<1999\text{JOC7618}>\). When esters of ordinary \(\alpha,\beta\text{-unsaturated acids} \)no Br at C-2) are used in these reactions, indolizines 740 are also formed but with much lower yields due to the oxidation required of the intermediate dihydro analogs of derivatives 740 that form first.
When treated with DBU at elevated temperature, 1-[(benzotriazol-1-yl)methyl]-2-aminopyridine salts eliminate rather the N–H proton than the C–H one. Intermediates can be trapped with aromatic aldehydes to create betaines. The consecutive cyclocondensation and elimination of benzotriazole results in formation of imidazolo[1,2-\text{a}]pyridines in good yields (Scheme 117) <2000JOC9201>. Aldehydes with enolizable \( \alpha \)-protons fail to give bicyclic systems, producing corresponding enamines instead.

Scheme 116

Scheme 117

\( \text{Ar} = 4\text{-Me-C}_6\text{H}_4, 4\text{-MeO-C}_6\text{H}_4, 4\text{-Cl-C}_6\text{H}_4, 2\text{-furyl}, 2\text{-thienyl}, \text{or PhCH=CMe} \)
5.01.8.7 Ring N–C(sp³)-O

Compounds of general structure 745 (and their benzotriazol-2-yl analogs) are discussed in this subsection.

5.01.8.7.1 Reactions with nucleophiles

Substitution of the benzotriazole moiety in compounds 745 with organomagnesium reagents has been discussed previously <1996CHEC-II(4)1>. Newer applications of organometallic reagents to reactions with α-benzotriazolyl ethers are outlined in Scheme 118. Thus, reactions of benzotriazolyl ethers 746 with sodium dialkynylediethylaluminates provide propargylic ethers 747 in high yields <1999JOC488>. 2-Benzotriazolyl-1,3-dioxolane 748 is a convenient equivalent of the formyl cation; its reactions with organozinc reagents lead to masked formylated products 749 <2000JOC1886>. In the presence of Lewis acids, N-(diethoxymethyl)benzotriazole 750 undergoes addition to enol ethers to produce 1-(benzotriazol-1-yl)-1,3,3-trialkoxypropanes 751. Reactions with Grignard reagents convert derivatives 751 into β-alkoxyalkanal acetals 752 <1997JOC700>.

5.01.8.7.2 Reactions with electrophiles

α-Protons in alkoxy derivatives 746 are acidic enough to be pulled out by Bu₃Li. Nascent anions 753 can be trapped with alkylating agents to give α-alkylated products 754. Geminal benzotriazol-1-yl and alkoxy substituents in compound 754 behave as a protected carbonyl group; they can be removed by acidic hydrolysis to furnish ketones 755 (Scheme 119). In this way, a conversion is made from aldehydes R¹CH=O (the precursor of 746) to ketones R¹R²C=O. Analogously, use of chlorosilanes as alkylating agents R³X leads to acylsilanes 755 (R¹ = aryl, R³ = SiMe₂R) in good yields <1996OM486>.

Scheme 118

1,2,3-Triazoles
Many other electrophiles can be used to trap anions 753; four classes of such compounds are presented in Scheme 119. Thus, the reactions with aldehydes or ketones lead to \( \alpha \)-hydroxyketones 760 via intermediates 756. The reactions with acylating agents lead to vicinal diketones 761 via intermediates 757. The reactions with imines give \( \alpha \)-aminoketones 762 via intermediates 758, and those with esters of \( \alpha, \beta \)-unsaturated carboxylic acids give \( \gamma \)-ketoacids 763 via intermediates 759. Examples of representative products 754–763 are collected in Table 9. Other electrophiles used in such reactions that are not shown in Table 9 include chlorotrimethylsilane <1995JOC7612>, isocyanates <1995JOC7612, 1998JOC1473>, isothiocyanates <1998JOC1473>, diethyl carbonate <1995JOC7612>, and ethyl chloroformate <1998JOC1473>.

Benzotriazolyloxiranes can be prepared in practically quantitative yields by epoxidation of the corresponding alkenes with dimethyldioxirane, for example, conversion of alkene 764 to oxirane 765 (Scheme 120). At very low temperatures, substitution of the \( \alpha \)-proton in oxirane 765 is possible; just its treatment with LDA at \(-116^\circ C\) followed by benzyl bromide leads to \( \alpha \)-benzoxirane 767, via lithiated intermediate 766. At higher temperatures, rearrangement of lithiated oxirane 766 to ketone 768 is observed. Stereochemistry of the molecule is preserved during these transformations. Significant stabilization of the oxirane ring by the benzotriazolyl substituent makes its opening difficult; thus, heating in 3N sulfuric acid was required to convert oxirane 767 into hydroxyketone 769 <2001ARK(v)68>.

Addition of a silyl substituent into \( \alpha \)-position of the \( \alpha \)-(benzotriazol-1-yl)alkyl ether brings additional possibilities. Thus, lithiation of silyl ether 770 followed by treatment with an aldehyde or ketone gives unstable \( \beta \)-hydroxy-\( \alpha \)-silyl-\( \alpha \)-(benzotriazol-1-yl)alkyl ether 771 that spontaneously eliminates silanol to give vinyl ether 772 (Scheme 121). Treatment with ZnBr\(_2\) followed by hydrolysis with a diluted acid removes both the benzotriazolyl and the methyl groups to furnish carboxylic acid 773. In this way, in a simple manner, aldehydes and ketones are converted to one-carbon homologated carboxylic acid <1996S1425>.
Table 9  \textit{N-(\alpha-Alkoxalkyl)benzotriazoles and products of their hydrolysis}

| Compound | Substituents | Yield (%) | Reference       |
|----------|--------------|-----------|-----------------|
| 754a     | R$^1$ = Ph, R$^2$ = Me, R$^3$ = Br(CH$_2$)$_4$ | 82        | 1999JOC2124     |
| 754b     | R$^1$ = Ph(=C), R$^2$ = Et, R$^3$ = Bu | 90        | 1996SC4049      |
| 755a     | R$^1$ = Ph, R$^3$ = Et | 94        | 1995JOC7619     |
| 755b     | R$^1$ = CH$_2$=CH, R$^3$ = PhCH$_2$CH$_2$ | 71        | 1995JOC7589     |
| 755c     | R$^1$ = 2-Furyl, R$^3$ = Br(CH$_2$)$_4$ | 89        | 2002JOC8489     |
| 756a     | R$^1$ = CH$_2$=CH, R$^2$ = Et, R$^3$ = PhCH$_2$, R$^4$ = H | 48        | 1995JOC7589     |
| 756b     | R$^1$ = Ph(=C), R$^2$ = Et, R$^3$ = R$^4$ = Me | 66        | 1995JOC7612     |
| 757a     | R$^1$ = Ph(=C), R$^2$ = Et, R$^3$ = Ph | 63        | 1997JOC4125     |
| 757b     | R$^1$ = n-C$_6$H$_{13}$, R$^2$ = Ph, R$^3$ = Bu | 86        | 1997JOC4125     |
| 758      | R$^1$ = PhCH(OEt)CH$_2$, R$^2$ = Ph, R$^3$ = p-MeC$_6$H$_4$, R$^4$ = Ph | 92        | 1998JOC1473     |
| 760      | R$^1$ = Ph(=C), R$^3$ = R$^4$ = Me | 100       | 1995JOC7612     |
| 761      | R$^1$ = n-C$_6$H$_{13}$, R$^3$ = Bu | 83        | 1997JOC4125     |
| 762a     | R$^1$ = PhCH=CH, R$^2$ = Et, R$^3$ = R$^4$ = Ph | 71        | 1997JOC706      |
| 762b     | R$^1$ = PhCH(OEt)CH$_2$, R$^3$ = p-MeC$_6$H$_4$, R$^4$ = Ph | 64        | 1998JOC1473     |
| 763      | R$^1$ = PhCH=CH, R$^2$ = Et, R$^3$ = Me | 50        | 1997JOC706      |

Scheme 120

Scheme 121
5.01.8.7.3 Rearrangements

When crude reaction mixtures containing derivatives 756 (Scheme 119) are treated with three-fold excess of ZnBr₂ and heated to reflux, benzotriazole is eliminated and the products rearrange to α-alkoxyketones 776 (Scheme 122). The proposed mechanism involves formation of oxiranes 774 (in some cases isolated intermediates) which then open to betaines 775. Subsequent migration of substituent R³ furnishes α-alkoxyketone 776. The conversion is characterized by remarkable regioselectivity with only one regioisomer formed from intermediates with R³ ≠ R¹ with the order of migration: H > Ar > alkyl (tert-alkyl > sec-alkyl > n-alkyl) <1996JOC7564>. A similar rearrangement of derivatives 756 (R¹ = H, R² = Ph, R³ = H, R⁴ = alkyl) is promoted by treatment with p-TsOH in acetic acid <1995TL841>.

![Scheme 122](image)

Treated with strong bases, α-(benzotriazol-1-yl)alkyl ethers 777 derived from benzyl alcohols undergo [1,2]-Wittig rearrangement to ketones 780 (Scheme 123). For the derivatives of aromatic aldehydes (R¹ = aryl), LDA is a base strong enough to pull the benzylic proton from ether 777 to give anion 778. The subsequent [1,2]-Wittig rearrangement produces alkoxide 779 which spontaneously expels benzotriazole anion to furnish ketone 780 <2002ARK(vii)146>. In the case of formaldehyde derivatives (R¹ = H), a stronger base, Bu²Li, is required to do the job; however, it is difficult to stop the reaction sequence at the ketone stage, and alcohols 781 are obtained as the major products <2000H(53)1783>.

![Scheme 123](image)

5.01.8.7.4 Allyl ethers

α-(Benzotriazol-1-yl)allyl ethyl ether 782 can be readily alkylated to give tertiary ethers 783. Grignard reagents attack ethers 783 exclusively in γ-position (SN₂ reaction) producing enol ethers 784 which are hydrolyzed during acidic work-up to ketones 785 (Scheme 124). High regioselectivity of these reactions is rationalized by substitution of the α-carbon atom with bulky groups <1995JOC7605>. 

![Scheme 124](image)
Treated with a suspension of metallic lithium at low temperatures, ethers 786 are reduced to anions 787. Addition of an aldehyde or ketone to the reaction mixture allows trapping these anions with formation of β-hydroxyethers 788 and enol ethers 789 (Scheme 125). For R1 = H, in reactions with aliphatic aldehydes and ketones, the α-attack prevails to give hydroxyethers 788 as the major products. In other cases, products 789 resulting from the γ-attack of anion 787 on a carbonyl group become dominant. Stereochemistry of products 789 (cis : trans) also depends strongly on substituents R1 with the cis geometry prevailing (98:2 to 4:2) for R1 = H or Pr. When R1 = Ph, mostly trans isomers (1:2) are formed <1998TL6437>.

For allyl ethers 790 with R1 = Ph, treatment with LDA generates anions 791 which undergo [2,3]-Wittig rearrangement to more stable alkoxides 792 (Scheme 126). Spontaneous expulsion of benzotriazole anion from 792 generates β,γ-unsaturated ketones 793 that are isolated in high yields (86-92%) <1996JOC4035>. In the case of

**Scheme 124**

**Scheme 125**

**Scheme 126**
R<sup>1</sup> = H, stronger bases required to pull the α-proton from ethers 790 react also with intermediate aldehydes 793 to convert them into alcohols 794. In all these reactions, exclusive formation of the products with the (E) configuration is observed.

5.01.8.7.5 Cyclocondensations
Condensation of benzotriazole with 2-carboxybenzaldehyde gives 3-(benzotriazol-1-yl)phthalide 795 (Scheme 127). The anion derived from phthalide 795 adds to the β-carbon atom of α,β-unsaturated carbonyl compounds E to produce anion 796 that by intramolecular nucleophilic attack on the phthalide carbonyl group is converted to anion 797. Spontaneous expulsion of benzotriazole from molecules 797 followed by aromatization leads to 1,4-dihydroxynaphthalenes 798 <1997SC3951>.

Scheme 127

Alkylation of 2-hydroxybenzophenone with 1-(α-chloroalkyl)benzotriazoles provides ethers 799. Treated with LDA, ethers 799 lose α-proton. Nucleophilic intramolecular attack of the obtained anions on the carbonyl group leads to alkoxides 800 (Scheme 128). When a treatment with ZnBr<sub>2</sub> follows, an arrangement occurs resulting in formation of 2,3-dihydrobenzofuran-2-ones 803. The suggested mechanism involves elimination of benzotriazole with formation of epoxides 801. Promoted by ZnBr<sub>2</sub>, the epoxides open to cations 802 which rearrange to final products 803 <2004ARK(vi)27>.

Scheme 128
Two examples discussed above involve participation of an ortho substituent on the aromatic ring in the cyclization process; however without such a substituent, α-(benzotriazol-1-yl)alkyl aryl ethers can also be employed as the starting materials for introduction of an additional ring. Thus, lithiation of ether 804 followed by treatment with an aldehyde generates β-hydroxyether 805 (Scheme 129). Treated with ZnBr₂ and heated at 140 °C, derivatives 805 eliminate benzotriazole and rearrange to α-aryloxyketones 806. When heating with ZnBr₂ is continued at even higher temperature (175–180 °C), cyclocondensation of ketones 806 with involvement of the phenyl ortho carbon atom leads finally to benzofurans 807.<1998J(P1)1059>

![Scheme 129](image.png)

5.01.8.8 Ring N–C(sp³)-X (X = heteroatom ≠ N or O)

5.01.8.8.1 Sulfur derivatives

The preparation of α-(benzotriazol-1-yl)alkyl thioethers and their reactions with nucleophiles have been discussed before <1996CHEC-II(4)1>. To some extent, α-(benzotriazol-1-yl)alkyl thioethers react similarly to the related ethers. Thus, thioether 808 can be lithiated with Bu²Li then treated with an aldehyde or a ketone to give a sulfur analog of α-(benzotriazol-1-yl)-β-hydroxyalkyl ether 756. Similarly to ethers 756, their sulfur analogs can be hydrolyzed to α-hydroxyketones 760 (Scheme 119) <1998JOC2110, 2004JOC303>. Lithiated, then treated with an aldehyde or ketone followed by ZnBr₂, thioether 809 is converted to the corresponding benzothiophene <1998J(P1)1059>, in analogy to conversion of ether 804 to benzofuran 807. Similarly to conversion of ethers 799 to 2,3-dihydrobenzofuran-2-ones 803 (Scheme 128), thiethers 810 are converted to the corresponding 2,3-dihydrobenzothiophen-2-ones <2004ARK(vi)27>. In general, due to better stabilization of the adjacent carbocation than it is possible in ethers, properties of α-(benzotriazol-1-yl)alkyl thioethers resemble in some aspects those of α-(benzotriazol-1-yl)alkyl amines. However, in other aspects, properties of thioethers are quite unique.

