Regioselective Synthesis of 1-(2,6-Dichloro-4-Trifluoromethyl-phenyl)-4-Alkyl-1H-[1,2,3]-Triazoles

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Abstract: A new and efficient method for the synthesis of 1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkyl-1H-[1,2,3]-triazoles by the room temperature 1,3-dipolar cycloaddition of (2-azido-1,3-dichloro-5-trifluoromethyl)benzene with terminal alkynes in the presence of Cu (I) salt as catalyst is reported. All the reactions gave 1,4-disubstituted products with high regioselectivity, as no 1,5-disubstituted product was formed. The structures of all the title compounds have been confirmed by elemental analysis, 1H- and 13C-NMR and in addition, the structure of compound 5a was investigated by X-ray crystallography.

Keywords: 1,3-Dipolar cycloaddition, 1,2,3-triazole, internal alkyne, regioselective

Introduction

[1,2,3]-Triazoles have found wide use in pharmaceuticals, agrochemicals, dyes, photographic materials and corrosion inhibition, etc. [1]. For example, there are numerous examples in the literature of the biological activity of triazole compounds, including anti-HIV activity [2], antimicrobial activity
against Gram positive bacteria [3] and selective $\beta_3$ adrenergic receptor agonism [4]. Several methods have been described for the synthesis of [1,2,3]-triazoles. Among them, the most important and useful one is the 1,3-dipolar cycloaddition of azides with alkynes [5]. However, this reaction suffers from some drawbacks, usually needs elevated temperature and also forms a mixture of 1,4 and 1,5 regioisomers when unsymmetrical alkynes are used.

It has been known for some time that fluorine atom can lead to unexpected biological activity results arising due to the special properties of the fluorine atom, such as the highest electronegativity of fluorine and high carbon-fluorine bond energy [6]. As a consequence, trifluoromethyl-containing molecules have seen considerable utilization in pharmaceutical and agrochemical industry [6-8]. For example, heterocyclic compounds containing the (2,6-dichloro-4-trifluoromethyl)phenyl group are important intermediates in synthesis of biologically active compounds used as medicines and agrochemicals [9-11]. We desired to develop a new and convenient method for synthesizing (2,6-dichloro-4-trifluoromethyl)phenyltriazoles with good biological activity [10-11]. Herein, we present a method for the synthesis of (2-azido-1,3-dichloro-5-trifluoromethyl)benzenes 3 and their regiospecific reaction with terminal alkynes in the presence of Cu(I) salt as catalyst, and further studies on the reaction of other fluorine-containing azides with terminal alkynes.

**Results and Discussion**

**Synthesis of the azides**

Azides 3 were synthesized from the appropriate fluorine-containing phenylamine (Scheme 1) [3]. Phenylamine was diazotizated with sodium nitrite, and then the azide derivatives were prepared in more than 90 % yields by the reaction of the diazotizated solution with sodium azide using NaOAc as a stabilizer. The results are summarized in Table 1.

**Scheme 1** Synthesis of azides 3.

![Scheme 1](image)

**Table 1.** The results of the synthesis of azides 3.

| Entry | $R^1/R^2$ | $R^3$ | Product 3 | Yield/% 3 |
|-------|-----------|-------|-----------|-----------|
| 1     | Cl        | CF$_3$ | 3a        | 95        |
| 2     | H         | F      | 3b        | 92        |
| 3     | H         | CF$_3$ | 3c        | 93        |
Synthesis of [1,2,3]-Triazoles

