Alkoxyallenes – Building Blocks in Organic Synthesis

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This review describes the preparation of alkoxyallenes and their reactions with organometallic reagents, nucleophilic and electrophilic compounds. Cycloaddition reactions of alkoxyallenes as 2π-components with electron-poor heterocycles lead to a variety of six-membered N,O-heterocycles (1,2-oxazines), tetrahydropyrans, and tetrahydropyridines, respectively. Syntheses of natural products or biologically interesting compounds by means of allyl ethers as key intermediates are also reported.

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1. Introduction

In the past two decades, synthesis and use of allene derivatives have been rapidly expanded in preparative organic chemistry.1–3 Beside acceptor-substituted allenes, electron-rich allenes, in particular methoxyallene, are versatile key building blocks for several natural products or related compounds. This review reports on recent synthetic applications of alkoxyallenes and their derivatives.

Methoxyallene (3), the unsubstituted parent compound, is easily accessible by a two-step reaction from 1-propargyl alcohol 1 which is O-methylated with dimethyl sulfate to provide 3-methoxy-1-propyne (2)4 (eq 1) followed by the isomerization of 2 with potassium tert-butoxide to form 3 in high yield (eq 2).5,6 Further alkoxyallenes, e.g. 4–7, are also accessible by this route.

Methoxyallene (3); Typical Procedure:
Finely divided KOBu-t (9.10 g, 81 mmol) was added to 3-methoxy-1-propyne (2; 56.4 g, 0.81 mol) under N2. After 3 h at reflux temperature (52–55°C) the condenser is replaced with a distillation head and condenser to afford 51.3 g (91%) of 3, bp 51–52°C.

Synthesis of substituted alkoxyallenes is possible by conversion of 2-alkynyl ethers into 1-alkylated allenyl ethers.7,8 A typical example is given by the metalation of alkyne 8 with butyllithium in tetrahydrofuran/hexane as solvent, followed by alkylation with propyl bromide to form allene derivative 9 (eq 3). It is frequently essential to perform the alkylation with hexamethylphosphoric triamide (HMPA) as co-solvent and to add potassium tert-butoxide.9 Without these additives the alkylation provides regioisomeric 3-substituted allenic ethers (see 10 to 11 in eq 4).8,10

Further convenient methods to produce alkoxyallenes are described by Hoffmann,11 Vermeer,12 Reich,13 Bestmann
and Saalfrank\textsuperscript{14} (e.g., 13 and 15 in eqs 5, 6). The synthesis of preparative useful push-pull substituted allenenes are performed by Saalfrank and co-workers (e.g., 17 from 16 in eq 7).\textsuperscript{15,16}

This highly flexible route allows the use of carbonyl compounds as electrophiles providing hydroxyalkylated allenenes 19 in good yields (eq 9). Examples of such C-1-substituted methoxyallenes are given in Table 1.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Product & R\textsubscript{1} & R\textsubscript{2} & Yield (\%) & Ref. \\
\hline
19\textsubscript{a} & Me & H & 80 & 18 \\
19\textsubscript{b} & Et & H & 80 & 18 \\
19\textsubscript{c} & Ph & H & 87 & 19 \\
19\textsubscript{d} & PhMeCH & H & 84\textsuperscript{a} & 20 \\
19\textsubscript{e} & PhCH=CH & H & 42 & 21 \\
19\textsubscript{f} & Me & Me & 82 & 18 \\
19\textsubscript{g} & Et & Et & 84 & 18 \\
19\textsubscript{h} & Ph & Ph & 67 & 19 \\
19\textsubscript{i} & -(CH\textsubscript{3})\textsubscript{3} & & 88 & 18 \\
\hline
\end{tabular}
\caption{Synthesis of C-1-Substituted Methoxyallenes 19 from 3 and Different Carbonyl Compounds}
\end{table}

\textsuperscript{a} anti/syn = 86:14.