![Scheme 129](image.png)

1-(Mercaptomethyl)benzotriazole 815 is conveniently prepared by treatment of 1-(chloromethyl)benzotriazole 811 with sodium trithiocarbonate followed by hydrolysis of the obtained hemi ester 812 with ammonium chloride (Scheme 130). In the presence of triethylamine, mercaptan 815 reacts readily with arylmethyl halides to give sulfides 814 in high yields. Alkylation of mercaptan 815 with chloromethyl methyl ether provides methoxymethyl thioether 816 that can be substituted at the α-carbon atom by treatment with Bu²Li followed by an electrophile to
furnish thioethers 817. Repeated treatment with Bu'Li and an electrophile (benzyl bromide) allows substitution of the remaining \(\alpha\)-proton to get derivative 813. Among other reactions performed on mercaptan 815 are substitution of the chlorine atom in 2-chlorocyclohexanone to give product 818, addition to electron deficient vinyl groups (products 819) and condensation/addition with 1,3-cyclohexanediene and benzaldehyde to produce derivative 820 <1996JHC1927>.

The readily available benzotriazolyl derivative of dimethyl sulfide, compound 821, can be alkylated on \(\alpha\)-carbon in a stepwise manner to provide (\(\alpha,\alpha\)-disubstituted)alkyl thioethers 823 (Scheme 131). Hydrolysis of these thioethers under mild conditions (5% \(\text{H}_2\text{SO}_4\) at room temperature) furnishes ketones 824 in high yields. The anion derived from mono substituted (benzotriazol-1-yl)methyl thioether 822 adds to butyl acrylate to give intermediate 826 that can be hydrolyzed to \(\gamma\)-ketoester 825. In another example of reactivity of \(\alpha\)-(benzotriazol-1-yl)alkyl thioethers, treatment of thioether 822 with Bu'Li followed by phenyl isocyanate converts it into \(\alpha\)-ketoanilide 828, via intermediate adduct 827 <1998JOC2110>.

Treated with ZnBr\(_2\) followed by enamines, phenyl thioethers 829 derived from aryl aldehydes are converted to \(\beta\)-(phenylthio)alkyl ketones or aldehydes 830 in moderate to good yields (Equation 19). Enamines used in these syntheses are: (1) morpholine enamine derived from diethyl ketone, (2) diethylamine enamine of propiophenone, (3) piperidine enamine derived from isovaleraldehyde, and (4) pyrrolidine enamine of cyclohexanone <2000H(53)331>.

Scheme 130
Treatment of \(\alpha\)-(benzotriazol-1-yl)alkyl thioethers with \(\text{ZnBr}_2\) weakens the bond with benzotriazole, and the obtained complex may partially dissociate to thionium cation that can be trapped by even mild nucleophiles. Thus, trimethylsilyl cyanide added to the reaction mixture causes substitution of the benzotriazole moiety by the CN group to give \(\alpha\)-(phenylthio)carbonitrile. In a similar manner, treatment with allylsilane leads to \(\gamma,\delta\)-unsaturated thioether. Addition of species to the double bond of a trimethylsilyl \(\alpha\)-arylvinyl ether followed by hydrolysis of the silyloxy group furnishes \(\beta\)-(phenylthio)aryl ketones (Scheme 132).

Introduction of trimethylsilyl substituents attached directly to the \(\alpha\)-carbon atom of \(\alpha\)-(benzotriazol-1-yl)alkyl thioethers provide new opportunities. Thus, treatment of lithiated monosubstituted \(\alpha\)-(benzotriazol-1-yl)alkyl thioethers with chlorotrimethylsilane produces \(\alpha\)-(trimethylsilyl)alkyl thioethers. In reactions with hexamethyldisilathiane and cobalt dichloride, thioethers are converted to thioacylsilanes that can be trapped in a Diels–Alder reaction with 2,3-dimethylbutadiene to form 2-alkyl-4,5-dimethyl-2-trimethylsilyl-3,6-dihydro-2\(H\)-thiopyrans.

All reactions of benzotriazole derivatives of the type \(\text{Br-\(\text{CR}_1\text{R}_2\text{S}\)}\) discussed above are based on electrophilic or nucleophilic substitutions at the \(\alpha\)-carbon, but radical reactions are also possible. Thus, the first report on unsubstituted carbon-centered (benzotriazol-1-yl)methyl radical involves derivatives of (benzotriazol-1-yl)methyl mercaptan. \(\text{\(\delta\)}-(Benzotriazol-1-yl)methyl-\(\alpha\)-ethyl xanthate is readily prepared in a reaction of 1-(chloromethyl)benzotriazole with commercially available potassium \(\alpha\)-ethyl xanthate. Upon treatment with radical initiators (lauroyl peroxide), the C–S bond is cleaved to generate radical that can be trapped by alkenes to generate new radicals allowing repetition of the process (Scheme 134). Maleinimides are also satisfactorily used as radical traps in these reactions.
5.01.8.8.2 Phosphorus derivatives

Methanesulfonates 844, obtained by addition of diphenyl phosphite to aldehydes $\text{Ar}_1\text{CHO}$ and mesylation of the hydroxyl group of the adducts, react with benzotriazole to give diphenyl $\alpha$-(benzotriazol-1-yl)benzylphosphonates 845. Lithiation and treatment with aldehydes $\text{Ar}_2\text{CHO}$ converts phosphonates 845 into stilbenes 846, which can eliminate benzotriazole to give diarylacetylenes 847 (Scheme 135) <2002ARK(xiii)17>.
[(Benzotriazol-1-yl)methyl]triphenylphosphonium chloride 848 reacts with Bu\textsuperscript{−}Li and aldehydes to give 1-(alken-1-yl)benzotriazoles 849. Addition of bromine to the double bond of derivatives 849 followed by a reaction with amines furnishes amides 850. A variety of primary or secondary amines can be used. This way aldehydes are conveniently homologated and converted to amides with a one-atom longer chain (Scheme 136) \textsuperscript{<2004ARK(ix)44}.

\begin{center}
\begin{tikzpicture}
\node [text width=0.5\textwidth] at (-2.5,0) {\textbf{Scheme 135}};
\node at (-2.5,-3) {\textbf{Scheme 136}};
\end{tikzpicture}
\end{center}

5.01.8.8.3 Silicon derivatives

[(Benzotriazol-1-yl)methyl]trimethylsilane 852 reacts with acyl chlorides under mild conditions to provide (benzotriazol-1-yl)methyl ketones 851 in high yields (Scheme 137) \textsuperscript{<2001J(P1)2483, 2001JOC5606>}. Reactivity of benzotriazolyl derivatives of type 851 and their application in organic synthesis are discussed in Section 5.01.8.4. 1,4-Addition of silane 852 to 2-cyclohexen-1-one produces derivative 853 that is unstable to the air; however, direct treatment of the reaction mixture with a base generates an anion that can be trapped by various electrophiles. Final hydrolysis of the silyloxy group and elimination of benzotriazole give rise to 3-substituted 2-cyclohexen-1-ones 854 \textsuperscript{<1995TL5491>}.

5.01.8.8.4 1-(Chloromethyl)benzotriazole

1-(Chloromethyl)benzotriazole 856 is an important starting material for preparation of many derivatives of benzotriazole that are discussed in this section. All these reactions rely on the nucleophilic substitution of chlorine in 856 with nucleophiles to give derivatives 855 \textsuperscript{<1996CHEC-II(4)1>}. However, it appears that compound 856 can also be converted into its anion by treatment with LDA at −40°C. The anions generated this way can be trapped by ketones to provide a convenient method for the synthesis of (benzotriazol-1-yl)oxiranes 857 (Scheme 138) \textsuperscript{<2003JOC407>}. 

\begin{center}
\begin{tikzpicture}
\node [text width=0.5\textwidth] at (-2.5,0) {\textbf{Scheme 136}};
\end{tikzpicture}
\end{center}
5.01.8.9 Ring N–C(sp$^2$)–C

5.01.8.9.1 Alkenyl group not activated
In the presence of a palladium catalyst, 1-vinylbenzotriazole 859 reacts with iodoarenes to give derivatives 858 (Scheme 139). Exclusive addition to the β-carbon and (E) geometry of molecules 858 are confirmed by NMR data <1999H(50)767>. To introduce substituents on the α-carbon, 1-vinylbenzotriazole is lithiated first with 1 molar equivalent of Bu$^t$Li to give intermediate 860 and then treated with electrophiles to furnish products 861 <2003JOC5713>. Use of 2 equiv of Bu$^t$Li produces dilithiated intermediate 863 giving rise to disubstituted products 862. When reagents with two electrophilic centers are used, like (PhCO)$_2$ or (PhCO)$_2$CH$_2$, an additional ring is added to the heterocyclic system involving atoms C-α and C-7. Initial addition of two isocyanate groups to C-α/C-11 is followed by an intramolecular nucleophilic addition of the amide N-H to the vinyl bond resulting in products 864 <2003JOC5713>.

1-Alkenylbenzotriazoles 865 are readily prepared by isomerization of the corresponding allyl derivatives catalyzed by Bu$'OK$. Lithiated compounds 865 are treated with electrophiles to provide α-substituted derivatives 866. Epoxidation of the double bond with m-chloroperbenzoic acid converts intermediates 866 into oxiranes 867 that can be hydrolyzed to furnish α-hydroxyketones 868 in good yields (Scheme 140) <1996SC2657>.

5.01.8.9.2 Electron-withdrawing substituents
Compounds of this type with an electron-withdrawing substituent at C-α can be easily prepared by condensation of 2-(benzotriazol-1-yl)acetophenone 869 with aldehydes. Exclusively (E) isomers of α,β-unsaturated ketones 870 are formed. Treatment with hydrazines converts derivatives 870 into pyrazolines 871. Elimination of benzotriazole from 871 in the presence of mild bases furnishes pyrazoles 872. When in these reactions hydroxylamine is used instead of hydrazines, the corresponding isoxazoles are obtained (Scheme 141) <2001JOC6787>. 

**Scheme 137**

**Scheme 138**

RCOCl $\rightarrow$ RuCl $\rightarrow$ CoCl $\rightarrow$ RuCl $\rightarrow$ CoCl $\rightarrow$ RuCl $\rightarrow$ CoCl $\rightarrow$ RuCl $\rightarrow$ CoCl

R = alkyl, aryl, or ClCH$_2$
E = alkyl, ArCH$_2$, PhCO, PhCHOH, Ph$_2$COH, or ArNHCS

**Scheme 139**

$\text{Nu} \rightarrow \text{R}^1\text{R}^2\text{C}=\text{O} \rightarrow \text{LDA}$

$\text{R}^1 = \text{Me, Et, Ph, 4-MeC}_6\text{H}_4$ or $\text{4-ClC}_6\text{H}_4$
$\text{R}^2 = \text{Et or Ph, or}$
$\text{R}^1\text{R}^2 = (\text{CH}_2)_5$
Scheme 139

Scheme 140

Scheme 141
Compound 874, as a representative of derivatives with an electron-withdrawing substituent at C-β of the vinyl group, is easily prepared by elimination of one benzotriazole from 2,2-bis(benzotriazol-1-yl)ethyl methyl ketone 873. The stereoselective elimination catalyzed by NaOH gives exclusively the (E) isomer of derivative 874. Addition of nucleophiles to the double bond of vinyl ketone 874 followed by elimination of benzotriazole leads to α,β-unsaturated ketones 875. Amines used as nucleophiles do not need any catalysis, but reactions with carbon and sulfur nucleophiles require addition of a base. The total effect is nucleophilic substitution of the benzotriazolyl group at the β-carbon of α,β-unsaturated ketone (Scheme 142) <1996SC3773>.

5.01.8.9.3 Electron-donating substituents
α-(Benzotriazol-1-y1)enamines 877 can be conveniently prepared in reactions of amides 876 with benzotriazole and POCl₃. Enamines 877 are stable enough to be separated by column chromatography as pure stereoisomers; however, their long storage in a solution showed partial isomerization between benzotriazol-1-yl and benzotriazol-2-yl isomers. Nucleophilic substitution of benzotriazole with organozinc reagents furnishes enamines 878 (Scheme 143) <2000ARK(v)667>.

Triflate 880 can be formally considered as an ester of the enol form of ketone 879. Treatment with a base causes elimination of the triflate group to afford 1-(benzotriazol-1-yl)alkynes 881 (Scheme 144) <2000OL3789>.

\[
\text{Scheme 142}
\]

\[
\text{Scheme 143}
\]

\[
\text{Scheme 144}
\]
5.01.8.9.4 Allylic derivatives

The benzotriazolyl derivative of acrolein acetal, compound 882, is lithiated, treated with chlorodiphenylphosphine, and the obtained intermediate is oxidized with hydrogen peroxide to phosphine oxide 883 (Scheme 145). The relatively acidic proton in derivative 883 is easily removed by a base, and the obtained anion adds to a carbonyl group of aldehyde or ketone. Subsequent rearrangement and elimination of the phosphorane group generates diene 884. For the derivatives of aldehydes (884, R² = H), (E)-(E) stereoselectivity of the elimination is observed. Acidic alcoholyis of dienes 884 affords esters of β,γ-unsaturated carboxylic acids 885 <1997JOC4131>.

![Scheme 145](image)

\[ R^1 = n-C_3H_7, n-C_7H_{15}, Ph, \text{or} PhCH_2CH_2 \]
\[ R^2 = H, \text{Me}, n-C_3H_7, \text{or} Ph, \text{or} \]
\[ R^1R^2 = (CH_2)_5 \]

Scheme 145

The allylic chlorine atom in derivatives 886 can be easily substituted by nucleophiles <2002EJO493>. Reactions of chlorides 886 with sodium benzeneselenide provide allylic selenides 887. Oxidation of the selenium atom in selenides 887 with m-chloroperbenzoic acid generates unstable selenoxides 888. Contrary to the corresponding sulfoxides <2002EJO493>, and due to good leaving ability of the benzeneselenenate moiety, selenoxides 888 may dissociate to cations 889 that are readily hydrolyzed to vinyl ketones 890 (Scheme 146) <2002TL3021>.

![Scheme 146](image)

\[ Ar = Ph, 2-MeC_6H_4, 4-FC_6H_4, \text{or} 4-(MeO)C_6H_4 \]
\[ R = \text{Me, Bu}, \text{Ph, 4-MeC_6H_4, 2,5-Me_2C_6H_3, or 2-naphthyl} \]

Scheme 146

5.01.8.10 Ring N–C(sp²)–N

1-Imidoylbenzotriazoles 892 are prepared in good yield (50–90%) in reactions of amides 891 with benzotriazole and oxalyl chloride in the presence of pyridine <2006JOC3375>. Derivatives 892 are convenient reagents for imidoylation of methylene groups activated by electron-withdrawing substituents. Thus, in their reactions with ester enolates,
generated from the corresponding esters by addition of Bu'OK, 1-imidoylbenzotriazoles 892 give β-enaminooesters 893 in 77–88% yield. Similarly, β-iminoamides 894 are obtained in 48–69% from reactions of compounds 892 with amides deprotonated by Bu'Li. The anions generated from nitroethane, alkyl phenyl sulfones, or sulfoxides by action of Bu'OK react with 1-imidoylbenzotriazoles 892 to provide derivatives 895, 896, and 897, respectively, in generally good yields. All of these products can exist in equilibria between the enamine and imine forms; however, the NMR data indicate that the enamine forms are strongly predominant for derivatives 893, 895, and 897 (Scheme 147) <2007ARK(v)263>.