Several different methods have been described for the synthesis of [1,2,3]-triazoles, including the intramolecular cyclization of bishydrazones or mixed hydrazones, miscellaneous oxidations, as well as the 1,3-dipolar cycloaddition of azides to alkynes [1,12,13]. The cycloaddition between azides and alkynes is typically carried out in refluxing toluene, but labile molecules may not survive these conditions. Nevertheless, by using sodium [14], lithium or magnesium [15] salts of the alkyne, lower temperatures can be employed, although often with limited or little success. In a word, these methods are typically difficult to perform, need elevated temperature or, in the case of unsymmetrical alkynes, lead to a mixture of 1,4- and 1,5-regioisomers. Recently, studies on 1,4- versus 1,5-regioselectivity were reported. Sharpless [16] used a Cu(I) salt as a catalyst to promote the reaction of azide with terminal alkynes to give 1,4-substituted products with high regioselectivity. However, Chen has reported that when they used similar conditions as described by Sharpless, after stirring for 20 h at room temperature, the isolated yield of fluoroalkylated [1,2,3]-triazoles in their reactions was very poor [15]. Meldal [17] also regioselectively synthesized 1,4-substituted [1,2,3]-triazoles by 1,3-dipolar reaction of azides with polymer-supported terminal alkynes. The resin-bound copper acetylide was reacted with primary, secondary, and tertiary alkyl azides, aryl azides, and an azido sugar at 25 °C, affording diversely 1,4-substituted 1H-[1,2,3]-triazoles with quantitative conversions and purities ranging from 75 % to 99 %. The mechanism of that reaction may be suitable for other types of reactions, so we used similar conditions as described by Meldal (Scheme 2), and produced a series of 1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkyl-1H-[1,2,3]-triazoles in good yields. No 1,5-disubstituted product was found in these reactions.

Scheme 2 1,3-Dipolar reaction of azide with terminal alkynes.

![Scheme 2](image)

With another two fluorine-containing azides in hand, we started the study on the 1,3-dipolar cycloaddition reaction of other two fluorine-containing azides with 1-ethynylbenzene and hex-1-yne. We also observed that all the reactions were highly regioselective towards 1,4-disubstitution, and no 1,5-disubstituted products were seen. The results are summarized in Table 2.

As proposed by Sharpless [16], the following reaction mechanism is suggested: Cu(I) first is inserted into the terminal alkyne, forming copper(I) acetylide I, then compound I reacts with azide to
form the final product (Scheme 3). Because of the existence of copper(I) acetylide I, the reaction was regiospecific in that only a 1,4-disubstituted 1,2,3-triazole was formed.

**Table 2.** The results of the reactions of azide with terminal alkynes.

| Entry | R¹/R² | R³ | Terminal alkyne(4) | Product (5) | Yield/%(5)* |
|-------|-------|----|-------------------|-------------|-------------|
| 1     | Cl    | CF₃| ![Ph](4a)         | 5a          | 93          |
| 2     | Cl    | CF₃| ![n-Bu](4b)      | 5b          | 91          |
| 3     | Cl    | CF₃| ![SiMe₃](4c)     | 5c          | 88          |
| 4     | Cl    | CF₃| ![OH](4d)       | 5d          | 86          |
| 5     | Cl    | CF₃| ![NEt₂](4e)    | 5e          | 82          |
| 6     | Cl    | CF₃| ![](4f)        | 5f          | 87          |
| 7     | Cl    | CF₃| ![OH](4g)        | 5g          | 85          |
| 8     | Cl    | CF₃| ![O–Bn](4h)  | 5h          | 87          |
| 9     | Cl    | CF₃| ![Br](4i)       | 5i          | 88          |
| 10    | H     | F  | ![Ph](4j)     | 5j          | 83          |
| 11    | H     | F  | ![n-Bu](4k)   | 5k          | 91          |
| 12    | H     | F  | ![n-Bu](4l)   | 5l          | 90          |
| 13    | H     | CF₃| ![Ph](4m)     | 5m          | 92          |
| 14    | H     | CF₃| ![n-Bu](4n)   | 5n          | 90          |

* Isolated yields.
**Scheme 3.** Mechanism of 1,3-dipolar reaction catalyzed with Cu(I) salt.

\[
\begin{align*}
\text{N}_2\text{N}_2\text{N}_2 + \text{CuLn} \rightarrow [\text{CuLn}]^+ \\
\text{R} \equiv \equiv \text{CuLn} \\
\text{R} \equiv \equiv \text{H}
\end{align*}
\]

**X-ray diffraction**

To verify the structural assignment compound 5a was selected as an example for an X-ray diffraction study. The purified product 5a was dissolved in 50% ethanol/acetone (1:1 v/v) and kept at room temperature for 5 days until single crystals of 5a had formed. The structure of 5a assigned on the basis of its X-ray crystal structure (Figure 1 and Table 3) [18].