2. Deprotonation of Alkoxylallenes and Reactions with Electrophiles

A most important aspect for applications of alkoxylallenes is the relatively high acidity of the hydrogen atom at C-1. Methoxyallene (3) can smoothly be deprotonated at this position by butyllithium in diethyl ether\textsuperscript{17} (eq 8). The resulting lithio compound 18 can react with different electrophiles leading to C-1-substituted derivatives of 3.

\begin{equation}
\text{OMe} \quad \text{BuLi} \quad -30^\circ \text{C}, 10 \text{ min} \quad \rightarrow \quad \text{OMe} \quad \text{Li}
\end{equation}

2-Methoxy-1-phenyl-2,3-butanedione (19\textsubscript{c});\textsuperscript{19} Typical Procedure:

A solution of 3 (3.50 g, 50 mmol) in dry Et\textsubscript{2}O (100 mL) was treated at \(-40^\circ\text{C}\) with BuLi (2.5 M in hexane, 22 mL, 55 mmol) under N\textsubscript{2} (deprotonation time: 5 min). Then, benzaldehyde (5.83 g, 55 mmol) dissolved in dry Et\textsubscript{2}O (55 mL) was added within 5 min. The mixture was stirred for 0.5 h at \(-40^\circ\text{C}\) and quenched with H\textsubscript{2}O (100 mL). Warm up to r.t. was followed by extraction with Et\textsubscript{2}O (3 \times 100 mL), drying (Na\textsubscript{2}SO\textsubscript{4}), concentration in vacuo and distillation leading to the product; yield: 7.62 g (87\%); bp \(80^\circ\text{C}/0.5\text{Torr}\).

Experiments with chiral aldehydes, e.g., 2-phenylpropanal, and 18 demonstrate that this reagent displays good diastereofacial selection. Optically active, protected \(\alpha\)-amino aldehydes 20 add to carbamion 18 to provide the allenylale amino alcohols 21 with very good diastereoselec-

\begin{figure}

\textit{Bibliographic Sketch}

Reinhold Zimmer was born in Wiesbaden, Germany, in 1959. He studied chemistry at the Technische Hochschule Darmstadt and received his doctoral degree in 1990 with Prof. Dr. H.-U. Reißig. In 1992, he moved to the Sandoz Forschungsinstitut Wien/Austria, where he started as a “Karl-Landsteiner-Stipendiat”.

\end{figure}
tivity.20 The anti-stereochemistry in the major diastereomer of 21 is established by X-ray analysis of a furanone derivative obtained from 21b (see section 5).22

After deprotonation of 3 with butyllithium in tetrahydrofuran or a mixture of diethyl ether and tetrahydrofuran as solvent, 18 can also be alkylated by alkyl halides (eq 11, Table 2). The preparation of methylated allene 22, however, has to be performed in tetrahydrofuran,23 although complete removal of the solvent could not be achieved; alkylation of 18 with methyl iodide in diethyl ether as solvent was not successful.23,24

| R  | anti/syn | R  | anti/syn |
|----|---------|----|---------|
| H  | —       | c  | 89:11   |
| Me | 95:5    | d  | 80:20   |

Table 2. Alkylation of Methoxayllene (3) (eq 11)

| R—X | Product | R  | Yield (%) | Ref. |
|-----|---------|----|-----------|------|
| MeI | 22      | Me | 6         | 23   |
| PrBr | 23     | Pr | 47        | 17   |
| BuBr | 24     | Bu | 67        | 17   |
| BnBr | 25     | Bn | 64        | 17   |
| H₂C=CHCH₂Br* | 26 | H₂C=CHCH₂ | 32   | 24   |

* THF as solvent.
* THF/ Et₂O (1:1) as solvent.
* No yield given.

The use of alkali amide in liquid ammonia as base for the deprotonation of alkoxayllenes followed by alkylation, leads to a mixture of C-1- and C-3-substituted allenes 27 and 28, respectively, in low yields and moderate regioselectivities (eq 12).17

The lithiated species 18 and 34 also react with several other electrophiles such as dimethyl disulfide, trimethylstannyl chloride,4 trimethylsilyl chloride,8,10,13,25 ethylene oxide,26 and iodine,27 respectively, to provide the products 29–33 and 35 (Scheme 1). In 1980 Suzuki

Reactions of lithiated allene 18 with several iron carbonyl compounds are also known.29
3. Reactions with Organometallic Compounds

Quite a number of reports deal with the behavior of alkoxyallenes towards organometallic reagents. The most important organometallic species are copper (cuprate),[12,27,30–35] zinc,[35,36] tin,[37,39] and titanium compounds.[39]

3.1. Cuprates and Copper Compounds

In the mid-seventies Vermeer described a convenient synthesis of 1-alkynes 41 by reaction of methoxyallene (3) and Grignard reagents in the presence of catalytic amounts of copper(I) halides in diethyl ether (eq 13). A heterocuprate [RCuX]MgX is probably the active species in this $S_N2$-type substitution.