Reactions of N-(α-aminoalkyl)benzotriazoles 898 with isonitriles catalyzed by boron trifluoride etherate give N-(α-aminoalkylimidoyl)benzotriazoles 899 in high yield. Upon treatment with hydrochloric acid, derivatives 899 are conveniently converted to α-aminoamides 900 (Scheme 148) <2005JSC319>.

A reaction of benzotriazole with cyanogen bromide carried out in ethanol in the presence of NaOH provides dibenzotriazolylmethanimine 904 as a mixture of benzotriazol-1-yl and 2-yl isomers <1996POL4011, 2000JOC8080>. To simplify the picture, only the benzotriazol-1-yl isomer is shown in Scheme 149. Treatment with amines converts methanimine 904 under mild conditions into carboxyimidamides 905 as sole benzotriazol-1-yl isomers. Upon treatment with other amines at slightly elevated temperature, the second benzotriazolyl moiety can be replaced to provide guanidines 906 bearing up to four different groups <2000JOC8080>. Acyl derivatives 902 undergo cyclocondensation with alkyl or aryl hydrazines to give 3-amino-1,2,4-triazoles 901 in good yields.
Cyclocondensation of derivative 902 with ureas provides 1,3,5-triazin-2-ones 903, whereas a similar reaction with thioureas gives 1,3,5-triazin-2-thiones. Hydrazides derived from aromatic carboxylic acids react with imine 904 to give oxadiazoles almost quantitatively, whereas only 42% yield was achieved in an analogous reaction of acetyl hydrazide. Cyclocondensation of imine 904 with methylhydrazine produces 1,2,4-triazole; however, in the case of arylhydrazines, a more complex process involving condensation of 904 with two molecules of hydrazine, elimination of ammonia and oxidation with atmospheric oxygen leads to azo derivatives 909. 5.01.8.11.1 Ring N–(C<sp>2</sp>)–O

Considering benzotriazolyl moiety in compounds of the general structure R-(C<sp>2</sp>)=O (X = benzotriazol-1-yl or benzotriazol-2-yl) as a synthetic equivalent of a halogen atom, the formyl derivative (R = H) is of special interest due to unavailability of the halogen analogs. 1-Formylbenzotriazole 911 can be conveniently prepared in a reaction of benzotriazole with formic acid in the presence of dicyclohexylcarbodiimide. Its reactions with amines provide conveniently formamides 910 under mild conditions. Even unreactive 2-nitroaniline and 2-aminopyridine can be efficiently formylated this way (Scheme 150). In reactions of 1-formylbenzotriazole 911 with alcohols, the corresponding formates are readily obtained. Treatment of compound 911 with triphenylphosphine and CCl<sub>4</sub> results in formation of 1-(2,2-dichlorovinyl)benzotriazole 913, a convenient starting material in the synthesis of 1-ethynylbenzotriazoles (see Section 5.01.8.13).
A wide range of N-acylbenzotriazoles 915 have been prepared under mild conditions in reactions of carboxylic acids with thionyl chloride in the presence of fourfold excess of benzotriazole, including \( R = \text{alkyl, } \alpha\text{-haloalkyl, } \alpha\text{-alkoxyalkyl, alkenyl, alkynyl, aryl, and heteroaryl} <2003S2795, 2004RQM275> \). They represent convenient acylating agents for variety of nucleophiles. Synthetic applications of such compounds have been reviewed <2005SL1656>.

Some examples of C-acylation by 1-acylbenzotriazoles 915 are collected in Scheme 151. Thus, acylation of aromatic rings involves reactions of derivatives 915 with thiophene in the presence of ZnBr\(_2\) or TiCl\(_4\) to give corresponding 2-acylthiophenes 914 in high yield <2004CCA175>. Furan reacts similarly. C-2 acylation of pyroles and C-3 acylation of indoles under these conditions does not require N-protection <2003JOC5720>. Ketones are acylated in the presence of LDA to give \( \beta\)-diketones 916 <2000JOC3679>; the reaction can also be carried out on a polymer support <2001JCO167>. Acylation of aliphatic nitriles leads to the corresponding \( \beta\)-ketonitriles <2003JOC4932> and that of sulfones to \( \beta\)-keto sulfones <2003JOC1443>. Imines delivered from methyl ketones are effectively acylated by derivatives 915 on their methyl groups to give enamiones 917 <2000S2029>. 2-Picoline is readily acylated by 915 to produce (pyridin-2-yl)methyl ketones 918; 4-picoline, 4-methylquinoline and the corresponding benzyl derivatives react similarly <2005ARK(vi)329>.

In a reaction with thionyl chloride and methanol, L-aspartic acid 919 is converted to its monoester, which is subsequently treated with ethyl trifluoroacetate to give N-protected aminoacid 920. Upon treatment with benzotriazole and thionyl chloride, acid 920 is converted to 1-acylbenzotriazole 921 that can be used as an acylating agent for electron-rich aromatics. Thus, in its reaction with di- and trimethoxybenzene, the corresponding \( \gamma\)-keto-\( \beta\)-aminocarboxylic acid esters 922 are obtained in 35% and 50% yield, respectively. Ketones 922 are smoothly reduced with triethylsilane to \( \beta\)-aminoacid derivatives 923 (78–79% yield). Higher yields of ketones 922 (54–89%) are obtained from reactions of acylating agent 921 with reactive heteroaromatics like pyrrole, indole and their N-methyl derivatives. Starting from glutamic acid, an analogous reaction sequence provides derivatives of the corresponding \( \gamma\)-aminoacids (Scheme 152) <2007JOC407>.
Acylbenzotriazoles 915 are convenient acylating agents for all kinds of amines. Thus, in their reactions with ammonia (30% aqueous solution), primary amides 928 are formed in high to quantitative yields. Primary amines react similarly well to give amides 929. In the case of secondary amines, the yields of amides 930 are generally high, except when there is too much steric hindrance; for example, \( N \)-ethylisopropylamine does not react at all (Scheme 154) <2000JOC8210>. Reactions of compounds 915 with 2,2-dimethyl-2-aminoethanol produce oxazolines 931 <2004JOC811>. Analogously, thiazolines are formed in reactions of acylbenzotriazoles 915 with 2-aminoethanol <2004JOC811>. Due to simplicity and high efficiency of these reactions, 1-acylbenzotriazoles 915 are currently used in drug derivatization <2001JIP129, 2003CCA335> and preparation of \(^{14}\)C-labeled compounds <2003JLR449>. The synthesis of amides 928–930 can be further facilitated by application of microwaves <2006JOC3375> or a solid phase support <2002BML1809>. 

\[
\begin{align*}
\text{Scheme 152} \\
\text{Scheme 153}
\end{align*}
\]
N-Acylation by derivatives 915 is applicable to the formation of N-acylsulfonamides 932 <2004ARK(xii)14>, hydroxamic acids and Weinreb amides 933 <2002ARK(xi)39, 2003S2777> in high yields (Scheme 154). Application of this methodology allows direct conversion of hydroxy carboxylic acids into their amides without any protection on the hydroxy group. Thus, in reactions with amines, compound 915 derived from 2-hydroxy-3-phenylpropionic acid gives amides 934 in 72–75% yield <2006JOC3364>. 1-Acylbenzotriazole 915 derived from salicylic acid reacts smoothly with amines to give salicylamides 935 <2006JOC3364> and with isocyanates to afford benzoxazine-2,4-diones 936 <2007ARK(vi)6>. Many other hydroxy carboxylic acids, with various distances between the hydroxy and carboxylic groups, produce similarly good results <2006JOC3364>.

N-Protected 1-(α-aminoacyl)benzotriazoles 938 derived from chiral α-aminocarboxylic acids can be conveniently prepared by mixing 4 molar equivalents of benzotriazole with 1 equiv of thionyl chloride followed by addition of 1 equiv of N-protected α-aminocarboxylic acid. Acylbenzotriazoles 938 react with chiral amines to give corresponding amides with retention of chirality <2002ARK(viii)134>. Condensation of 938 with unprotected α-aminocarboxylic acids in MeCN/H2O in the presence of triethylamine at room temperature gives readily chiral dipeptides 939 <2004S2645, 2005S397, 2005TL6537>. The methodology can be readily extended to tripeptides <2006S411>. Reactions of derivatives 938 with amidoximes lead to 5-(α-aminoalkyl)-1,2,4-oxadiazoles 939 in high yields and with preservation of chirality <2005ARK(vii)36> (Scheme 155). Reactions of aminoacylbenzotriazoles 938 with pyrrole and N-methylpyrrole in the presence of AlCl3 give chiral 2-(aminoacyl)pyroles 940. Analogous reactions with indoles lead to their 3-(aminoacyl) derivatives <2005JOC4993>.

5.01.8.11.4 Ring N-(C═O)-R, O-, and S-acylation
Despite the many simple methods for preparation of carboxylic esters and thioesters, in some instances, use of 1-acylbenzotriazoles 915 as O and S acylating agents may be advantageous. For example, easy to prepare salicylic acid derivative 941 reacts with cyclopentanol under microwave irradiation to give 92% yield of cyclopentyl salicylate in 10 min <2006JOC3364>. In another example, L-phenylalanine derivative 942 reacts with benzyl mercaptan
and triethylamine at 25°C for 1 h to produce the corresponding thioester in 97% yield <2004S1806>. 1-(4-Undecyloxybenzoyl)benzotriazole 943 is conveniently used for acylation of a complex phenol in preparation of liquid crystals <2004JA1161>. Esters are also formed with good yields in reactions of 1-acylbenzotriazoles 915 with organozinc reagents in the presence of a palladium catalyst <2001ARK(xi)41>. The unusual course of these reactions must involve oxidation of the intermediates with atmospheric oxygen.

Scheme 155

Carbonyl oxygen atoms of aldehydes can also be efficiently acylated by 1-acylbenzotriazoles 915 in the presence of mild bases (K₂CO₃, Et₃N). The released benzotriazolide anions are consecutively attached to the aldehyde carbonyl carbon atoms to produce esters 944 (Equation 20). Aliphatic aldehydes react quickly at room temperature, but aromatic aldehydes require elevated temperatures. The yields are good to quantitative. The amounts of benzotriazol-2-yl isomers of esters 944 in the products mixtures is strongly dependent on the reaction conditions and the character of groups R¹ and R², and it may vary from 5% to 25% <1999JHC777>.

(20)
Similarly to the reaction depicted in Equation (20), acylation of the oxygen atom of aldehydes or ketones by pyrrole derivative \(\text{945}\) produces intermediate cations \(\text{946}\). However, instead of being trapped by benzotriazole to give ester \(\text{944}\), the intramolecular electrophilic attack of the cation on the pyrrole nitrogen atom produces pyrrolo[1,2-oxazol-1-one] \(\text{947}\). According to an alternative path, the adduct of pyrrole to the carbonyl group of aldehyde is formed first, and then its oxygen atom is intramolecularly acylated to give product \(\text{947}\). The reaction is catalyzed by DBU. The indole analog of \(\text{945}\) reacts similarly with aldehydes and ketones to produce tricyclic systems (Scheme 156) \(<2004\text{JOC9313}>\).

\[
\begin{align*}
\text{945} & \xrightarrow{\text{DBU}} \text{946} \xrightarrow{\text{intramolecular electrophilic attack}} \text{947} \\
\text{R}_1\text{R}_2\text{C}=\text{O} = \text{Pr}^\text{I}\text{CH}=\text{O}, \text{4-MeC}_6\text{H}_4\text{CH}=\text{O}, \text{2-furyl-CH}=\text{O}, \text{Me}_2\text{C}=\text{O}, \text{Et}_2\text{C}=\text{O}, \text{cyclohexanone, or acetoephene}
\end{align*}
\]

Scheme 156

Intramolecular acylation of oxygen atoms plays also an important role in reactions of carbanions derived from acylbenzotriazoles \(\text{949}\) with aldehydes and ketones. Thus, anion \(\text{948}\) obtained in the first step undergoes intramolecular cyclocondensation to \(\beta\)-lactone \(\text{951}\) (Scheme 157) \(<1996\text{LA881}>\). A similar addition of anions derived from acylbenzotriazoles \(\text{949}\) to cinnamaldehydes provide unstable \(\beta\)-lactones that undergo spontaneous ring opening and decarboxylation to dienes \(\text{952}\) (a mixture of (\(E, E\)) and (\(E, Z\)) isomers). However, in the case of chalcones, the nucleophilic attack goes on the \(\beta\)-carbon atom to yield 3,4-dihydropyran-2-ones \(\text{953}\), via intramolecular acylation of the oxygen atom in anionic intermediates \(\text{950}\) \(<2002\text{JOC3104}>\).

\[
\begin{align*}
\text{948} & \xrightarrow{\text{i, LDA, ii, } \text{R}_2^2\text{R}_3\text{C}=\text{O}} \text{951} \\
\text{949} & \xrightarrow{\text{i, LDA, ii, chalcone}} \text{950} \\
\text{952} & \xrightarrow{\text{i, LDA, ii, } \text{R}_6^6\text{CH}=\text{CH}-\text{CHO}} \text{953}
\end{align*}
\]

Scheme 157

5.01.8.11.5 Ring N-(C\(\equiv\text{O})\)-R, elimination of benzotriazole

Treated with a base, 1-(arylacetyl)benzotriazoles \(\text{954}\) eliminate benzotriazole to form ketenes \(\text{955}\). When no other reagent is added, ketene \(\text{955}\) is acylated by another molecule of \(\text{954}\) to produce \(\alpha\)-ketoketene \(\text{956}\) which upon addition of water and decarboxylation during the work-up is converted to symmetrical dibenzyl ketone \(\text{957}\).
Trapping of ketenes by aronesulfonates generates unstable adducts that consecutively undergo ring opening (intermediate) and decarboxylation to aryl benzyl sulfoxides. Upon heating at 210 °C, even simple acylbenzotriazoles (R = alkyl) eliminate benzotriazole and generate corresponding ketenes that can be conveniently trapped by isocyanates.