**Conclusions**

In summary, we have successfully developed a general method for the synthesis of a series of 1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkyl-1H-[1,2,3]-triazoles by the room temperature 1,3-dipolar cycloaddition of (2-azide-1,3-dichloro-5-trifluoromethyl)benzene and other two fluorine-containing azides with terminal alkynes in the presence of Cu (I) salt as catalyst for a short reaction time. All the reactions were performed in highly regioselective with only 1,4-disubstituted and no 1,5-disubstituted product being formed.

**Figure 1.** ORTEP drawing of the compound 5a showing the atom numbering scheme.
Table 3 Crystal data and summary of data collection and structure refinement.

| Compound | C_{15}H_{8}Cl_{2}F_{3}N_{3} |
|----------|-----------------------------|
| Color    | Colorless                   |
| Formula weight | 358.14                     |
| Crystal system | Orthorhombic          |
| Temperature, °K | 25(298K)                 |
| Cell constants |
| a (Å)   | 15.5358(16)                  |
| b (Å)   | 10.4697(11)                   |
| c (Å)   | 9.3675(9)                      |
| α (°)   | 90                           |
| β (°)   | 90                           |
| γ (°)   | 90                           |
| Volume (Å³) | 1523.7(3)                   |
| Formula units | 4                           |
| Calculated density (g/cm³) | 1.561                      |
| F(000)  | 720                          |
| Absorption coefficient, μμ⁻³ | 0.459                      |
| Limiting indices | -9<=h<=18, -12<=k<=12, -11<=l<=10 |
| Reflections collected / unique | 7651 / 2703 [R(int) = 0.0371] |
| Absorption correction | Multi-scan                  |
| Max. and min. transmission | 0.958 and 0.921            |
| Refinement method | Full-matrix least-squares on F² |
| Data / restraints / parameters | 2703 / 35 / 208            |
| Goodness-of-fit on F² | 1.160                      |
| Final R indices | R₁ = 0.0973, wR₂ = 0.2342   |
| Largest diff. peak and hole (e Å⁻³) | 0.678 and -0.372            |

Experimental

General

All melting points were determined on an XT-4A apparatus and are uncorrected. TLC was performed using precoated silica gel GF_{254} (0.25mm), column chromatography was performed using silica gel (200-300 mesh). The \(^1\)H- and \(^1\)C-NMR spectra were measured at 25 °C at 300 and 75 MHz, respectively, on a Bruker Advance 300 spectrometer, using TMS as internal standard. \(J\)-values are given in Hz. The IR spectra were taken on a Bruker Vector 55 spectrometer. Elemental analyses were carried out with an EA 1112 elemental analyzer. All the reagents used were AR grade.

General procedure for the preparation of fluorine-containing azides 3

Phenylamine (7.5 mmol) was dissolved in concentrated HCl (10 mL) and water (10 mL) and then cooled to 0 °C, sodium nitrite (0.62 g, 9.0 mmol) was added and the yellow solution was stirred at 0 °C
for 2 h. A solution of NaN₃ (0.97 g, 15 mmol) and NaOAc (12.3 g, 150 mmol) was added dropwise to the mixture, the mixture was extracted with EtOAc and the combined extracts were washed with brine, and then dried by Na₂SO₄. Removal of solvent gave the products 3a-c as brown oils that were used without further purification.

(2-azido-1,3-dichloro-5-trifluoromethyl) benzene (3a). ¹H-NMR (CDCl₃) δ: 7.57 (s, 2H, Ar-H); ¹³C-NMR (CDCl₃) δ: 136.1, 133.8 (q, J = 33.8 Hz), 129.5, 125.6, 123.2 (q, J = 271.6 Hz); IR (film, cm⁻¹) ν: 3055 (ArH), 2115 (N₃).