Formation of enol ethers is observed by treatment of 3 with an excess of preformed homocuprates R₂CuMgX or heterocuprates [RCuBr]MgX in tetrahydrofuran, leading to an E/Z-mixture of adducts 44 (Scheme 3). The formation of a copper(III) species 42 has been proposed, which is followed by a 1,3-shift of the R¹ group to the terminal unsubstituted sp²-C to afford the cuprate 43. Hydrolysis of this intermediate gives the isolated enol ethers 44.

Recently, Vermeer and Kleijn described the preparation of highly functionalized alllysilanes such as 47 and 49.[32] [(Trimethylsilyl)methyl]cupper(I) (46) is a recommended reagent for the conversion of 4,5-epoxy-1,2-pentadiene 45 and 2,3-butenediyl methanesulfinate 48 into the corresponding dienes 47 and 49 (Scheme 4). Compound 45 is prepared by treatment of 18 with 1-chloro-2-propanone followed by epoxidation under basic conditions. Then, the initially formed alcohol is converted into the O-silylated derivative 47; the configuration of the tetrasubstituted C=C double bond in 47 has not been determined. In both reactions only one regioisomer could be detected. Similar transformations with alkyl(aryl)cuprates as nucleophiles were reported earlier by the same group.[33]
copper or cuprate derivatives may react further with various electrophiles leading to polysubstituted enol ethers.\textsuperscript{34}

### 3.2. Zinc, Tin, and Titanium Compounds

Allyl-substituted allenes are obtained from alkoxyallenes by a straightforward procedure.\textsuperscript{35} Addition of allylzinc bromide to 3-methoxy-1,2-decadiene (53) provides intermediate 54. After $\beta$-elimination of zinc alkoxide allyllene 55 is produced (Scheme 6). When this transformation is applied to 1-ethoxy-4,4-dimethyl-1,2-pentadiene (15), the corresponding allyl compound 56 is formed together with the ether 57 as a 1:1 mixture.\textsuperscript{35}

```latex
\begin{align*}
\text{MeO} & \quad \text{OEt} \\
53 & \xrightarrow{1. \text{ZnBr}} 54 & \xrightarrow{2. \text{H}_2\text{O}} 55 \\
\text{OEt} & \quad \text{OEt} \\
56 & \quad \xrightarrow{1. \text{H}_2\text{O}} 57 \\
\end{align*}
```

**Scheme 6**

An access to functionalized allyl- or vinylstannanes is given by the free-radical initiated hydrostannation of methoxyallene (3).\textsuperscript{36,41} Reaction of 3 with trimethylstannane affords a mixture of tin compounds 58 and 59 (R = Me).\textsuperscript{38} On the other hand, Koreeda et al.\textsuperscript{41} obtained an $E/Z$-mixture of 60 (R = Bu) in a 1:1 ratio by hydrostannation of 3 employing tributylstannane (eq 14, Table 3). Photochemical hydrostannation of 3 is also possible.\textsuperscript{38}

```latex
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
3 & \xrightarrow{R_3\text{SnH}} 58 \quad \text{R} = \text{Me} \\
& \quad \text{OEt} \\
58 & \xrightarrow{R_3\text{SnH}} 59 \quad \text{R} = \text{Me} \\
& \quad \text{OEt} \\
59 & \xrightarrow{R_3\text{SnH}} 60 \quad \text{R} = \text{Bu} \\
\end{align*}
```

**Table 3. Reaction of 3 with Trialkylstannanes (eq 14)**

| $R_3\text{SnH}$ Conditions | Yield of 58/59 (%) | Ratio (E)-58 (Z)-58 (E)-59 (Z)-59 |
|-----------------------------|-------------------|----------------------------------|
| Me AIBN (cat.), 70 °C       | 70                | 10:46:37:7:38                    |
| Me hv                       | 66                | 33:36:22:9:38                    |
| Me Pd(PPh$_3$_4) (cat.)     | 75                | 12:0:12:76:38                   |
| Bu AIBN, 80 °C              | 60*               | 0:0:50:50:41                    |

* Product 60.