Scheme 158

5.01.8.11.6 Ring N-(C\text{O})-X

1-Chloroformylbenzotriazole is prepared in a reaction of benzotriazole with phosgene or more conveniently with trichlorophosgene. In reactions with alcohols in the presence of pyridine, the chlorine atom in derivative is substituted by an alkoxy group. Obtained esters react with aminoacids to provide their N-protected forms. The reaction of compound with benzyloxyamine provides 1-(benzyloxycarbamoyl)benzotriazole. Deprotection of the hydroxy group by hydrogenation gives acid that is treated then with phenethylamine to afford N-hydroxy-N-phenethylurea.
1,1′-Carbonyldibenzotriazole 967 is conveniently prepared by stirring a THF solution of 2 molar equivalents of benzotriazole and 1 equiv of phosgene for 3 d. Successive treatment with two different amines provides an efficient synthetic method for asymmetrically substituted ureas 969 via intermediate amidobenzotriazoles 968 (Scheme 160) \(<1997\text{JOC}4155\>). The benzotriazole moiety in amides 968 can be readily displaced by aryl and heteroaryl organomagnesium or organolithium reagents to provide benzamides (or heterocyclic amides) 970 in moderate to good yields \(<1999\text{JCM}230\>.

Scheme 160

5.01.8.12 Ring N-C(sp²)–S

Benzotriazole thioamides 971 react with amines to produce thioamides 972 under mild conditions (Equation 21). It is the preferred route to thioamides with reactive groups \(R^1\) and \(R^2\) where direct conversion of the corresponding amides to thioamides 971 is not feasible \(<2002\text{J(P1)}2243\>). More stable 6-nitrobenzotriazolyl analogs of 971 are more convenient to use in some instances \(<2005\text{TA}1905, 2005\text{JOC}7866\>\). A significant drawback of this method is lengthy preparation of derivatives 971 \(<2002\text{J(P1)}2243\>\) or their 6-nitrobenzotriazolyl analogs \(<2005\text{JOC}7866\>\) involving several steps that start from the corresponding ortho-phenylenediamine and include formation of the triazole ring (see Section 5.01.9).

Bis(benzotriazol-1-yl)methanethione 974 is easily prepared from thiophosgene and 1-(trimethylsilyl)benzotriazole \(<1978\text{JOC}337\>). In reactions with thiols and triethylamine, thiones 974 are converted to derivatives 973 in modest yields; the main side products result from nucleophilic attacks of the thiolate anions on the thione sulfur atom to produce disulfides \(<2005\text{JOC}7866\>\). In reactions with amines, compounds 974 are smoothly converted to 1-(thiocarbamoyl)benzotriazoles 975 \(<2004\text{JOC}2976\>\). Substitution of one of the benzotriazolyl groups in 974 by phenolate anions yields 1-(arylthiothioacyl)benzotriazoles 978 (Scheme 161) \(<2005\text{JOC}7866\>\).

Reactions of thiocarbamoyl benzotriazoles 975 with organolithium or Grignard reagents provide thioamides 976 in moderate to good yields \(<2005\text{JOC}7866\>\). Substitution of the benzotriazolyl moiety in 975 by alkoxide anions leads to thiocarbamates 979 \(<2005\text{JOC}7866\>\). In reactions with amines, substitution of the first benzotriazolyl group in

\begin{equation}
\text{R}^1\text{N}^2\text{NH} = \text{Bu}^3\text{NHMe, PhNH}_2, \text{morpholine, or 1-methylpiperazine}
\text{R}^3\text{N}^4\text{NH} = n-\text{C}_8\text{H}_{17}\text{NH}_2, \text{Bu}^3\text{NHMe, PhNHMe, Ph}_2\text{NH, morpholine, or piperidine;}
\text{R}^5 = \text{aryl or heteroaryl}
\end{equation}
bis(benzotriazol-1-yl)methanethione 974 occurs readily at room temperature to give 1-(thiocarbamoyl)benzotriazoles 975. However, when the amines are used in 2:1 molar ratio, and the reaction mixtures in dichloromethane are heated at reflux, symmetrical thioureas 980 (R₁ = R⁶ and R₂ = R⁵) are obtained. Unsymmetrical thioureas 980 are prepared in good yields by reactions of intermediates 975 with different amines <2004JOC2976, 2005JOC7866>. In the presence of triethylamine, 1-(thiocarbamoyl)benzotriazoles 975 react with mercaptans to give dithiocarbamates 981 <2005JOC7866>. Similarly to their amine analogs 975, the benzotriazolyl moiety in oxygen derivatives 978 can be readily substituted with organometallic reagents to provide thionoesters 977, with amines to give thiocarbamates 979, with alkoxides to afford thiocarbonates 982 and with mercaptans to yield dithiocarbonates 983 (Scheme 161) <2005JOC7866>.

Scheme 161

\[
\begin{align*}
\text{RSH} & \rightarrow \text{RSH} & \text{R}^1 \text{R}^2 \text{NH} & \rightarrow \text{R}^1 \text{R}^2 \text{NH} & \text{R}^3 \text{M} & \rightarrow \text{S} \\
973 & & 974 & & 975 & & 976 \\
\text{ArONa} & \rightarrow & \text{ArONa} & \rightarrow & \text{ArONa} & \rightarrow & \text{ArONa} \\
977 & & 978 & & 979 & & 980 & & 981 \\
\text{R}^8 \text{ONa} & \rightarrow & \text{R}^8 \text{SH} & \rightarrow & \text{R}^8 \text{SH} & \rightarrow & \text{R}^8 \text{SH} \\
982 & & 983 & & & & & \\
\text{R} = \text{Ph, PhCH}_2, \text{or EtOCOCH}_2 \\
\text{R}^1 = \text{alkyl, allyl, benzyl, or aryl} \\
\text{R}^2 = \text{H, Me or Et; or R}^1 \text{R}^2 \text{N} = \text{pyrrolidinyl, or 2,3-dihydroindolyl} \\
\text{R}^3 = \text{alkyl, allyl, or aryl; R}^4 = \text{Ph}_2 \text{CH} \\
\text{R}^5 = \text{alkyl, phenethyl, benzyl, or aryl} \\
\text{R}^6 = \text{H, Me, or aryl; or R}^1 \text{R}^2 \text{N} = \text{piperidinyl or morpholinyl} \\
\text{R}^7 = \text{alkyl or benzyl; R}^8 = \text{alkyl or aryl; R}^9 = \text{alkyl or aryl}
\end{align*}
\]

5.01.8.13 Ring N–C(sp)

5.01.8.13.1 Ring N–C≡C–R

1-Formylbenzotriazole 984 reacts with triphenylphosphine and CCl₄ to provide 1-(2,2-dichloroethenyl)benzotriazole 985 in 68% yield as a crystalline solid. Treatment of derivative 985 with 2 molar equivalents of Bu⁴Li followed by alkylating agents leads to 1-alkynylbenzotriazoles 986 in 58–84% yield. Alternatively, propargyl alcohols 989 (32–84% yield) are obtained in a reaction of 985 with Bu⁴Li and aldehydes or ketones. p-Toluenesulfonic acid adds readily to the triple bond of derivatives 986 to give intermediates 987 that are easily hydrolyzed to carboxylic acids 988. Similarly, esters 992 are obtained by addition of methanol to derivatives 986 under basic conditions followed by acidic alcoholysis of intermediate 991. Addition of Grignard reagents to alkynes 986 provides alkenes 990 in 72-91% yield (Scheme 162) <2000OL3789, 2002JOC7526, 2006T3794>.

1-(Arylethynyl)benzotriazoles 994 are prepared conveniently in a reaction of aryl (benzotriazol-1-yl)methyl ketones 993 with triflic anhydride in the presence of 2,6-lutidine. Nucleophilic attacks in derivatives 994 occur on the C-α atoms; thus, their reactions with Grignard reagents give alkynes 995 in 51–83% yield. Lithiated heteroaromatics react similarly to give alkynes 996 in 58–70% yield (Scheme 163) <2002JOC7526>. 
Ring N=O

5.01.8.13.2 Ring N=O

1-Cyanobenzotriazole 998 is readily prepared in 92% yield by treatment of benzotriazole with sodium hydride followed by cyanogen bromide. Solid and stable derivative 998 is a convenient reagent for introduction of the nitrile functional group into activated methylene compounds R-CH₂-X, which are lithiated with LDA prior to the reaction. Less acidic materials such as Ph-CH₂-Ph and 2-pyridyl-CH₂-Me are lithiated with Bu₄Li. Nitriles 997 are obtained under mild conditions in average 65% yield (Scheme 15). Hydrolysis of 1-cyanobenzotriazole 998 with 30% H₂O₂ provides (benzotriazol-1-yl)carboxylic acid amide 999 in 79% yield. Substitution of the benzotriazolyl moiety in product 999 by amines occurs readily at room temperature to furnish ureas 1000 in 61–96% yield (Scheme 164).
5.01.8.14 Ring N–X (X = heteroatom)

5.01.8.14.1 Ring N–O
Due to its wide application in peptide synthesis, 1-hydroxybenzotriazole 1001 is the most commonly used benzotriazole derivative with hundreds of references in Chemical Abstracts each year. Utility of compound 1001 comes from its readiness to form esters with carboxylic acids in the presence of dehydrating agents (DAs). Obtained esters 1002 react eagerly with amines to produce amides 1003 in high yields (Scheme 165). More details about this application are given in Section 5.01.12.

![Scheme 165](image)

Scheme 165 shows application of this methodology for preparation of hydrazide 1007. Thus, the reaction of acid 1004 with 1-hydroxybenzotriazole and EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] gives ester 1005 that can be separated and characterized, but it rearranges slowly to isomeric form 1006 in solutions. However, both derivatives, 1005 and 1006, are found to be equally reactive toward hydrazine and afford hydrazide 1007 in 98% isolated yield (<2002JOC9471>).

![Scheme 166](image)
Polymer-bound 1-hydroxybenzotriazole 1008 reacts with carboxylic acids in the presence of 1,3-diisopropylcarbodiimide (1,3-DIC) and DMAP to produce esters 1009. Treated with hydroxylamine, esters 1009 are converted to hydroxamic acids 1010 (Scheme 167) <2003OBC850>. Starting 1-hydroxybenzotriazole 1008 is recycled in the process and can be used for other syntheses. This method is well suited for automated synthesis of a library of hydroxamic acids. In similar applications of polymer-supported 1-hydroxybenzotriazole 1008, a wide variety of amides is synthesized <1997JOC2594, 2002JCO576>.

![Scheme 167](image)

Although most common, application of esters 1002 is not limited to formation of C–N bonds. Such esters are also effectively used for regioselective benzoylation of sugars <2004CEJ399> and even for acylation of activated methylene groups <2003S2015>. Biological activity of some esters of the 1-hydroxybenzotriazole against SARS virus is attributed to their ability to acylate the cysteine sulfur atom in a key viral enzyme <2006CBO261>. Esters of 1-hydroxybenzotriazole 1001 with phosphoric acid are used for phosphorylation of nucleosides in a viral genome linked peptide <2003T1589>.

5.01.8.14.2 Ring N–S
1-Sulfonylbenzotriazoles 1012 are readily available from reactions of benzotriazole with sulfonyl chlorides <2000JOC8210> or reactions of 1-chlorobenzotriazole with sulfinic acids <2004JOC1849>. Condensation of 1012 with primary or secondary nitrides under basic conditions provides corresponding α-cyanoalkyl sulfones 1011 in good to excellent yields (Scheme 168). In a convenient manner, sulfonyl derivatives 1012 convert lithiated heterocycles into heterocyclic sulfones; for example, 2-ethylfuran is converted to sulfone 1013. In similar reactions, alkylheterocycles give α-(sulfonylalkyl)heterocycles, enolizable carboxylic esters give α-sulfonylcarboxylic esters 1014, and sulfones give α-sulfonylalkyl sulfones 1015 <2005JOC9191>.

5.01.8.14.3 Ring N–Cl
1-Chlorobenzotriazole 1017 is known as a mild oxidizing and chlorinating agent. Its reactions with aldehydes in the presence of catalytic amounts of AIBN lead to acylbenzotriazoles 1016 (Scheme 169) <2003ARK(xiv)131>. 1-Benzoylbenzotriazoles 1019 can also be obtained by oxidation of the corresponding benzyl alcohols with 2 equiv of compound 1017 <2003ARK(xiv)131>. Under similar conditions, toluenes are converted to the corresponding benzylbenzotriazoles 1020 <2003ARK(xiv)131>. Catalyzed by TiCl4 and other Lewis acids, reactions of chlorobenzotriazole 1017 with ethers provide 1-(α-alkoxyalkyl)benzotriazoles 1018 <1999H(50)1877>. Reactions of 1017 with ketone silyl enol ethers give 1-(α-acylalkyl)benzotriazoles 1021 <1998JCM334>. Reactive aromatic rings can be efficiently chlorinated by chlorobenzotriazole 1017 as it is demonstrated by chlorination of norharmane, one of β-carbolines, to its chloro-derivative 1022 in 83% yield <2003JHC419>. 
5.01.9 Ring Synthesis from Acyclic Compounds

5.01.9.1 Ring Synthesis from Acetylenedicarboxylates

Cycloadditions of azides to alkynes and their derivatives \(<\text{1996CHEC-II}(4)\>\) continue to be the main synthetic route to 1,2,3-triazoles. Some aspects of these reactions with focus on cycloadditions at low temperature are discussed in a review \(<\text{2003H}(60)1225\>\). Recent advances in this area make the synthesis easy and high yielding to allow quick assembly of complex structures from relatively simple fragments. Drug design, proteomics, and nanotechnology are the scientific fields of great contemporary interest in such synthesis.
Esters of acetylenedicarboxylic acid 1023 are commercially readily available, are very reactive as dipolarophiles, and the carboxylic groups in products of their reactions can be easily converted to many other functionalities. Therefore, they are often the first choice as substrates for 1,3-dipolar cycloaddition to azides 1024 (Huisgen reaction). The reactions are carried out at room or elevated temperature, and the yields of 1,2,3-triazoles 1025 are usually high to quantitative (Equation 22). Several products obtained in this way are presented as structures 1026–1034. Some details about the reactions leading to these products are given in Table 10.

\[
\text{R}^1\text{O}\text{CO} + \begin{array}{c} \text{N}^- \text{N}^- \text{N}^- \\ \text{R}^2 \end{array} \rightarrow \begin{array}{c} \text{R}^1\text{O} \text{C} \text{O} \\ \text{R}^2 \end{array}
\]

(22)

\[\text{Product} \quad \text{Reaction conditions} \quad \text{Yield (%)} \quad \text{Purpose} \quad \text{Reference}\]

| Product   | Reaction conditions     | Yield (%) | Purpose                                  | Reference     |
|-----------|-------------------------|-----------|------------------------------------------|---------------|
| 1026      | toluene, r.t., 72 h     | 100       | inhibitor of hepatitis A virus 3C proteinase | 2004BML3655   |
| 1027      | toluene, reflux, 24 h   | 90        | derivatives of \(\alpha\)-tocopherol       | 2006EJO2081   |
| 1028      | toluene, reflux, 72 h   | 73        | nucleoside analogs                        | 2002BKC437    |
| 1029      | toluene, reflux, 72 h   | 73        | nucleoside analogs                        | 2002JCM264    |
| 1030      | benzene, reflux, 3 h    | 100       | nucleoside analogs                        | 2002TL8351    |
| 1031      | toluene, \(130^\circ\)C, 40 h | 65       | study of microwave methodology            | 2005T4701     |
| 1032      | toluene, \(80^\circ\)C, 24 h | 84       | antitumor nucleoside analog               | 2002NN361     |
| 1033      | toluene, reflux, 24 h   | 90        | disaccharide carbohybrids                 | 2005H(65)1035 |
| 1034      | (1,2,3-triazol-1-yl)calix[4]arenes, CH₂Cl₂, reflux, 6 h | 84       | molecular hosts                           | 2002JOC6136   |
An example of application of the [1,3]-dipolar cycloaddition reactions between azides and esters of acetylenedicarboxylic acid in nanotechnology is given in Scheme 170. In solutions, molecules of tris(crown ether) 1035 and tris(benzyl azide) 1036, where R is a large template of $C_3$ symmetry, are self-assembled into a bundle with benzyl azide groups poking through the crown-ether rings. When di(tert-butyl) acetylenedicarboxylate is added, the azide groups are converted to triazoles 1037, that are too bulky to be pulled out of the crown-ether rings, and the assembly remains permanently mechanically interlocked <2004CEJ1926>.

