The Development and Use of Ketene Equivalents in [4+2] Cycloadditions for Organic Synthesis

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1) Introduction and Scope

The inability of ketenes to undergo satisfactory [4+2] cycloadditions with 1,3 dienes has been established since the pioneering work of Staudinger in the early 1910s.1-4 In recent years the attention paid to ketene equivalents has increased dramatically4-8 culminating in the advent of chiral ketene equivalents.9
The first reports of chiral ketene equivalents (based on α, β-unsaturated sulfoxides) were received in the early 1980s. Since then chiral ketene equivalents have received much attention. Many of the examples reported herein involve vinyl sulfoxides, which offer high levels of diasterecontrol and ease of conversion to the carbonyl group. What follows is a survey of the literature up to the end of 1997 with emphasis given to novel chiral ketene equivalents and especially their applications in Diels-Alder reactions. Earlier non-chiral methods were reviewed comprehensively by Ranganathan through to the end of 1977 and so the discussion on non-chiral methods will be selective, focusing on α-acrylonitrile derivatives not presented in that review.

2) Mechanistic Considerations

The current state of mechanistic theory regarding ketene [2+2] vs [4+2] has been highlighted recently by Yamabe, who has shown by a series of ab initio calculations that for the reaction of ketene 2 with 1, the [4+2] addition is calculated to have the smallest activation energy amongst all the computationally obtained cycloadditions. This work has led to a new proposal by Yamabe that ketenes undergo a two-step reaction mechanism with 1,3-cyclopentadiene: initial [4+2] cycloaddition at low temperature followed by [3,3] sigmatropic rearrangement (Scheme 1) to give the cyclobutanone 4.

Validation for these theoretical studies has been provided by experimental studies leading most recently to the spectroscopic observation of the [4+2] adduct 3 at low temperature.

3) Captodative Olefins as Ketene Equivalents

(i) α-Substituted Acrylonitriles

a) α-Acetoxyacrylonitrile

The first example of a ketene equivalent was reported in 1956 by Bartlett and involved the reaction of α-acetoxyacrylonitrile with cyclopentadiene. Although satisfactory yields of the ketene adduct were obtained, subsequent conversion to the ketone required forcing conditions (NaOH, reflux, 100°C). Another limitation of α-acetoxyacrylonitrile is its long reaction times (the reaction with 6,6-dimethylfulvene, for example, is reported to take 15 days to completion). Oku et al., however, have reported that pyridine can be used as an effective promoter in the reaction of fulvene with α-acetoxyacrylonitrile (Scheme 2). The modest yields previously reported for this reaction were greatly improved as a result of the addition of pyridine and, furthermore, the formation of the unwanted adduct 8 was suppressed (Scheme 2).
Lewis acids (in particular Cu(I) and Cu(II) catalysts) also promote the Diels-Alder reactions of \(\alpha\)-acetoxyacrylonitrile and \(\alpha\)-chloroacrylonitrile giving cycloadducts in 20-62% yield with furan (Scheme 3).\(^{16}\) The highest yields were obtained with the more reactive dienophile\(^{17-25}\) \(\alpha\)-chloroacrylonitrile.

\(\alpha\)-Acetoxyacrylonitrile was used in the synthesis of a range of 16-functionalized 14\(\alpha\), 17\(\alpha\)-ethano-19-norsteroids.\(^{26}\) The cycloaddition to the dienyl acetate 14\(a\) initially gave a complex mixture of cycloadducts 15\(a\) (13%), 16 (4%) and 17\(a\) (32%). Optimisation (Scheme 4) gave an 81% yield of a single cycloadduct 17\(a\) together with 16% starting material.

\[\text{Furan} + \text{Acetoxyacrylonitrile} \xrightarrow{\text{Cu(OAc)}_2} \text{Cycloadducts}\]

\[\begin{array}{ccc}
\text{X = OAc} & 6 & 22\% >90:10, 10:11 \\
\text{X = Cl} & 9 & 62\% 50:50, 12:13 
\end{array}\]

Scheme 3

\[\text{Reagents: a) } \text{H}_2\text{C}=\text{C(OAc)}\text{CN, 100-180}^\circ\text{C; b) KOH, H}_2\text{O, DMSO, THF, 0}^\circ\text{C}\]

Scheme 4

Alkaline hydrolysis of 17\(a\) furnished the 17\(\beta\) hydroxy 16-ketone 18 (Scheme 4) in excellent yield (82%).