Synthesis of functionalized allylstannanes is also achieved by palladium-catalyzed hydrostannation of substituted alkoxyallenes.\textsuperscript{37} The $E/Z$-ratios of products 60 and 62–66 are moderate to excellent (Scheme 7).

```latex
\begin{align*}
\text{R}^1 & \quad \text{Me, Et} \\
\text{OEt} & \quad \xrightarrow{E/Z = 60, 62-65} \text{R}^2 \\
\text{SnBu$_3$} & \quad \xrightarrow{E/Z = 66 (65:55)} \text{OEt} \\
\end{align*}
```

**Scheme 7**

A titanium substituted methoxyallene 67 is generated by sequential deprotonation of 22 with butyllithium and transmetalation with titanium(IV) isopropoxide. Intermediate 67 reacts with aldehyde 68 leading to an isomeric mixture of 69. Hoffmann, Hoppe and co-workers have employed this reaction for proving the configurational stability of the titanium species 67.\textsuperscript{39}

```
\begin{align*}
\text{MeO} & \quad \xrightarrow{1. \text{Bu Li, } -30^\circ \text{C}} \text{MeO} \\
\text{22} & \quad \xrightarrow{2. \text{Ti(OPr$_3$)$_3$, } -78^\circ \text{C}} \text{67} \\
\end{align*}
```

**Scheme 8**

### 4. Acidic Hydrolysis of Alkoxyallenes

The preparatively very useful $\alpha,\beta$-unsaturated carbonyl compounds,\textsuperscript{42,43} e.g. 70 in equation 15, are easily accessible by acidic hydrolysis of alkoxyallenes with trifluoroacetic acid, dilute sulfuric acid, or dilute hydrochloric acid.\textsuperscript{7,10,11,13,18,23,25,43–47} Typical examples are given in Table 4. A comprehensive review dealing with synthesis and reactions of acylsilanes (analogue eq 15, X = SiMe$_3$) has recently been published by Ricci and Degl'Innocenti.\textsuperscript{43}

```
\begin{align*}
\text{MeO} & \quad \xrightarrow{H^+} \text{MeO} \\
\end{align*}
```

**Table 4**
Table 4. Acidic Hydrolysis of substituted Alkoxynallenes (eq 15)

| R¹ | R² | R³ | X   | Product Method* Yield (%) |
|----|----|----|-----|---------------------------|------------------------|
| H  | H  | Me | ClOHMe₂ | 70a A 88                  |
| H  | H  | Me | CH(OH)Et | 70b A 85                 |
| H  | H  | Me | CH(OH)Ph | 70c A 76                 |
| Bu | H  | Me | SiMe₃ | 70d B 76                 |
| Bu | H  | Me | H   | 70e C 92                 |
| Et | H  | Me | Bu   | 70f A 91                 |
| H  | CH(OEt)Me | SnMe₂ | 70g D 91 |

* A: 5% aq H₂SO₄, 0°C, 1–2 h. B: CF₃CO₂H, r.t., 12 h. C: 1 Bu₄NF, r.t., 12 h. D: 2 N aq HCl. E: 2 N aq H₂SO₄, r.t., 12 h.

1-Hydroxy-1-phenyl-3-buten-2-one (70b): Typical Procedure

To 5% aq H₂SO₄ (10 mL) was added dropwise the allene 19 (0.7 g, 4 mmol) at 0°C and the mixture was stirred for 1.5 h. After warming up to r.t., the solution was saturated with solid NaCl, then extracted with Et₂O (5 × 5 mL). The combined extracts were washed with brine and dried (Na₂SO₄). After evaporation of the solvent a yellow oil was obtained which was purified by Kugelrohr distillation (80°C/0.01 Torr) leading to pure 70b; yield: 0.53 g, 76%.48

Overman et al. described the preparation of octahydropyrindolizine derivatives by application of acidic hydrolysis of hydroxyalkylated methoxynallenes. As outlined in Scheme 9, treatment of 72 with p-toluenesulfonic acid and hydrochloric acid gives 74.47

![Scheme 9](image)

In 1990, it was reported that allenyl acetals, e.g. 75, are successfully rearranged by Lewis acid catalysis in dichloromethane at -78°C to give α,β-unsaturated carbonyl compounds 76 in good yields (eq 16).49

![Scheme 10](image)

3-Alkoxynhydrofurans 83a–d yield the dihydro-3(2H)-furanes 84a–d upon treatment with dilute acid (Scheme 10). Typical examples are collected in Table 5. The stereochemistry in the major diastereomer of 83c is established by X-ray analysis of the furanone derivative 84c.22