Reactivity of azides towards acetylenedicarboxylates is very dependent on their electron density (energy HOMO). Thus, strongly electron-deficient 3,5-dicyano-2,4,6-triazidopyridine 1039 reacts slowly with dimethyl acetylenedicarboxylate to give triazole derivative 1038 in 34% yield with most of the starting material recovered unchanged. Under comparable conditions, less electron-deficient 3,5-dichloro-2,4,6-triazidopyridine 1040 reacts with dimethyl acetylenedicarboxylate to provide 2,6-bis(1,2,3-triazol-1-yl)pyridine derivative 1041 in 75% yield (Scheme 171) <2001CHE861>.
An example of asymmetric synthesis involving cycloaddition of an azide to dimethyl acetylenedicarboxylate is depicted in Scheme 172. Thus, asymmetric auxiliary 1042 reacts with styrene and sodium azide to generate azide 1043 in 90% yield and 94% diastereomeric purity. The following reaction (Scheme 172) with dimethyl acetylenedicarboxylate converts azide 1043 into triazole 1044 in 75% yield. Finally, the bond with selenium is cleaved by treatment with triphenyltin hydride and AIBN to furnish triazole 1045 in 80% yield and preserved optical purity (94%) <2003AGE3131>.

Treatment of ruthenium azido complex 1046 with dimethyl acetylenedicarboxylate in CH₂Cl₂ at room temperature for 24 h results in ruthenium triazole complex 1047 with 90% isolated yield. Surprisingly, product 1047 forms also in reactions of complex 1046 with dimethyl fumarate and dimethyl maleate in comparable yields, but the reactions are slower and require one week for completion. Presumably, the intermediate that forms in cycloaddition of azide 1046 to the double bond of fumarate undergoes consecutive dehydrogenation catalyzed by ruthenium. Treatment with alkylating agents cleaves the ruthenium–nitrogen bond and releases N-1 alkylated triazoles 1048 (Scheme 173) <2003OM3107>.

5.01.9.2 From other Symmetrically Substituted Acetylenes

Use of unsubstituted acetylene as a substrate in 1,3-dipolar cycloadditions with azides results in 4,5-unsubstituted triazoles. The reactions have to be carried out under pressure. In an example given in Equation (23) showing synthesis of an antibacterial agent, a solution of azide 1049 in dimethoxyethane is transferred to a pressure bomb that is then charged with acetylene and heated at 90°C for 12 h to give triazole derivative 1050 in 74% yield <2003BMC35>.
2-Butyn-1,4-diol 1053 is a common 1,3-dipolarophile used in cycloadditions with azides; however, its reactivity is lower in comparison with esters of acetylenedicarboxylic acid, and the yields of its cycloaddition products are also lower. The advantage of using it in syntheses is direct introduction of two hydroxymethyl groups in positions 4 and 5 of the triazole system that may be useful as anchoring points for assembly of more complex structures. In the first example given in Scheme 174, cycloaddition of alkyne 1053 to 3-azido-4-aminofurazan 1052 is carried out in an ionic liquid at 120°C to give triazole 1051 in 65% yield. In the second example, azide 1054 derived from acetylated glucose reacts with alkyne 1053 in refluxing toluene/pyridine mixture to afford triazole derivative 1055 in 38% yield which is used as an intermediate in synthesis of anticancer agents. Alternatively, the same final product is obtained when more reactive dimethyl acetylenedicarboxylate is used as the polarophile in cycloaddition with the glucose derived azide, and the carbomethoxy groups are consecutively reduced to hydroxymethyls. However, in the second approach, a different protection of the hydroxy groups in glucose is required adding a couple of additional steps to the process. In the third example, the reaction of alkyne 1053 with protected hydroxyethylazide 1056 is carried out by heating a neat mixture of the reagents at 80°C to give triazole 1058 in 65% yield. The same neat approach is used in synthesis of sugar derivative 1059 that is obtained in 85% yield from a reaction of alkyne 1053 with protected sugar azide 1057.
Due to molecular strain, cyclooctyne is a very reactive species. Its reactions with azides proceed rapidly even at room temperature making it a convenient tool for probing structures of unstable azides. Thus, the reaction of cyclooctyne with diazide 1061 carried out in CH₂Cl₂ at room temperature is accomplished within 2 h and provides ditriazolyl derivative 1060 in 76% yield. A similar reaction of cyclooctyne with diazide 1062 leads to ditriazolyl derivative 1063 in 90% yield (Scheme 175) <2005T8904>.

Scheme 175

Scheme 176 represents the opposite situation, with stable phenyl azide used as a probe to trap very reactive and short living alkynes. Thus, diazirine 1064 generates cyclohexyne 1066 that is too reactive to be isolated and characterized. However, when phenyl azide is added to the reaction mixture, it traps species 1066 in situ to give triazole 1068 in 84% yield. Similarly, even more strained norbornyne 1067, generated from diazirine 1065, is trapped by phenyl azide to afford triazole 1069 in 22% yield <2006AGE309>.

Scheme 176

5.01.9.3 From Nonsymmetrical Acetylenes – Problem of Regioisomers

After acetylenedicarboxylates, esters of propiolic acid are the second common group of reagents for 1,3-dipolar cycloaddition with azides. They react fast, and the yields of products are high. However, because the reacting
partners can approach each other in two ways, two regioisomers are formed, with the 4-alkoxycarbonyl derivative usually strongly predominant. The results of an interesting study investigating influence of substituents in arylazides 1070 on a cycloaddition reaction with methyl propiolate are presented in Equation (24). The reactions are carried out in refluxing CCl₄, and the combined yields of products 1071 and 1072 are 91–96%. To explain product distribution between the regioisomers, authors calculate chemical potential differences between the reactants and energies of their transition states<2003CEJ2770>.

Some examples of the reactions between propiolates 1073 and azides leading to triazoles 1074 and 1075 (Equation 25) are collected in Table 11. As can be seen (entries 1 and 2), water as a reaction medium can improve the product yield, but it does not improve the regioselectivity. Microwave assisted synthesis (entry 3) can reduce dramatically the reaction time, but the regioselectivity is poor. Larger aliphatic groups in azides do not affect much the reactions (entries 4–7). An interesting novel approach to the problem of regioselectivity represents entry 8 where cycloaddition between 2-aminophenyl azide and ethyl propiolate is carried out in polymer nanocavities imprinted by regioisomer 1074 used as a template. In comparison with a regular reaction carried out in a solvent (entry 9), entry 8 shows a great improvement.

Table 11 Reactions of propiolates 1073 with azides

| Entry | R¹ | R² | Reaction conditions | Total yield(%) and ratio of 1074:1075 | Reference |
|-------|----|----|---------------------|---------------------------------------|-----------|
| 1     | Et | Ph | EtOH, reflux, 8 h   | 69, 83:17                             | 2004AP156 |
| 2     | Et | Ph | H₂O, 120 °C, 24 h   | 90, 85:15                             | 2003CC2450|
| 3     | Et | PhCH₂ | Toluene, μW, 5 min | 89, 64:36                              | 2003MDV171|
| 4     | Me | AcO(CH₂)₂OCH₂ | Toluene, reflux, 72 h | 66, 92:8                              | 2002JCM264|
| 5     | Me | MeO(CH₂)₂O(CH₂)₂ | Toluene, 65 °C, 48 h | 83, 80:20                             | 2005T4983 |
| 6     | Me | (1S,2S) (MeO)₂P(O)-CH(OH)CH₂ | Toluene, 100 °C, 4 h | 98, 80:20                             | 2004TA1457|
| 7     | Me | (1R,2S) (MeO)₂P(O)-CH(OH)CH₂ | Toluene, 100 °C, 4 h | 100, 86:14                            | 2004TA1457|
| 8     | Et | 2-NH₂-C₆H₄ | Imprinted polymer nanoreactor | 94:6                                  | 2006JA4178|
| 9     | Et | 2-NH₂-C₆H₄ | In solution          | 70:30                                 | 2006JA4178|
In a new approach to the synthesis of 1,2,3-triazoles, polymer supported azide 1076, based on monomethyl ether of polyethylene glycol with molecular weight of 5000 Da, reacts with methyl propiolate in refluxing toluene to give a mixture of two regioisomeric triazoles 1077 and 1078 in 98% yield. However, the ratio of isomer 1077 to 1078, 83:17, is not improved and remains comparable to that observed in simple addition of alkyl azides to methyl propiolate. The advantage of this method is high yield of the products and easy separation by precipitation from a solution in diethyl ether. Deprotection from the polymer is easily accomplished by treatment the mixture with formic acid. Both regioisomers give the same monosubstituted product which is a rapidly equilibrating mixture of tautomers 1079 and 1080 (Scheme 177) <2003TL1133, 2005T4983>.

![Scheme 177](image)

A simple procedure is developed for conversion of aliphatic bromides into methyl 1-alkyl-1,2,3-triazole-4-carboxylates 1083. In the first step, alkyl bromide reacts with polymer-supported azide 1081 to provide a solution of azide 1082 in DMA. The best results are obtained with Merrifield resin. After the first step, the resin is simply filtered off, and the solution of azide 1082 is used directly in the next step for a reaction with methyl propiolate. In this way, the procedure is significantly simplified, and alkyl azides, that may be explosive in a concentrated form, do not require any additional work-up. As can be seen from the examples given in Scheme 178, the yield and purity of products 1083 are high <2003TL2153>.

![Scheme 178](image)

Regioselectivity in reactions of acetylenes with azides depends strongly on electronic and steric factors of both reagents. Usually less electron-deficient and therefore less reactive acetylenes tend to be less regioselective. To compare reactivity of ethyl propiolate and phenylacetylene, reactions of both with tocopheryl azide 1084 are presented in Scheme 179. The reactions are carried out in refluxing toluene for 1–3 d. From the reaction with ethyl propiolate, 1,4-disubstituted triazole 1085 is obtained in 55% isolated yield and 1,5-disubstituted derivative 1086 in 28% yield. For phenylacetylene, the regioselectivity is slightly higher in this reaction, although the isolated yields of products are lower: 52% for derivative 1087 and 18% for isomer 1088. Hydrolysis of derivative 1087 with 10% NaOH in methanol cleaves the bond with tocopherol releasing 4-phenyl-1,2,3-triazole 1089 <2006EJO2081>.

Not always 1,4-regioisomers are predominant in 1,3-cycloadditions of azides to alkynes. Thus, in preparation of new building blocks for glycopeptides, ethynyl C-glucoside 1090 is subjected to a reaction with azide 1091 to give a mixture of triazole derivatives 1092 (32%) and 1093 (48%). For the ethynyl C-galactoside analog of 1090, the ratio between the products is shifted even more towards the 1,5-regioisomer (Scheme 180) <2004OL2929>. 

| Entry | R           | 1083 Yield (%) | 1083 Purity (%) |
|-------|-------------|----------------|-----------------|
| 1     | Me2CHCH2CH2 | 73             | 99              |
| 2     | c-C9H11CH2CH2 | 99            | 95              |
| 3     | Me2C=CH2     | 88             | 84              |
| 4     | MeO2C(CH2)4  | 99             | 85              |
| 5     | PhCH2        | 98             | 97              |
| 6     | PhOCH2CH2    | 100            | 75              |
To facilitate parallel synthesis and purification of triazolyl derivatives of sugars, the products are tagged with an azulene chromophore. For this purpose, guajazulene, an inexpensive azulene, is converted to propargylic ester 1094 and reacted with mannose derivative 1095 to provide a mixture of regioisomers 1096 (44%) and 1097 (32%). Separation of the products can be easily achieved by chromatography because they are visible on the column (Scheme 181) <2006EJO1103>.

To facilitate DNA sequencing, oligonucleotides are tagged with fluorophores. For this purpose, azido-labeled DNA 1099 is subjected to a reaction with alkyne 1098, derived from 6-carboxyfluorescein and propargylamine, to give derivative 1100 (together with its 1,5-regioisomer) in 91% total isolated yield (Equation 26) <2003JOC609>.
Copper Catalysis in Cycloadditions of Alkynes to Azides

Discovery of copper(I) catalysis in 1,3-dipolar cycloadditions of terminal alkynes to azides in 2002 <2002AGE2596, 2002JOC3057> has revolutionized the field. The so-called ‘click chemistry’ has become very popular creating a new ‘gold rush’ resulting in hundreds of scientific publications on the subject. It is not only that the catalyzed reactions proceed faster under mild conditions, but full regioselectivity of the products is achieved as well. Terminal alkynes generate only 1,4-disubstituted triazoles. Some aspects of this new methodology are discussed in a recent review <2007ALD7>.

The fact that only reactions of terminal alkynes with azides are catalyzed by Cu(I) suggests participation of Cu acetylenides in the catalytic process. This conclusion is supported quantum-mechanical calculations of the transition state energies <2005JA210>. Brief outline of the reaction mechanism is given in Scheme 182. Thus, alkyne 1101 reacts with Cu⁺ to give copper(I) acetylenide 1102. In the key step, copper coordinates additionally a molecule of azide to form a complex 1103. Both entities brought to close proximity undergo facile cycloaddition to give triazole organocopper derivative 1104. Final exchange with proton generates neutral triazole 1105 and releases the copper catalyst.
There are many studies comparing thermal and catalytic 1,3-dipolar cycloadditions between alkynes and azides. In an example given in Equation (27), azide 1106 reacts with methyl propiolate in refluxing toluene to give a mixture of regioisomeric triazoles 1107 and 1108 in total yield of 59% and the ratio of 75:25, respectively. The same reaction carried out in water at room temperature with 10 mol% of a CuI catalyst, added as a suspension, results in exclusive formation of regioisomer 1107 with 94% isolated yield (Equation 27) <2005TA4056>.