**Chiral \(\alpha\)-acyloxyacetonitriles**

Vogel has developed a class of chiral acetoxyacetonitrile analogues. Their Diels-Alder reactions with furan provide (after recrystallisation) single isomers of compounds which have been referred to as "naked sugars" due to their ability to act as synthons for hexoses, whilst lower in functional density. Two systems have been used, one based upon camphanates\(^{27}\) 20 and an improved analogue bearing a tartrate-derived chiral auxiliary\(^{28}\) 21. Although the diastereoselectivities in the Diels-Alder reaction are moderate, diastereomerically pure products are readily obtainable \textit{via} recrystallisation. The ketone functionality is realised by mild saponification to recover the chiral auxiliary and furnish optically pure \((-\text{-7-oxabicyclo[2,2,1]hept-5-en-2-one 22 (Scheme 5), which was subsequently elaborated to a range of sugars and nucleosides.}
3 (i) (b) α-Chloroacrylonitrile

The versatility of α-chloroacrylonitrile as a ketene equivalent is demonstrated in the construction of the [3.3.3] propellane and tricyclo [5.3.1.0]4,11 undecane ring systems. Mehta and coworkers have shown in studies directed towards the total synthesis of the sesquiterpene (±)- modiphene 28 that α-chloroacrylonitrile is superior to nitroethylene as a ketene equivalent, particularly in terms of ease of conversion to the carbonyl compound.29 Thus, diene 23 was subjected to cycloaddition in the presence of α-chloroacrylonitrile to afford a mixture of the adducts 24 and 25 in 40% yield (Scheme 9). Conversion to the carbonyl functionality proved trouble free using Evans methodology (sodium sulfide nonahydrate in refluxing ethanol)30 giving a mixture of β,γ unsaturated ketones 26 and 27 (58% yield) in a 4:1 ratio, respectively (Scheme 6).

![Scheme 5](image)

**Scheme 5**

The syntheses of β-amino acids (including asymmetric syntheses using α-methylbenzyl instead of benzyl), via nitrone cycloaddition to ketene equivalents including α-chloroacrylonitrile have been reported by Overton.31 The reaction is significant in that the cycloadducts are easily converted (by hydrolysis either directly to the isoxazolidinone, or via the lactol and oxidation) to β-amino acids e.g. 32 (Scheme 7) which are themselves useful synthetic intermediates.32,33

![Scheme 6](image)

**Scheme 6**

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![Scheme 7](image)

**Scheme 7**

\[ R^* \left\{ \begin{array}{l} \text{Cl} \\
\text{OAc} \\
\text{Me} \\
\end{array} \right. \]

Reagents: a) A neat; 30a 67%, 30b 74%; b) K₂CO₃, 83%; c) Jones reagent, 36%; d) H₂/Pd, EtOAc, 80%(R=Ph); e) NEt₃, THF, H₂O, 74%.
The successful conversion to the ketone group represents a pivotal step in the use of any ketene equivalent
and Shiner and coworkers\textsuperscript{34} have undertaken an extensive study of the hydrolysis of $\alpha$-chloronitriles. The
authors surmise that although pathways involving nucleophilic displacement of chloride or cyanide have been
proposed,\textsuperscript{35} they are unlikely.\textsuperscript{34} A more likely scenario is the formation of $\alpha$-chloro amides \textsuperscript{34} followed by
base-induced conversion to ketones (Scheme 8) and indeed $\alpha$-chloro amides have been isolated as intermediates.\textsuperscript{34}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {33}; \node at (1.5,0) {34};
\draw[->] (33) -- (34); \node at (2.5,0) {Reagents: a) KOH, ROH, 0-25 °C b) KOH, ROH, $\Delta$}
\end{tikzpicture}
\end{center}