**Preparation of 3-Alkoxyn-2,5-dihydrofurans 83 from (Hydroxynallenes; General Procedure:**

The corresponding allene derivative (0.1 mol) in DMSO (25 mL) was added over 30 min to a stirred solution of KOBu-t (3 g) in DMSO (150 mL) at 50°C. After additional stirring for a further 1.5 h at the same temperature the solution was cooled, ice-water (200 mL) and the mixture was extracted with pentane/ Et₂O (2:1). The combined organic layers were washed with small amounts of H₂O and dried (Na₂SO₄). After removing the solvent, the residue was distilled through a Vigreux column under reduced pressure.

Treatment of the β-hydroxyallene 32 (preparation see Scheme 1) under basic conditions provides a mixture of isomeric 3-alkoxyfurans 86 and 87 (ratio 43:57) in moderate yield (eq 18).26

5. Formation of 3-Alkoxynhydrofurans and Dihydro-3(2H)-furanes

An interesting application of 1-hydroxynalkyl-substituted derivatives of methoxyallene is the synthesis of 3-alkoxyn-2,5-dihydrofurans 83 under basic conditions (Scheme 10, Table 5).20,26,28,51–53 The cyclization of 82 with potassium tert-butoxide in the presence of a crown ether leads to epoxide 85, whereas all examples in Table 5 (21b and 78–81) form under similar conditions 2,5-dihydrofurans 83a–e. Epoxide 85 does not rearrange under the cyclization conditions or thermally into the corresponding dihydrofurano derivative. The reaction giving epoxide 85 can be considered as a 3-exo-trig cyclization, whereas the addition of the alkoxide moiety to the terminal methylene group of the allene to form 83a–e is a 5-endo-trig process. Magnus and Albaugh-Robertson suggested a single electron-transfer (S.E.T.) mechanism for this intramolecular alkoxyn-allene cyclization.22
Table 5. Formation of 83 and 84 (Scheme 10)

| Substrate | 83       | Yield (%) | 84       | Yield (%) | Ref. |
|-----------|----------|-----------|----------|-----------|------|
| [Formula] | [Structure] |           | [Structure] |           |      |
| 78        | [Structure] | 61        | [Structure] | 80        | 26   |
| 79        | [Structure] | 74*       | [Structure] | 68        | 51   |
| 21b        | [Structure] | 77d       | [Structure] | 79        | 20   |
| 80        | [Structure] |           | [Structure] |           | 57f  |
| 81        | [Structure] | 95*       |           |           | 51f  |
|           | [Structure] |           |           |           | 52f  |

* Reaction was performed in the presence of 18-crown-6.

b *anti/syn-21b* = 95:5.

c Diastereomeric ratio = 92:8.

d Overall yield from 3 (see section 2).

e Only one diastereomer was found.

f Overall yield from the allene 80.

6. Cycloaddition Reactions with Alkoxyallenenes

6.1. Diels–Alder Reactions with Inverse Electron Demand

Since the first [4 + 2] cycloaddition reactions of ethoxylalene (4) and α,β-unsaturated aldehydes, such as acrolein by Arens and co-workers, a considerable number of different hetero Diels–Alder reactions with inverse electron demand have quite recently been published. One of the applications of alkoxyallenenes as dienophiles in hetero Diels–Alder reactions, is the preparation of the synthetically useful 5,6-dihydro-4H-1,2-oxazines. The cycloaddition reaction is performed by trapping α-nitrosoalkenes 89, generated in situ from the corresponding α-halo oximes 88 in presence of sodium carbonate, with methoxyallene (3) or a derivative thereof (Scheme 11, Table 6). The isomerization of the primary adducts 90 to 6H-1,2-oxazines 91 can be achieved either by base or acid catalysis (Table 6).
### Table 6. Formation of 5-Methylene-4H-1,2-oxazines 90 and Their Isomerization Into 6H-1,2-Oxazines 91\(^{19}\) (Scheme 11)