In one approach to catalytic synthesis of 1,2,3-triazoles, copper(I) is introduced to the reaction mixture as CuI. Compounds 1109–1115 are obtained this way. As can be seen in Table 12, a tertiary amine is often added as a base. The reaction conditions are mild and yields of the products are high. In some cases, the reaction can be carried out in water (compound 1115). For the synthesis of triazole 1116, addition of Cu powder is enough to generate catalytic amounts of Cu(I).
A separate preparation of azides is not always necessary. Scheme 183 illustrates a case where azides are generated in situ from the corresponding halides. The reactions are carried out in ionic liquid–water system. Triazole 1117 is obtained in 94% yield from a reaction carried out at room temperature for 4 h. Butyl derivative 1118 is obtained in 90% yield under similar conditions (<2006TL1545>).

| Product | Reaction conditions | Yield (%) | Purpose of synthesis | Reference |
|---------|---------------------|-----------|----------------------|-----------|
| 1109    | CuI, Pr₂N₂Et, MeCN, rt, 2 h | 96        | Bioactive glycoconjugates | 2006JOC3664 |
| 1110    | CuI, Et₃N, THF, rt, 12 h | 98        | Antiviral nucleosides  | 2006JME1140 |
| 1111    | CuI, Pr₂N₂Et, THF | 97        | Inhibitors of galectins-1 and -3 | 2006CC2379 |
| 1112    | CuI, Pr₂N₂Et, MeCN, rt, 6 d | 80        | Inhibitors of galectin-1 | 2006CAR1353 |
| 1113    | CuI, Pr₂N₂Et, silica gel, microwave | 95        | Triazolyl nucleosides | 2006TL4807 |
| 1114    | CuI, DMSO, 80°C, 1 h | 90        | Novel organotrifluoro-borates | 2006OL2767 |
| 1115    | CuI, H₂O, rt, 20 h | 100       | Synthesis of 1,2,3-triazoles in water | 2006SL957 |
| 1116    | Cu powder, BuOH/H₂O (2:1), 40°C, 24 h | 95        | Chiral 4-(α-aminoalkyl)-1,2,3-triazoles | 2005SL2796 |

A separate preparation of azides is not always necessary. Scheme 183 illustrates a case where azides are generated in situ from the corresponding halides. The reactions are carried out in ionic liquid–water system. Triazole 1117 is obtained in 94% yield from a reaction carried out at room temperature for 4 h. Butyl derivative 1118 is obtained in 90% yield under similar conditions (<2006TL1545>).

Scheme 183

In another approach, Cu(II) salts which are more soluble and easier to handle are used together with reducing agents to generate catalytic amounts of Cu(I) in reacting mixtures. In the first such example, presented in Scheme 184, phenylazide reacts with 1-phenyl-4-propargylpiperazine in isopropanol to give triazole 1119 in 65% yield (<2006BML2955>). The reaction is catalyzed by the CuCl₂–sodium ascorbate system. In the second example, borane complex with propargyl-diphenylphosphine reacts with phenyl azide in a mixture of tert-butanol and water. The reaction is catalyzed by CuSO₄–sodium ascorbate and provides triazole derivative 1120–borane complex in 96% yield. Treatment of the product with DABCO removes borane protection to give free triazole 1120 in 89% yield (<2006OL3227>). In one more example of the reaction catalyzed by copper(II)–ascorbic acid system, propargylamide 1121, derived from protected glucoronic acid, reacts with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide 1122 to give triazole derivative 1123 in 91% yield (Equation 28) (<2006CAR1081>).
To obtain N-unsubstituted triazoles by this method, readily available azidomethyl tert-butyrate 1124 or carbamates 1126 and 1129 are treated with alkynes to provide triazolyl derivatives 1125, 1127, or 1130, respectively. The N-protecting groups can be easily removed by treatment with NaOH to give monosubstituted triazoles 1128. Compound 1125 is very sensitive to bases and loses its protecting group after 10 min treatment with 2.2 molar equivalents of NaOH in methanol–water. Deprotection of derivative 1127 is much slower under these conditions, and deprotection of 1130 requires heating at 85 °C. For base sensitive groups R, use of protection 1125 gives the best results. However, in other cases, more stable protections 1127 and 1130 provide better yield of products 1128 (Scheme 185) <2005SL2847>.

(Trimethylsilyl)acetylene is a versatile reagent in triazole synthesis. Two ways of its application in synthesis of adenosine agonists are depicted in Scheme 186 <2006JME7373>. Thus, iodide 1132 is first treated with sodium azide to be converted to azide 1131. Thermal cycloaddition of (trimethylsilyl)acetylene to azide 1131 gives C-silylated triazole 1134 (and possibly its regioisomer). Regioselectivity in this reaction is not important because the trimethylsilyl group is subsequently removed by treatment with tetrabutylammonium fluoride to give triazol-1-yl derivative 1136 without additional substituents on the ring. Alternatively, iodide 1132 is treated with (trimethylsilyl)acetylene in the presence of CuI and a palladium–phosphine complex as a catalyst to give (trimethylsilyl)ethyl derivative 1133. Removal of the silyl protection by treatment with methanolic ammonia to give compound 1135 followed by regular cycloadditions with benzyl azides, catalyzed by CuSO₄–sodium ascorbate, furnishes triazolyl derivatives 1137 in 73–80% yield.
Scheme 185

Scheme 186
5.01.9.5 Reverse Regioselectivity

1,5-Disubstituted 1,2,3-triazoles are the minor products of thermal cycloaddition of terminal alkynes to azides, and they are completely absent when the reactions are catalyzed by Cu(I). However, under strongly basic conditions, when magnesium or lithium acetylenides are used as the substrates, reverse regioselectivity is observed, and 1,5-disubstituted triazoles are separated as the only products. The proposed mechanism begins with a nucleophilic attack of the alkyne anion on the terminal nitrogen atom of azide 1138. The resulting intermediate anion 1139 undergoes spontaneous cyclization to organomagnesium derivative 1140. Work-up with aqueous ammonium chloride furnishes 1,5-disubstituted triazoles 1141. When instead of work-up, the reaction mixture is treated with an electrophile, 1,4,5-trisubstituted triazoles 1142 are obtained (Scheme 187) <2004OL1237>. The reactions are typically carried out in THF at room temperature. In the case of more reactive azides with electron-deficient groups R¹, the reactions are exothermic and can be accomplished in less than 1 h. Less reactive azides require longer, 1 d, time to completion. The yields are high to quantitative <2004OL1237, 2005OL4907, 2006JOC3928>.

According to the recent finding <2005JA15998>, catalysis by ruthenium complexes used in 1 mol% amounts leads also exclusively to 1,5-disubstituted 1,2,3-triazoles. The reactions, carried out in benzene or dioxane, are relatively fast (typically 2–4 h) and high yielding (80–94%). The method tolerates groups that may not be compatible with organomagnesium reagents. Contrary to the copper(I) catalysis, this method works also well with disubstituted acetylenes to provide 1,4,5-trisubstituted 1,2,3-triazoles. The suggested mechanism <2005JA15998> is presented in Scheme 188. Simultaneous replacement of two ligands in ruthenium catalyst 1143 (e.g., triphenylphosphine) by the azide and alkyne molecules generates active transition state 1144 promoting bond formation between the terminal atoms of the new ligands to give a six-membered ruthenocycle 1145. Finally, formation of the second bond between the reacting partners releases a molecule of triazole 1146 and recycles the catalyst.
5.01.9.6 Other Synthetic Methods for 1,2,3-Triazoles

Heated in methanol for an extended period of time, propargyl azide 1147 experiences a [3,3] sigmatropic shift to allenyl azide 1148 that undergoes rapid cyclization to triazafulvene 1149. Addition of a molecule of methanol converts reactive intermediate 1149 to triazole 1150 that is isolated in 68% yield. In concentrated solutions, two molecules of intermediate 1149 may undergo cycloaddition to form dimer 1151 as a side product (Scheme 189) <2005EJO3704>.

\[
\begin{align*}
\text{C} & \equiv \text{C} \equiv \text{S} \\
\text{N}_3 & \quad \text{[3,3]} \\
\text{MeOH} & \quad \text{reflux, 60 h} \\
\text{1147} & \quad \text{1148} \\
\text{1149} & \quad \text{MeOH} \\
\end{align*}
\]

\[
\text{1147} \quad \text{1148} \quad \text{1149} \quad \text{1150} \\
\]

Scheme 189

Condensation of diazonium salts 1152 with activated nitriles provides hydrazones 1153. Treatment of hydrazones 1153 with hydroxylamine affords amidoximes 1154 in high yield. Upon heating with anhydrous sodium acetate in refluxing DMF, compounds 1154 undergo intramolecular cyclocondensation to provide 5-substituted 4-amino-2-aryl-2H-1,2,3-triazoles 1155 in 75–85% yield (Scheme 190) <2006ARK(xv)53>.

\[
\begin{align*}
\text{N}_2 \text{Cl}^+ & \quad \text{AcONa} \quad \text{EtOH} \\
\text{RCH}_2\text{CN} & \quad \text{H}_2\text{NNOH-HCl} \quad \text{AcONa} \quad \text{EtOH} \\
\text{1152} & \quad \text{1153} & \quad \text{1154} & \quad \text{1155} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{Ph, COPh, benzimidazol-2-yl, or benzothiazol-2-yl} \\
\text{X} = \text{H or Cl} \\
\end{align*}
\]

Scheme 190

Upon heating with tosyl azide and sodium ethoxide in ethanol, amidohydrazides 1156 derived from malonic acid are converted into diazo compounds 1157. Under the reaction conditions, derivatives 1157 undergo cyclization to triazoles 1158. Salts 1158 are isolated in good yield (52% for X=OMe and 82% for X=F). Methylation and benzylaion of products 1158 occurs selectively on the triazole N-3 atom giving rise to mesoionic systems 1159 (Scheme 191) <2002J(P1)211>. Under similar reaction conditions, dihydrazide 1160 is converted to triazole 1163 via intermediate diazo derivative 1161 (Scheme 192) <2004T5367>. Resonance form 1162 and others with definitely positive charge on the diazo nitrogen atoms seem to be responsible for the cyclization.
5.01.10 Ring Syntheses by Transformation of Other Rings

5.01.10.1 1,2,3-2H-Triazoles from 1,2,5-Oxadiazoles

Treatment of 4-acetamido-3-arylazo-1,2,5-oxadiazole 2-oxides (furoxans) 1164 with aqueous NaOH results in formation of 4-acetamido-2-aryl-5-nitro-2H-1,2,3-triazoles 1169. According to the proposed mechanism, the anion derived from the acetamido group attacks N-5 of the furoxan system (form 1165) causing ring opening and formation of another oxadiazole ring (form 1166). Rotation of the large substituent at C-3 in oxadiazole 1166 brings the arylazo group to proximity of the ring (form 1167). In the following step, which is reverse to that shown as form 1165, an intramolecular attack of the arylazo group on oxadiazole 1167 causes ring opening with release of the acetamido group and formation of a new ring (form 1168). Acidification with hydrochloric acid stabilizes the system as triazole derivative 1169. This cascade rearrangement is fast (20 min at room temperature) and provides triazoles 1169 in 54–62% yield (<2001MC230>).

Reaction of amines 1170 with ethoxycarbonyl isocyanate, carried out in ethyl acetate at ~20°C, provides 3-arylazo-4-(3-ethoxycarbonylureido)furoxans 1171 in 82–86% yield. Compounds 1171 are much less reactive than their acetamido analogs 1164. To promote a cascade rearrangement similar to that depicted in Scheme 193, furoxans 1171 have to be heated with potassium tert-butoxide in DMF. The probable reason for reduced reactivity of anion 1172 is the fact that it can exist in several tautomeric and resonance forms rendering the carbonyl oxygen atom less nucleophilic. However, at 100°C, a nucleophilic attack of the oxygen atom on N-5 of the furoxan system results in its ring opening and formation of a new ring of oxadiazole 1173. By rotation of the substituent at C-3, the arylazo group comes to a suitable position for
nucleophilic attack on N-2 resulting in opening of the oxadiazole ring and formation of triazole 1174. During work-up, even under very mild conditions, the ureido group is hydrolyzed and 3-amino-2-aryl-4-nitro-2H-1,2,3-triazole 1175 is obtained. Compounds 1175 are isolated in 45–65% yield (Scheme 194) <2003RCB1829>.

![Scheme 193](image)

Substitution of the 4-nitro group in 3,4-dinitrofuroxan 1176 by ammonia occurs readily, even at low temperature. Subsequent treatment of the obtained amine, product 1177, with t-butylamine results in formation of 4-amino-2-(t-butyl)-5-nitro-1,2,3-triazole 1-oxide 1178. However, there must be some additional side products in the reaction mixture, as the isolated yield of compound 1178 is only 17%. Upon treatment with trifluoroperacetic acid, the t-butyl group is removed. The obtained triazole system can exist in two tautomeric forms, 1179 and 1180; however, the 1-oxide form 1179 is strongly favored (Scheme 195) <2003CHE608>.

![Scheme 194](image)
5.01.10.2 1,2,3-1H-Triazoles from 1,2,3-Thiadiazoles

In a reaction with ortho-phenylenediamine, carried out in DMF at room temperature, ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate 1181 is converted to ethyl 5-[(2-aminophenyl)amino]-1,2,3-thiadiazole-4-carboxylate 1182 with 76% yield. Upon treatment with a mild base, amine 1182 undergoes Dimroth rearrangement to 5-mercapto-1,2,3-triazole 1183 (isolated in 93% yield). In a reaction with second molecule of bromide 1181, mercaptan 1183 is converted to sulfide 1184 (93% yield). Treatment of derivative 1184 with Et$_3$N in refluxing ethanol leads to a nucleophilic attack of the amino group on the thiadiazole ring resulting in elimination of hydrogen sulfide and formation of the second benzotriazole ring. Benzothiadiazepine 1185 obtained this way is isolated in 54% yield. Hydrolysis of the carbethoxy groups in derivative 1185 followed by decarboxylation of the obtained acid furnishes di[1,2,3]triazolo[1,5-a:5',1'-d][3,1,5]benzothiadiazepine 1186 (Scheme 196) <2002J(P1)1574>.