\textbf{Scheme 8}

3 (i) (c)$\alpha$-Alkylthio and $\alpha$-alkylaminoacrylonitriles

Stella \textit{et al.}\textsuperscript{36} investigated the captodative olefins \textsuperscript{35, 36} as ketene equivalents. $\alpha$-
Morpholinoacrylonitrile \textsuperscript{35} and $\alpha$-methylthioacrylonitrile \textsuperscript{36, 37} are both easily prepared and have been shown to
react with dienes to afford $[4+2]$ cycloadducts in good yields (62-92\%) (Scheme 9). The conversion of $\alpha$-
aminonitriles\textsuperscript{38} and $\alpha$-thionitriles\textsuperscript{39} to ketones has been accomplished (Scheme 9)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {35}; \node at (1.5,0) {36}; \node at (2.5,0) {37}; \node at (4,0) {38}; \node at (5.5,0) {39}; \node at (7,0) {40};
\draw[->] (35) -- (37); \draw[->] (36) -- (38); \node at (3.5,0) {Reagents: a) D, 160 °C, 6h; b) CuSO$_4$, MeOH/H$_2$O, $\Delta$, 85 \% (x=morpholine); NBS, MeCN/H$_2$O (X= SR, see ref. 39)}
\end{tikzpicture}
\end{center}

\textbf{Scheme 9}

Also noteworthy is work by Ahlbrect \textit{et al.}\textsuperscript{40} who has shown that 1-cyanoenamines are effective ketene
equivalents and add to cyclohexenone enolates in a tandem-Michael addition fashion to provide bicyclo
[2.2.2]octanones.

3 (ii) $\alpha$-Substituted Acrylates

\textbf{a) 2-Alkyl-5-methylene-1,3-dioxolan-4-ones}

It has been demonstrated that the Diels-Alder reactions of 2-alkyl-5-methylene-1,3-dioxolan-4-ones
proceed with high \textit{exo} selectivity, in contrast to the normally favoured \textit{endo} addition. This applies to both their
thermal and Lewis acid catalysed reactions, with both cyclic\textsuperscript{41} and acyclic\textsuperscript{42} dienes. The Diels Alder reactions of
chiral 2-alkyl-5-methylene-1,3-dioxolan-4-ones, in addition to the high \textit{exo} selectivity, also show high
diastereoselectivity. The work of Roush, while mainly directed towards natural product synthesis in which the
dioxalanone is otherwise transformed, has also demonstrated the use of these compounds as chiral ketene
equivalents.\textsuperscript{43} Thus the chiral dienophile 41 reacts with cyclopentadiene to give only two products 42, 43, the
\textit{exo} isomer 42 being favoured by a ratio of 94:6. Metal hydride reduction of the chromatographically purified \textit{exo}
isomer gave the diol 44 (Scheme 10). As (+)-44 has previously been converted\textsuperscript{44} to norbornenone, it was possible to assign the absolute configuration of the product (-) and calculate the e.e. (99 %), while formally demonstrating the potential of these dienophiles to act as chiral ketene equivalents. The high selectivities and ease of conversion to the ketones make these valuable chiral ketene equivalents.

\[
\begin{array}{c}
\text{RO}_2\text{C}^\text{NHAc} + \text{PH} \xrightarrow{-70^\circ \text{C}} \text{NHAc} + \text{CO}_2\text{R} \xrightarrow{70\%} 1:99 \\
\text{R} = \text{Ph} \quad \text{NHAc} \quad \text{CO}_2\text{R} \quad \text{NHAc} \quad \text{CO}_2\text{R} \quad \text{NHAc}
\end{array}
\]

\textit{Scheme 11}

Studies on the selectivity in cycloadditions of a different class of chiral \(\alpha\)-amidoacrylate were undertaken by Reetz, in which the chirality was located at the allylic position.\textsuperscript{48} These \(\gamma\)-amino-\(\alpha,\beta\)-didehydroamino esters 45 (prepared from aminoacids, via reduction to the aldehyde and olefination by the Schöllkopf isonitrile method\textsuperscript{49}) gave adducts with both cyclopentadiene and diazomethane in generally good yields and excellent diastereoisomer ratios.

\[
\text{Bn}_2\text{N} \quad \text{CO}_2\text{Et} \quad \text{NHCHN} \quad \text{Bn}_2\text{N}
\]

\textit{Reagents:} a) Et\textsubscript{2}AlCl, -10-0\(^\circ\) C, 74%; b) \text{CH}_2\text{N}_2, \text{Et}_2\text{O}, \text{RT}, 20 h, 71 %.