| Alkoxyallene | Oxime | R\(^1\) | R\(^2\) | 4H-1,2-Oxazine 90 | Yield\(^{a}\) (%) | Method of Isomerization\(^{b}\) | 6H-1,2-Oxazine 91 | Yield\(^{a}\) (%) |
|-------------|-------|---------|---------|------------------|----------------|----------------------|------------------|----------------|
| 3           | a     | Ph      | H       | a                | 85             | A                    | a                | 97              |
| 3           | b     | CO\(_2\)Et | H       | b                | 89             | A                    | b                | 89              |
| 3           | c     | CF\(_3\) | H       | c                | 92             | A                    | c                | 93              |
| 3           | d     | CH=CHCO\(_2\)Me | H | d                | 64             | C                    | d                | 73              |
| 22          | a     | Ph      | Me      | e                | 36             | A                    | e                | 71              |
| 19f         | a     | Ph      | C(OH)Me\(_2\) | f       | 59             | D                    | f                | 90              |
| 19a         | a     | Ph      | CH(OH)Me | g               | 56 : 40        | A                    | g                | 84 : 40         |
| 19c         | a     | Ph      | CH(OH)Ph | h               | 28 : 55 : 45   | E                    | h                | 56 : 62 : 38    |
| 31          | c     | CF\(_3\) | SiMe\(_3\) | i               | 90             | -                  | -                | -               |

\(^a\) Ratio of diastereomers in parentheses.

\(^b\) A: Et\(_3\)N; r.t., 1 h–30 d. B: CF\(_3\)CO\(_2\)H, r.t., 3–4 h. C: DBU, r.t., 2.5 h. D: DBU/1,4-dioxane, reflux, 2 d. E: Et\(_3\)N/1,4-dioxane, reflux, 7 d.

By means of competition experiments Reissig and co-workers recently studied the relative reactivity of various olefins, including methoxyallene (3), towards \(\alpha\)-nitrostyrene 89a. Thus it was established that 3 is slightly less reactive than ethyl vinyl ether.\(^{56}\)

An unexpected product 92 is formed in the reaction of the sterically hindered allene 19h with \(\alpha\)-nitrostyrene 89a.\(^{19}\) The corresponding 6-methoxy-substituted 1,2-oxazine 90j could not be detected. The formation of 92 can be explained by an electrophilic attack of 89a to the central allenic carbon atom of 19h followed by a [1,6] ring closure (Scheme 12). Thus, a two-step mechanism seems to operate in this example, while for other nitrosoalkene cycloadditions the one-step process is more likely.\(^{19,54,64}\)

![Scheme 12](image)

Further investigations employing alkoxyallenes as useful electron-rich dienophiles in \([4+2]\) cycloaddition reactions have been performed by Boger,\(^{56,59,60}\) Tietze,\(^{57}\) Mattay,\(^{58}\) and co-workers. Some examples are given in equations 19–24. It was found that the activated enone derivatives 96, 98, and 100 react with 3 to afford the 3,4-dihydro-2H-pyranes 97, 99, and 101, respectively, in moderate to good yields. Diels–Alder reactions of unactivated \(\alpha,\beta\)-unsaturated carbonyl compounds, e.g. 102 or crotonaldehyde, with alkoxyallene require high reaction temperature, high pressure or promotion by Lewis acids [i.e. SiO\(_2\), Yb(fod)\(_3\)].\(^{18,58}\) An exception with respect to regioselectivities has been reported by Mattay et al.\(^{58}\) The less reactive 3-buten-2-one (102) reacts with ethoxyallene (4) to give a mixture of \([4+2]\) cycloadduct 103 and \([2+2]\) product 104 (eq 22).

![Scheme 13](image)

The \(\alpha,\beta\)-unsaturated imines 105 and 107 react with 3 in LUMO-diene-controlled \([4+2]\) cycloaddition reactions and provide substituted 1,2,3,4-tetrahydropyridines 106 and 108, respectively, with high \textit{endo} selectively.\(^{39,60}\)
C,C double bond. Geometrical restrictions may be responsible for this behavior.

One of the rare photochemical reactions of alkoxyallenes involves phenanthroquinone 109 and 3 which forms on irradiation the 1,4-dioxine 110 in 65% yield (eq 25).

6.2. [3+2] Cycloaddition Reactions

1,3-Dipolar cycloadditions are frequently used for the synthesis of five-membered N,O-heterocycles. In 1989, Padwa et al. reported [3+2] cycloadditions of methoxyallene (3) with nitrones, i.e. 111 (R = Me) and 112 (R = Ph) to afford isoxazolines 113 and 114, respectively, in moderate yield (Scheme 14). It is proposed that these adducts are formed via cycloadduct 115, which undergoes a facile rearrangement to 116, followed by a ring closure to afford 113 (or 114).