Scheme 195

Scheme 196
Treatment of 1,2,3-thiadiazole derivative 1188 with PCl₅ in refluxing benzene results in formation of the 1,2,3-triazol-5-yl disulfide 1187. The reaction must proceed by Dimroth rearrangement of the thiadiazole ring followed by oxidation of the obtained thiol, possibly with PCl₅. However, when the reaction is carried out in refluxing toluene, triazole derivative 1189 is obtained instead (isolated yield 65%). In this case, apart of Dimroth rearrangement of the starting material, a reaction of PCl₅ with the solvent generates benzyl chloride that benzylates the thiol group. Hydrogen chloride released in this reaction converts the ethoxycarbonyl group into an acid chloride function in product 1189. To prove the structure of derivative 1189, it is converted to ester 1191, which appears to be the same compound as the product obtained by regular Dimroth rearrangement of thiadiazole 1188 catalyzed by Et₃N followed by treatment of intermediate 1190 with benzyl chloride (Scheme 197) <2003CHE126>.

Scheme 197

5.01.10.3 1,2,3-Triazoles from Pyrimidine Derivatives

Diazotization of the 5-aminopyrimidine 1192 gives the diazonium cation 1193. Due to strong electron deficiency at C-2 of the pyrimidine system, species 1193 exists partially as the covalent hydrate 1194. Under acidic conditions, the 1,2-dihydropyrimidine ring of intermediate 1194 can be easily opened. One of such open forms is structure 1195. Among many tautomeric forms of species 1195, there are structures with a single bond between the carbon atoms, which allow free rotation to bring the NH₂ and N₂⁺ groups to close proximity. Nucleophilic intramolecular attack of the amine N atom on the diazonium group leads to triazolyl derivative 1196. In the aqueous hydrochloric acid reaction medium, 1196 is hydrolyzed to (1,2,3-triazol-4-yl)amidine 1197 (Scheme 198) <2003PCJ298>.

As shown in Scheme 199, the 5-aminopyrimidine structure may be also incorporated into a more complex bicyclic system. Thus, diazotization of 3-amino-4-oxo-4H-pyrimido[1,2-b]pyridazines 1198 followed by treatment with 50% aqueous tetrafluoroboric acid results in precipitation of salts 1199. When heated with alcohols, nucleophilic attack on the carbonyl group opens the pyrimidine ring. The obtained species 1200 assume conformation 1201 that is more suitable for bond formation between the opposite charged nitrogen atoms. Alkyl 1-(pyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylates 1202 are obtained in 31–66% yield <2002ARK(viii)143>.
A nucleophilic attack of morpholine on the pyrimidine ring in 1,2,3-triazolo[1,5-α]pyrimidinium salts 1203 leads to unstable intermediates 1204. Spontaneous opening of the pyrimidine ring results in formation of 1,2,3-triazole derivatives 1205 that are isolated in 80–85% yield. A similar nucleophilic attack of the hydroxide anion (from aq. K₂CO₃) on dimethoxy derivative 1203 provides transition species 1206 that opens to intermediate 1207, and finally tautomerizes to ester 1208, isolated in 87% yield (Scheme 200) <2003T4297>.
5.01.10.4 Benzotriazoles and Higher Fused Systems

Treatment of benzimidazole with ozone and NO₂ results in a complex mixture of mono- and di-nitrated benzimidazoles and triazoles. However, nitration of 5-nitrobenzimidazole results in two major products, benzotriazoles and . The mechanism of ring conversion from benzimidazole to benzotriazole is not clear (Equation 29).

Reduction of benzo-1,2,3,4-tetrazine 1,3-diones results in formation of benzotriazoles , which are isolated in high yield (95–98%). Common agents used for reduction of nitro groups, Na₂S₂O₄, SnCl₂, or Fe/HCl, work well here; however, the required reaction conditions are milder allowing a nitro group survive untouched in product . The proposed mechanism starts from a single electron transfer with generation of radical . After protonation leading to intermediate , the N(2)–N(3) bond is cleaved furnishing form . Another protonation and elimination of water leads to diazonium ion . Transfer of a second electron converts radical into anion that is in position to undergo cyclization to N-nitrosobenzotriazole . Under the reaction conditions, intermediate hydrolyzes to benzotriazole . Intermediacy of nitroso derivatives is proven by running the reaction in the presence of morpholine with 4-nitrosomorpholine being isolated as the only side product (Scheme 201).
1,2,3-Triazoles fused with larger aromatic systems can be also obtained this way. Thus, in an example given in Equation (30), $2H$-phenanthro[9,10-$d$]-1,2,3-triazole 1221 is obtained in 84% yield from a reaction of 3-hydroxyphe
nanthro-1,2,4-triazine 1220 with NCS $<2000H(53)203>$. 

5.01.11 Synthesis of Particular Classes of Compounds

5.01.11.1 Derivatives of 1,2,3-Triazole

5.01.11.1.1 N-Substituted 1,2,3-triazoles

Reactions of salts of 1,2,3-triazole with electrophiles provide an easy access to 1,2,3-triazol-N-yl derivatives; although, usually mixtures of N-1 and N-2 substituted triazoles are obtained that have to be separated (see Section 5.01.5). Another simple method for synthesis of such derivatives is addition of 1,3-dipolar cycloaddition of acetylene or (trimethylsilyl)acetylene to alkyl or aryl azides (Section 5.01.9).

5.01.11.1.2 C-Substituted 1,2,3-triazoles

In the presence of copper and palladium catalysts, terminal alkynes 1222 react with trimethylsilyl azide and allyl methyl carbonate to provide 2,4-disubstituted 1,2,3-triazoles 1223 in moderate to good yield. Isomerization of the allyl substituent in the presence of a ruthenium catalyst gives 4-substituted 2-(1-propen-1-yl)-$2H$-1,2,3-triazoles 1224.
Deprotection of N-2 by ozonolysis furnishes triazoles 1225 (Scheme 202) <2003JA7786>. Finding that 1,3-dipolar cycloaddition of alkynes 1222 to trimethylsilyl azide, carried out in DMF/MeOH in the presence of CuI as a catalyst, leads directly to products 1225 with much higher yields provides a significant progress to the synthesis of N-unsubstituted 1,2,3-triazoles <2004EJO3789>.

**Scheme 202**

Scheme 203 provides a methodology for the conversion of aryl bromides onto 4-aryl-1,2,3-triazoles. In the given example, palladium–copper catalyzed substitution of the bromine atom in indole 1226 by trimethylsilylacetylene provides intermediate 1227. Hydrolysis of the trimethylsilyl protecting group releases terminal alkyne 1228, isolated
in 35% yield (two steps). 1,3-Dipolar cycloaddition of alkyne 1228 to trimethylsilyl azide leads to a mixture of regioisomeric triazoles 1229 and 1230, which is directly hydrolyzed by 2 N NaOH to give quantitatively triazole 1231 <2003JME265>.

In a quite different approach, shown in Scheme 204, cycloaddition of nitrile 1232 to trimethylsilyldiazomethane provides silylated triazole 1233, isolated in 75% yield. Treatment with tetrabutylammonium fluoride removes the trimethylsilyl group and simultaneously the silyl protection of the carboxylic group to afford 4-substituted triazole derivative 1234 in 81% yield <2003PEN699>.

Scheme 204

5.01.11.1.3 1,4-Disubstituted 1,2,3-triazoles
1,4-Disubstituted 1,2,3-triazoles are exclusive products of copper catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. A variety of substituents can be introduced in this way. Many examples of such reactions are discussed in Section 5.01.9.

5.01.11.1.4 1,5-Disubstituted 1,2,3-triazoles
1,5-Disubstituted 1,2,3-triazoles are formed in 1,3-dipolar cycloaddition of alkynylmagnesium reagents to azides. This reverse regioselectivity is also achieved in ruthenium-catalyzed cycloadditions. Examples of such reactions can be found in Section 5.01.9.

5.01.11.1.5 2,4-Disubstituted 1,2,3-triazoles
2,4-Disubstituted 1,2,3-triazoles are usually minor components in the product mixtures obtained from reactions of triazole with electrophiles (see Section 5.01.5). The few regioselective syntheses of such compounds include a reaction of aminoacetophenones 1235 with hydrazines. The reaction with methylhydrazine proceeds well without any catalysis, but that with phenylhydrazine requires cupric chloride as a catalyst. It is assumed that hydrazone 1236 that forms in the first step is in a tautomeric equilibrium with its azo form 1237. However, it is not clear how bond formation between the nitrogen atoms and oxidation to the triazole system occurs. 4-Aryltriazoles 1238 are obtained in 50–66% yield (Scheme 205) <2003SC3513>.

Scheme 205
It appears that treatment of phenacyl bromides with methylhydrazine in refluxing acetic acid leads also to 1,4-disubstituted triazoles. Fivefold excess of methylhydrazine is used in these reactions. According to the proposed mechanism, structures methylhydrazine has a double role, as a condensing agent and an oxidant. In the final account, three molecules of methylhydrazine have to be used to produce one molecule of triazole, two molecules of methylamine and one molecule of ammonia. The basic triazole \( \text{X} = \text{Y} = \text{H} \) is separated in 59% yield. The reactions go well with electron-donating substituents (for \( \text{X} = \text{OH} \), the yield is 81%), but electron-withdrawing substituents can lower the yield dramatically (11% for \( \text{X} = \text{NO}_2 \)) (Scheme 206).

\[
\begin{align*}
&\text{X} = \text{H, Me, OMe, OH, Cl, Br, or NO}_2 \\
&\text{Y} = \text{H or Cl}
\end{align*}
\]

Scheme 206

A simple procedure for the synthesis of 4,5-disubstituted 1,2,3-triazoles involves stirring a mixture of nitroethene with trimethylsilyl azide and tetrabutylammonium fluoride at 30 °C for 3 h. No solvent is needed. Triazoline, which forms in the first step of the reaction, eliminates nitrous acid, and the trimethylsilyl group is cleaved off by the fluoride anion to afford triazole. Various aryl and heteroaryl substituents \( R \) are used providing triazoles in 70–90% yield (Scheme 207).

\[
\begin{align*}
&\text{R} = \text{aryl or heteroaryl} \\
&\text{X} = \text{CO}_2\text{Et or CN}
\end{align*}
\]

Scheme 207
The synthesis of 4,5-disubstituted triazoles shown in Scheme 208, carried out on a polymer support with microwave assistance, is based on a similar principle. In the first step, sulfinate 1248 is converted to sulfone 1249. Condensation with aldehydes provides vinyl sulfones 1250. Cyclocondensation of sulfones 1250 with sodium azide generates corresponding triazoline intermediates that eliminate sulfinate 1248 to provide triazoles 1251 in moderate to good yield <2006OL3283>.

Scheme 208

Azides 1253 obtained from propargyl halides or sulphonates 1252 undergo sigmatropic rearrangement to azidoalenes 1254, which subsequently undergo cyclization to triazafulvenes 1255. Under the reaction conditions, species 1255 react with another molecule of sodium azide to furnish triazoles 1256. Products 1256 are isolated in 65–97% yield (Scheme 209) <2005S1514>.

Scheme 209

5.01.11.1.7 Tri-substituted 1,2,3-triazoles
Compounds of this type are the most common products obtained from thermal 1,3-dipolar cycloaddition of disubstituted alkynes to azides. Many examples of such reactions can be found in Section 5.01.9.

5.01.11.2 Derivatives of Benzotriazole
5.01.11.2.1 N-Substituted benzotriazoles
Preparation of benzotriazolyl derivatives substituted at N-1 (or N-2) with variety of functional groups is described in detail in Sections 5.01.5 and 5.01.8. The basic strategy starts from a reaction of benzotriazole with an electrophile. In most cases, the reaction produces a mixture of benzotriazol-1-yl and benzotriazol-2-yl derivatives that is not difficult to separate. Further modification of the substituent in subsequent steps leads to the desired product.
5.01.11.2.2 C-Substituted benzotriazoles

There are only few commercially available C-substituted benzotriazoles. In some situations, the substituents can be readily converted to more complex groups in the desired products. However, in many instances, it is more convenient to design first the right substituent and build the heterocyclic ring later. An example of such approach is shown in Scheme 210. Thus, in a reaction with 2,4-dimethylpyrrole, followed by treatment with DDQ, benzaldehyde 1257 is converted to product 1258 in 26% overall yield. Deprotection of the amino group gives ortho-nitroaniline 1259 that is subsequently reduced to ortho-phenylenediamine 1260 with 95% yield. Complexation of the dipyrrolyl moiety with boron trifluoride gives product 1261 (71% yield), which by treatment with sodium nitrite in 2 N HCl is converted to desired triazole derivative 1262 in 29% yield <2004JA3357>.

\[
\begin{align*}
\text{NH}_2 & \quad \text{NO}_2 \\
\text{CHO} & \quad \text{TFA, cat.} \quad \text{DDQ} \quad \text{HCl aq} \quad \text{MeOH} \quad \text{reflux} \\
1257 & \rightarrow 1258 & \rightarrow 1259
\end{align*}
\]

Scheme 210

5.01.11.2.3 C,N-Disubstituted benzotriazoles

Direct N-substitution of benzotriazole in its reactions with electrophiles is a common practice. However, that strategy usually does not work well when a C-substituted benzotriazole is used as the starting material. Thus, in an example shown in Scheme 211, reaction of 5-methylbenzotriazole 1263 with 2-bromopropionic acid provides a mixture of three products 1264–1266 with the N(2)-substituted benzotriazole derivative 1264 being strongly predominant. Thus, the use of this approach for the synthesis of desired compound 1266, which appears to be the least abundant in the mixture, is very impractical. Synthesis of the benzotriazole system starting from 3,4-dinitrotoluene 1267 is a much better alternative. In the first step, heating of a solution of compound 1267 and sodium 2-aminopropionate in DMSO allows for selective substitution of the nitro group in position meta to provide 2-nitroaniline 1268. Reduction of the remaining nitro group to give diamine 1269 followed by cyclocondensation with nitrous acid furnishes the desired product 1266 <2003FA33>.

A similar approach, synthesis of a selectively substituted benzotriazole from the corresponding ortho-nitroaniline, is depicted in Scheme 212. The process starts from a microwave-assisted substitution of the fluoride atom in 4-fluoro-3-nitrobenzonitrile 1270 by isopropylamine to give ortho-nitroaniline 1271 in 99% yield. Reduction of the nitro group provides ortho-phenylenediamine 1272 that is directly converted to 5-cyano-1-isopropylbenzotriazole 1273, which is isolated in 83% yield <2006JME1227>.