2-azido-5-fluorobenzene (3b). ¹H-NMR (CDCl₃) δ: 7.79 (d, J = 7.5 Hz, 2H, Ar-H), 7.67 (d, J = 7.5 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃) δ: 135.3, 129.1 (q, J = 8.5 Hz), 126.3, 116.3 (q, J = 21.7 Hz); IR (film, cm⁻¹) ν: 3050 (ArH), 2114 (N₃).

(2-azido-5-trifluoromethyl) benzene (3c). ¹H-NMR (CDCl₃) δ: 7.65 (d, J = 8.6 Hz, 2H, Ar-H), 7.59 (d, J = 8.6 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃) δ: 135.9, 133.6 (q, J = 34.7 Hz), 126.5, 125.1, 123.0 (q, J = 272.4 Hz); IR (film, cm⁻¹) ν: 3049 (ArH), 2115 (N₃).

General procedure for the preparation of 1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkyl-1H-[1,2,3]-triazoles 5

The terminal alkyne (1 mmol) was added to a stirred solution of DIPEA (25 mmol), CuI (1 mmol), and RN₃ (1 mmol) and reacted for 16 h at 25 °C. Then, the volatile substances were removed under reduced pressure. The residue was subjected to a chromatography on a column of silica gel, eluting with petroleum ether and ethyl acetate, solution was removed under reduced pressure, giving compounds 5a–n as solids.

1-((2,6-Dichloro-4-trifluoromethyl) phenyl)-4-phenyl-1H-[1,2,3]-triazole (5a). White solid; yield: 93%; M.p. 160-161 °C (lit. [10] 158.2-158.6 °C); ¹H-NMR (CDCl₃) δ: 8.01 (s, 1H, triazole H), 7.96 (d, J = 9.6 Hz, 2H, Ar-H), 7.82 (s, 2H, Ar-H), 7.41-7.52 (m, 3H, Ar-H); ¹³C-NMR (CDCl₃) δ: 147.8, 135.9, 134.7, 133.6 (q, J = 34.5 Hz), 129.4, 128.8, 128.5, 125.8, 121.8 (q, J = 272.2 Hz), 121.2, 119.9; IR (KBr, cm⁻¹) ν: 3090, 1596 (ArH); Anal. Calcd. (%) for C₁₅H₈Cl₂F₃N₃: C, 50.30; H, 2.25; N, 11.73. Found: C, 50.40; H, 2.17; N, 11.82.

4-Butyl-1-((2,6-dichloro-4-trifluoromethyl) phenyl)-1H-[1,2,3]-triazole (5b). White solid; yield: 91%; M.p. 51-52 °C (lit. [10] 48.4-49.9 °C); ¹H-NMR (CDCl₃) δ: 7.75 (s, 2H, Ar-H), 7.50 (s, 1H, triazole H), 2.82 (t, J = 7.5 Hz, 2H, -CH₂CH₂CH₂CH₂CH₃), 1.70-1.76 (m, 2H, -CH₂CH₂CH₂CH₂CH₂CH₃), 1.37-1.44 (m, 2H, -CH₂CH₂CH₂CH₂CH₃), 0.94 (t, J=7.2Hz, 3H, -CH₃); ¹³C-NMR (CDCl₃) δ: 148.4, 136.2, 134.7, 133.6 (q, J = 34.3 Hz), 125.6, 122.3, 121.8 (q, J = 272.1 Hz), 31.0, 24.9, 21.9, 13.5; IR (KBr, cm⁻¹) ν: 3077 (ArH), 2963, 2930 (CH₃), 2863 (CH₂); Anal. Calcd. (%) for C₁₅H₁₃Cl₂F₃N₃: C, 46.17; H, 3.58; N, 12.43. Found: C, 46.20; H, 3.53; N, 12.46.
1-((2,6-Dichloro-4-trifluoromethyl) phenyl)-4-trimethylsilanyl-1H-[1,2,3]-triazole (5e). White solid; yield: 88%; M.p. 131-132 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 7.79 (s, 2H, Ar-H), 7.73 (s, 1H, triazole H), 0.42 (s, 9H, -CH$_3$); $^{13}$C-NMR (CDCl$_3$) $\delta$: 146.7, 136.0, 134.7, 133.6 (q, J = 34.2 Hz), 130.4, 125.7, 121.8 (q, J = 272.6 Hz), -1.35; IR (KBr, cm$^{-1}$) v: 3111(ArH), 2962 (CH$_3$); Anal. Calcd. (%) for C$_{12}$H$_{12}$Cl$_2$F$_3$N$_3$Si: C, 40.69; H, 3.41; N, 11.86. Found: C, 40.61; H, 3.51; N, 11.91.