7. Applications of Alkoxyallenes in Syntheses of Natural Products and Related Compounds

In recent years the use of alkoxyallenes as key intermediates for the preparation of natural products and biologically interesting compounds has considerably increased. Thus, the syntheses of the cytchalasin B 117, the forskolin intermediate 118, the γ-butyrolactone 119, the macrodile pyrenophorin 120,80 the euryfuran 121, the penta cyclic system 122 as a model compound for the antitumor quassinoid bruceantin,81 the lacrimin A 123,82 and the methylene homocyn A 12483 have been performed.

7.1. Formation of α-Methylene-γ-butyrolactone 119

A simple synthesis of lactone 119 was developed by Ueno et al. in a three-step sequence. Treatment of butoxyallene (125), which is prepared analogue to 3, and allyl alcohol 126 with N-bromosuccinimide (NBS) followed by
ring closure with tributyltin hydride affords the 3-methylene-substituted tetrahydrofuran 127, which is converted into tetrahydro-4-methyl-3-methylene-2-furanone (119) by Jones oxidation (eq 26).

7.2. Synthesis of Pyrenophorin 120

Linstrumelle’s group reported on a new formal synthesis of the macrolide (+)-pyrenophorin 120 with 3 as key intermediate.\(^6\) The crucial step is the sequential metalation, alkylation, metalation and carboxylation of 3. The \(\alpha,\beta\)-unsaturated ester 130 results after esterification, hydrolysis, and isomerization by 2-pyridinethiol (Scheme 15). Compound 130 is protected as the ketal 131, a known intermediate which has already been converted into 120.
7.3. Synthesis of Lacrimin A 123

A first total synthesis of lacrimin A 123 is reported by Kocienski and Tackle (Scheme 16). The protected alcohol 133 is easily prepared in excellent yield from 3 by metatation followed by reaction with the iodo compound 132. The 1,3-disubstituted methoxayllene 135 is obtained after metatation of 133 with tert-butyllithium and reaction with the optically pure epoxide 134. Then, 135 is desilylated with tetrabutylammonium fluoride and treated with p-toluenesulfonic acid and catalytical amounts of iodine to effect ring closure giving the spiro acetal 136. The key intermediate 136 is further converted into the lacrimin A 123.

Hydrolysis and cyclization of allenol ether intermediates to spiroketal is rather general making available 1,7-dioxaspiro[5.5]undec-4-enes 137 (n = 2) and 1,6-dioxaspiro[4.5]dec-3-enes 137 (n = 1).

8. Miscellaneous Reactions

Tius and Astrab developed a straightforward route to a-methyleneyclopentene derivatives, e.g. 139, by treatment of the corresponding allenes with boron trifluoride-diethyl ether complex in dichloromethane at 0°C. An example of this cationic cyclopentannulation reaction is shown in equation 27. This reaction is not limited to precursors like 138 with a siloxy group at the exomethylene unit. Compounds with a phenyl group, a thiophenyl group or hydrogen instead of the siloxy group also lead to the corresponding cyclopentenones under acid catalysis.

In 1989 Tius et al. published the preparation of quinone 141, which has been accomplished in four steps from 138 including the formation of the epoxide 140 as key intermediate (eq 28). The reaction mechanisms to 140 and 141, respectively, are given in Tius’ report.

Reactions of methoxayllene (3) towards several sulfur reagents lead to a variety of sulfur containing enol ethers, e.g. 142–145 (Scheme 17).

Other applications involving alkoxyallenes are reported by Martin, Dulcere, Brandsma, tom Dieck, Endo, Goré, Reich, and Saalfrank. Typical examples are collected in equations 29–38.
9. Conclusion

As was demonstrated in this article, the easily accessible alkoxyallenes and their derivatives have widely been used in organic chemistry providing interesting products such as \( \alpha,\beta \)-unsaturated carbonyl compounds, enol ethers and dihydrofuran derivatives, respectively.

In addition, alkoxyallenes serve as very potent 2π-components in a variety of cycloadditions leading to compounds which are convertible into several synthetically interesting products.

The different allenic ethers, which are described in this review, represent a number of useful synthetic equivalents for synths,\(^{10}\) as depicted in Scheme 18.

![Scheme 18](image-url)

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