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{NH}_2 & \quad \text{BF}_3\cdot\text{OEt}_2 \quad \text{Pr}_3\text{NH} \quad \text{NaNO}_2 \quad 2\text{N HCl} \\
1260 & \rightarrow 1261 & \rightarrow 1262
\end{align*}
\]
A series of para-substituted ortho-nitroanilines 1274 is converted in this way to benzotriazolyl derivatives 1277, which are of interest as potassium channel activators. In the first step, nitroanilines 1274 are treated with salicyl chloride to provide salicylamides 1275 in 70–95% yield. The nitro group is catalytically reduced, and the obtained intermediates 1276 are subjected to a reaction with nitrous acid, generated in situ from NaNO2, to afford 5-substituted 1-(2-hydroxybenzoyl)-1H-benzotriazoles 1277 in 52–96% yield (Scheme 213).
**Scheme 213**

1. $\text{R} = \text{H, Me, Ph, CF}_3, \text{F, or Cl}$

**Scheme 214**

1. $\text{MeO}_2\text{C}$

2. $\text{AcOH, 20 °C, 0.5 h}$
Three or more substituents

To get a complex set of substituents by direct derivatization of benzotriazole is not feasible. In such situations, it is better to have all the substituents in place first and later construct the heterocyclic ring. High reactivity of anilines and their well-developed chemistry makes them good starting materials. In an example shown in Scheme 215, acetanilide 1288 is nitrated to afford nitro derivative 1289 in 73% yield. Catalytic reduction of the nitro group provides methyl 4-acetamino-3-amino-5-chloro-2-methoxybenzoate 1290 in 96% yield. Nitrosation of compound 1290 in diluted sulfuric acid leads to intermediate 1291, which without separation is heated to be converted to 7-chloro-4-methoxy-1H-benzotriazole-5-carboxylic acid 1292, isolated in 64% yield <2002CPB941>.

Preparation of 4,5,6,7-tetrabromobenzotriazole and its tetrachloro analog by direct bromination or chlorination of benzotriazole is described in Section 5.01.7. However, other tetra-substituted benzotriazoles have to be constructed from a suitably substituted benzene ring. Thus, treatment of pentamethylbenzene 1293 with fuming nitric acid in concentrated sulfuric acid provides 3,4,5,6-tetramethyl-1,2-dinitrobenzene 1294 in 66% yield. Using routine procedures, derivative 1294 is reduced with SnCl2 in aqueous HCl, and the obtained diamine 1295 is subsequently treated with NaNO2 (in aq. HCl) to provide 4,5,6,7-tetramethyl-1H-benzotriazole 1296 (Scheme 216) <2004BMC2617>.

Important Compounds and Applications

Benzotriazole Methodology in Organic Synthesis

The last two decades have witnessed rapid development of organic synthetic methods based on benzotriazole derivatives. Thus, introduction of benzotriazole moiety to organic molecules provides several practical advantages. Among other benefits, a benzotriazolyl substituent activates the reaction center, stabilizes intermediates, increases regio- and stereoselectivity, and simplifies separation and purification of the products. After the desired molecular assembly is constructed, the bond with benzotriazole is cleaved off to provide the final product. A vast variety of
molecular structures is conveniently prepared in this way. The largest section of this chapter (Section 5.01.8) is devoted specifically to this topic. For this reason, benzotriazole itself and a hundred of its basic derivatives that are commercially available now have become important materials in organic synthesis.

### 5.01.12.2 Peptide Coupling Reagents

I-Hydroxybenzotriazole (HOBt) \(\text{1297 <1996CHEC-II(4)1>}\) has become an everyday reagent in many chemistry labs, and the number of reports of its application in organic synthesis is boosted to hundreds per year. Combined with a dehydrating agent and a tertiary amine, HOBt is an excellent auxiliary in preparation of amides (Table 13). The mechanism of its interaction with carboxylic acids is discussed in Section 5.01.8. Some of the dehydrating agents used in the process are also derivatives of HOBt \(\text{1298–1301}\). In some instances, these derivatives, HBTU \(\text{1298 <2002JC1184, 2004NAR623>, TBTU 1299 <2005HCA447, 2005HCA1040, 2005TL6239, 2006OL2851, 2006TL1737> and BOP 1300 <2005JA17894, 2005JOC660, 2006JA3011, 2006OL239, 2006OL511> are used alone without addition of HOBt. Combinations of HOBt with dehydrating agents, especially DIC \(\text{<2005JOC9622, 2005TL7443, 2006JCO150, 2006JME1833, 2006JME2388>, HBTU <2005AGE2534, 2005JOC697, 2005JOC7654, 2005TL4053, 2006TL2671> and BOP <2002BML2855, 2005AGE2887, 2005JOC703> are common reagents in solid-phase synthesis of peptides. Use of HOBt together with DCC \(\text{<2005CEJ6666, 2005JOC5339, 2005JOC3660, 2005TL4377, 2006JME2633, 2006OL531, 2006OL797, 2006SCI1317> or HBTU <2001NN1347, 2006JME2593> in preparation of carboxylic esters is also relatively common. HOBt can likewise promote formation of C–C bonds in coupling of carboxylic acids with cyanoacetates \(\text{<2002BCJ2691> and acetoacetates <2002SL1736>}.\)

In the presence of HBTU, amino acids react with diazomethane to give their higher homologs \(\text{<2003PES230>}.\)

### Table 13 Some of the recent applications of 1-hydroxybenzotriazole in the synthesis of amides

| Example | Character of \(R^1\)COOH | Character of \(R^2\)NH2 | Dehydr. agent | \(R^1\)CONHR2 application | Yield (\%) | Reference |
|---------|------------------------|----------------------|---------------|--------------------------|-----------|----------|
| 1       | Aminoacid              | Aminoacid            | EDC           | Peptide                  | 97        | 2005CC4908 |
| 2       | Aminoacid              | Peptide              | EDC           | Cyclic peptide           | 90        | 2005JOC9626 |
| 3       | Dipeptide              | Amino thioester      | DCC           | Peptide thioacid         | 93        | 2006OL823  |
| 4       | Oxazolidine-COOH       | L-Ser-OMe            | DCC           | Telomerase inhibitor     | 79        | 2006S1299  |
| 5       | Fmoc-Leu-OH            | PS-R-NH2             | TBTU          | Oxazole tripeptide       | 87        | 2006OL2417 |
| 6       | Cyclopentane-carboxylic acid | Methyl glycinate | TBTU          | Peptides                 | 98        | 2005HCA1711 |
| 7       | Aminosugar acid        | Aminosugar           | HBTU          | Oligosaccharide mimic    | 89        | 2005AGE2096 |
| 8       | Arenoxyacetic acid     | Methyl glycinate     | DCC           | Heteroditopic receptors  | 71        | 2006CJC58  |
| 9       | Aminoacid              | Aminosugar           | DCC           | Opioid receptor agonist  | 96        | 2006JME1773 |
| 10      | Aminoacid              | Aminosugar           | EDC           | Antibiotics              | 91        | 2006OL887  |
| 11      | Succinic acid          | Ar-1,3-di-[O(CH2)3]-NH2 | EDC  | Dentronized polymer      | 76        | 2006JAS091 |
| 12      | RCH(Bu')-COOH          | ArCH2NHNH2           | EDC           | HIV protease inhibitor   | 76        | 2006JME1828 |
| 13      | Fmoc-Gly-OH            | R-C(O2Me)-NH2        | DIC           | 6-Spiro-1,4-diazepepe    | 98        | 2005EJO907 |
| 14      | ArCOOCH                | R2R2-NH2             | EDC           | FKBPI2 ligand            | 68        | 2006JME1202 |
| 15      | ArCOOH                 | Morpholine           | EDC           | Growth factor-\(\beta\) inhibitor | 73 | 2006JME2210 |
| 16      | 2-Indole-carboxylic acid | 2,3-Dihydro-indole | EDC           | Antitumor antibiotic     | 96        | 2006JA7136 |

DCC = 1,3-dicyclohexylcarbodiimide, DIC = 1,3-diisopropyl-carbodiimide, EDC = 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide.
5.01.12.3 Biologically Active Derivatives

Due to their easy access and high enzymatic stability, benzotriazole and 1,2,3-triazole systems are frequently used as building blocks in drug design. Among antitumor agents, vorozole (structure 1302) is a high-affinity competitive aromatase inhibitor, designed for inhibiting estrogen synthesis in patients with breast cancer. Benzotriazole derivative 1303 exhibits remarkable activity against leukemia, ovarian, renal, and lung cancers. The structures may be complex, like compound 1304, or simple, like compound 1305, both of them exhibiting anti-inflammatory activities, although based on different principles. Nucleoside analog 1306 inhibits strongly helicase activity of hepatitis C virus, whereas compound 1307 and several of its analogs show strong activity against respiratory syncytial virus (RSV).

Very simple derivatives of benzotriazole with biological activity include 5,6-dimethylbenzotriazole, a very effective agent against cysts of *Acanthamoeba castellanii*, tetrabromobenzotriazole, which provides selective inhibition of protein kinase CK2 and induces apoptosis of Jurkat cells, 1-salicylyl-4-methylbenzotriazole, potassium channel activator and 1-isopropyl-1H-benzotriazole-4-carboxylic acid, a selective agonist of human orphan G-protein-coupled receptor GPR109b.

Several 1,2,3-triazole derivatives have been designed to target G-protein-coupled receptors. Among them are neurokine NK1 antagonists 1308 and 1309, selective A3 adenosine receptor agonist 1310 and highly selective α2 adrenoreceptor antagonists. Other 1,2,3-triazole derivatives are of interest as inhibitors of some key enzymes: acetylcholinesterase, glycogen synthase kinase-3, glycosidase, galectin-1, and α-2,3-sialyltransferase.
There are also 1,2,3-triazoles with antiviral \(<2006\text{BML}2693, \ 2006\text{JME}1140\>\), antibacterial \(<2002\text{BML}2771, \ 2003\text{BMC}35\>\), antithrombotic \(<2004\text{AP}156\>\), or antiplatelet \(<2003\text{BMC}2051\>\) activities. Some triazoles work as potassium channel activators \(<2004\text{FA}397\>\), others as calcium signal transduction inhibitors \(<2002\text{CLC}86\>\). 1,5-Diaryl-\(\Delta^2\)-1,2,3-triazolines are recognized anticonvulsant agents \(<2003\text{CME}2081, \ 2004\text{JLR}31\>\). Among biologically active benzotriazoles are also inactivators of the severe acute respiratory syndrome 3CL protease \(<2006\text{CBO}1261\>\), trichostatin suppressors \(<2003\text{CBO}397\>\), antagonists of the gonadotropin releasing hormone \(<2002\text{BML}827\>\), and nonpeptide inhibitors of protein tyrosine phosphatase 1B \(<2004\text{BML}1043\>\).

### 5.01.12.4 Other Applications

Due to strong complexing affinities to copper and some other ions, benzotriazole and its derivatives have found wide application in anticorrosion formulations. Hundreds of patents covering this subject are registered each year. One of the major applications of such formulations is in electronics that include thiol passivation of copper interconnects during semiconductor manufacturing, grinding composition for polishing of semiconductor devices, corrosion-preventing agents for etching of insulator films in manufacture of semiconductor devices, cleaning solutions for electrohydrodynamic cleaning of semiconductors, components of polymer coatings for silver-plated circuits, and in dispersants for preparation of nickel-coated copper powder for electricity-conducting inks. Benzotriazole is also commonly used as an anticlogging agent in jet inks for forming high-quality images.

Anticorrosion abilities of benzotriazole and its derivatives are also widely utilized in fluids for all kind of machinery. They are important anti-friction–antiwear additives for engine oils, components of antitrust greases for aircraft, biodegradable lubricants for turbines, brake liquids based on polyoxyalkylene synthetic oils, metal corrosion inhibitors in aqueous coolants containing acetic acid and propylene glycol, grease for gas compressors for fuel cell systems, emulsifiable oil for preparation of non-combustible oil–water hydraulic emulsions for coal mining, environment-protecting lubricating oil for refrigerators, antifreeze composition for diesel engines, and lubricating oil compositions for hot rolling aluminium plates. Benzotriazole derivatives can be also found in machine dishwashing detergents containing nonionic surfactants, corrosion inhibitors for thermoplastic polyurethanes in contact with metals, and in anticorrosion polymer coatings for guitar strings.

Due to strong UV absorption, benzotriazole derivatives have found application in cosmetic formulas for skin photoprotection, in cosmetic sunscreen compositions, in multifunctional eyeglass lenses with UV absorbers, in UV protecting films for radiation detectors in personal instant alert dosimeters, in polyester compositions reducing UV light penetration for production of bottles, in UV absorbers for decorative polyolefin sheets with improved weather resistance, in protective coatings containing UV absorbers for microporous sheets, in UV absorbers for plant protecting covers, in photographic emulsion of light-sensitive materials, and as UV absorber for a multilayer golf ball with a translucent cover.

### 5.01.13 Further Developments

Novel applications of benzotriazole methodology in organic synthesis include regiospecific preparation of 1,4,5-trisubstituted pyrazoles \(<2007\text{ARK(i)}9\>\), efficient synthesis of 1,5-disubstituted tetrazoles \(<2007\text{SL}1204\>\),
amidoalkylations of nitroalkanes, nitriles, alkynes, and esters, synthesis of cyano derivatives of N-alkly and N-aryl piperazines, and preparation of polyfunctional acyl azides. N-Acyl derivatives of benzotriazole are used for efficient peptide coupling of sterically hindered aminoacids and 5-amino-1-methyl-1H-[1,2,4]-triazole-3-carboxylic acid, expedient synthesis of N-Z-pyroglytum-aminoacid derivatives, synthesis of (+)-aphanorphine, and as Mosher-Bt reagents.

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Biographical Sketch

Stanislaw Rachwal was born in Jodlowka, Poland, in 1949 and raised in Krakow, Poland. In 1978, he received a PhD in organic chemistry from Jagiellonian University in Krakow and was nominated to a position of an Adjunct Professor at that university in 1980. His main research at that time was focused on chemistry of ferrocenophanes. During a sabbatical leave in 1984, he joined Professor Alan R. Katritzky at the University of Florida to lay a foundation for application of benzotriazole in organic synthesis. He returned to the University of Florida in 1988, where, as a group leader, he pushed forward the research on derivatives of benzotriazole. His collaboration with Professor Katritzky till 1993 resulted in 36 scientific papers on benzotriazole. Since 1993, he has been working in pharmaceutical industry specializing in CNS drugs with the primary focus on heterocyclic compounds.

Alan Katritzky was born in London, UK and educated at St. Catherine’s College, Oxford, of which he became, in 2006, an Honorary Fellow. He was a Founder Fellow of Churchill College, Cambridge, and then founding of Professor/Dean of the School of Chemical Sciences at the University of East Anglia before crossing the Atlantic in 1980 to become Kenan Professor and Director of The Center for Heterocyclic Compounds at the University of Florida. He has researched, published, lectured, and consulted widely in heterocyclic chemistry, synthetic methods, and QSPR. He created the not-for-profit foundation ARKAT and since 2000 has been organizing the annual ‘Florida Heterocyclic and Synthetic Conferences’ (Flohet) and publishes *Archive for Organic Chemistry* (Arkivoc) completely free on the Internet at arkat-usa.org. His honors from 20 countries include 14 honorary doctorates.