2-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-1H-[1,2,3]-triazole-4-yl]-propan-2-ol (5d). White solid; yield: 86%; M.p. 83-85 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 7.75 (s, 2H, Ar-H), 7.70 (s, 1H, triazole H), 3.32 (br, 1H, O-H), 1.70 (s, 6H, -CH$_3$); $^{13}$C-NMR (CDCl$_3$) $\delta$: 155.8, 136.0, 134.7, 133.6 (q, J = 34.5 Hz), 130.5, 125.7, 121.8 (q, J = 271.6 Hz), 68.4, 30.2; IR (KBr, cm$^{-1}$) v: 3370 (OH), 3115 (ArH), 2958 (CH$_3$); Anal. Calcd. (%) for C$_{12}$H$_{10}$Cl$_2$F$_3$N$_3$O: C, 42.38; H, 2.96; N, 12.35. Found: C, 42.41; H, 2.88; N, 12.46.

1-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-1H-[1,2,3]-triazole-4-ylmethyl]-diethyl-amine (5e). Light reddish solid; yield: 82%; M.p. 90-92 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 7.76 (s, 2H, Ar-H), 7.65 (s, 1H, triazole H), 3.93 (s, 2H, -CH$_2$-), 2.57 (q, J = 6.9 Hz, 4H, -CH$_2$CH$_3$), 1.10 (t, J = 6.9 Hz, 6H, -CH$_2$CH$_3$); $^{13}$C-NMR (CDCl$_3$) $\delta$: 145.4, 135.9, 134.7, 133.6 (q, J = 334.5 Hz), 125.8, 124.2, 121.8 (q, J = 272.0 Hz), 47.2, 46.8, 11.9; IR (KBr, cm$^{-1}$) v: 3112 (ArH), 2961 (CH$_3$), 2866 (CH$_2$); Anal. Calcd. (%) for C$_{14}$H$_{12}$Cl$_2$F$_3$N$_4$: C, 45.79; H, 4.12; N, 15.26. Found: C, 45.69; H, 4.20; N, 15.32.

4-(1-Cyclohexenyl)-1-((2,6-dichloro-4-trifluoromethyl) phenyl)-1H-[1,2,3]-triazole (5f). Light yellow solid; yield: 87%; M.p. 109-111 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 7.77 (s, 2H, Ar-H), 7.65 (s, 1H, triazole H), 6.68-6.71 (m, 1H, =CH), 2.42-2.47 (m, 2H), 2.23-2.27 (m, 2H), 1.68-1.82 (m, 4H); $^{13}$C-NMR (CDCl$_3$) $\delta$: 149.4, 136.1, 134.7, 133.6 (q, J = 34.6 Hz), 126.3, 126.1, 125.7, 121.8 (q, J = 272.2 Hz), 119.7, 26.1, 25.4, 22.2, 21.9; IR (KBr, cm$^{-1}$) v: 3135 (OH), 3016 (=CH), 2836 (CH$_2$), 1635 (C=C); Anal. Calcd. (%) for C$_{15}$H$_{12}$Cl$_2$F$_3$N$_3$: C, 49.74; H, 3.34; N, 11.60. Found: C, 49.83; H, 3.27; N, 11.71.

4-Benzylxomethyl-1-((2,6-dichloro-4-trifluoromethyl) phenyl)-1H-[1,2,3]-triazole (5g). White solid; yield: 88%; M.p. 129-130 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 7.80 (s, 2H, Ar-H), 7.77 (s, 1H, triazole H), 4.92 (d, J = 5.7 Hz, 2H, -CH$_2$), 4.06 (br, 1H, O-H); $^{13}$C-NMR (CDCl$_3$) $\delta$: 148.0, 136.0, 134.1, 133.8 (q, J = 34.6 Hz), 125.8, 123.7, 121.8 (q, J = 272.2 Hz), 55.9; IR (KBr, cm$^{-1}$) v: 3370 (OH), 3114 (ArH), 2825 (CH$_2$); Anal. Calcd. (%) for C$_{13}$H$_{14}$Cl$_2$F$_3$N$_3$: C, 47.39; H, 3.71; N, 11.05. Found: C, 47.27; H, 3.83; N, 11.00.

4-Benzylxomethyl-1-((2,6-dichloro-4-trifluoromethyl) phenyl)-1H-[1,2,3]-triazole (5i). White solid; yield: 88%; M.p. 72-73 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 7.80 (s, 2H, Ar-H), 7.77 (s, 1H, triazole H), 7.38-7.40
4-Bromomethyl-1-((2,6-dichloro-4-trifluoromethyl)phenyl)-1H-[1,2,3]-triazole (5j). White solid. yield: 83%; M.p. 135-137 °C; ¹H-NMR (CDCl₃) δ: 7.81 (s, 2H, J = 8.0 Hz, Ar-H), 7.77 (d, 2H, Ar-H), 7.47-7.52 (m, 4H, Ar-H), 7.25-7.29 (m, 2H, Ar-H); ¹³C-NMR (CDCl₃) δ: 147.8, 137.3, 134.7, 133.6 (q, J = 8.6 Hz), 129.6, 129.2, 127.9, 125.8, 121.2, 116.2 (q, J = 21.7 Hz); IR (KBr, cm⁻¹) v: 3111, 1596 (ArH); Anal. Calcd. (%) for C₁₀H₅BrCl₂F₃N₃: C, 32.03; H, 1.34; N, 11.21. Found: C, 32.16; H, 1.25; N, 11.24.

4-Butyl-1-(4-fluorophenyl)-1H-[1,2,3]-triazole (5l). White solid. yield: 90%; M.p. 54-55 °C; ¹H-NMR (CDCl₃) δ: 7.89 (d, J = 8.5 Hz, 2H, Ar-H), 7.76 (d, J = 8.5 Hz, 2H, Ar-H), 7.75 (s, 1H, triazole H), 2.82 (t, J=7.5Hz, 2H, -CH₂CH₂CH₂CH₃), 1.70-1.75 (m, 2H, -CH₂CH₂CH₂CH₃), 1.37-1.44 (m, 2H, -CH₂CH₂CH₂CH₃), 0.89 (t, J=7.2Hz, 3H, -CH₂CH₂CH₂CH₃); ¹³C-NMR (CDCl₃) δ: 147.4, 136.2, 134.5, 133.5 (q, J = 34.4 Hz), 2.82 (t, J=7.5Hz, 2H, -CH₂CH₂CH₂CH₃), 1.70-1.75 (m, 2H, -CH₂CH₂CH₂CH₃), 1.37-1.44 (m, 2H, -CH₂CH₂CH₂CH₃), 0.94 (t, J=7.2Hz, 3H, -CH₂CH₂CH₂CH₃); IR (KBr, cm⁻¹) v: 3079 (ArH), 2966, 2926 (CH₃), 2870 (CH₂); Anal. Calcd. (%) for C₁₃H₁₄F₃N₃: C, 57.99; H, 5.24; N, 15.61. Found: C, 56.81; H, 5.34; N, 15.80.

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18. CCDC 668922 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk

*Sample Availability*: Samples of the compounds *5a-n* are available from the authors.

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