\textit{Scheme 12}

Whilst in these examples the latent ketone was not liberated, the methodology exists for the conversion,\textsuperscript{39} and thus for these compounds to act as chiral ketene equivalents.
4) Sulfoxides

4 (a) α,β-Unsaturated sulfoxides

The emphasis in recent years towards homochiral synthesis prompted the development of chiral ketene equivalents. Initial attempts focused on the use of enantiomerically pure α,β-unsaturated sulfoxides and the first successful case was reported by Maignan et al. in 1983. Reaction of (+)-(R)-p-tolyl vinyl sulfoxide with cyclopentadiene gave a mixture of four separable diastereoisomers, two of which were transformed to the two enantiomers of dehydronorcamphor (bicyclo[2.2.2]hept-5-enone) possessing very high enantiomeric purity (Scheme 13).

Koizumi reported the use of (S,S)-1,1-bis(p-tolylsulfinyl)ethene which possesses C2 symmetry and thus leads to only two diastereomeric adducts. The reaction between (S,S)-1,1-bis(p-tolylsulfinyl)ethene and cyclopentadiene gave two diastereomeric adducts (4:1), which were converted to the known norbornenone with 54% ee (Scheme 14). A similar approach towards (+)- was adopted by Maignan et al. employing (+)-(R)-ethynyl p-tolyl sulfoxide.

Although these studies clearly demonstrated the viability of such a process, the full potential of the approach was not realized until 1991 when Carretero demonstrated that the Diels-Alder reactions of (+)-(S)-t-butylsulfonyl-1-p-tolylsulfinylethene with cyclopentadiene proceeded with very high stereoselectivity (Scheme 15). The reactions generally required mild Lewis acid catalysis (ZnBr2, Eu(fod)3 and SiO2) and gave good yields of the major diastereomer (62% yield, 92:8) (Scheme 15). The reaction is thought to proceed via an endo approach of the diene, with respect to the t-butylsulfonyl group, to the less hindered face of the S-cis conformation of the dieneophile.
The use of trans-dioxides of cyclic ketene thioacetals as highly selective chiral ketene equivalents have been reported by the Aggarwal group. Cyclic ketene thioacetals 59, 60 and 61 have been studied and it has been found that 61 is more reactive and more selective than both 59 and 60. Dienophile 61 was prepared in four steps (52%, overall) from readily available starting materials and found to undergo cycloaddition with a range of dienes with excellent selectivities (>97:3). The reaction of 61 with cyclopentadiene at -78°C using BF₃·OEt₂ gave 62a as a single diastereomer. This high selectivity is rationalised partly in terms of non-bonded steric interactions destabilising TS₂, and partly by invoking a repulsive interaction between the lone pairs on the sulfenyl oxygen and alkene π system further destabilising TS₂. The ketone is unmasked in two steps (82%) to give the formal product of ketene cycloaddition, norbornone 56, enantiomerically pure (Scheme 16).

One further example of a sulfoxide based ketene equivalent was reported by Fallis:⁵⁶ the reaction of (+)-6-methoxy-1,3-benzooxathiolan-(Z)-2-carbomethoxypropenyl-3-oxide 63 with cyclopentadiene. Optimum conditions required boron trichloride catalysis at -78°C to afford diastereomerically pure 64 in 77% yield (Scheme 17).

Since the reaction proceeds with complete $\pi$-facial control syn to the sulfoxide lone-pair, as illustrated in 65, it seems likely that the boron is coordinated to the sulfoxide oxygen and the carbonyl group. This leaves the opposite face exposed and hence leads to the selectivity observed. Hydrolysis of the acetals proved troublesome and required four steps to convert 64 into (+)-(1R,4R)-norbornone 56 in 60% yield.

4 (b) Vinyl sulfonium salts

Some inspired work by Kagan\textsuperscript{57} has demonstrated that $O$-alkylation of chiral vinyl sulfoxides (with trialkyl oxonium salts) activates them towards reaction with dienes, allowing a low temperature Diels-Alder to occur which shows very high selectivity. The reaction of (S)-(−)-p-tolyl vinyl sulfoxide with cyclopentadiene is sluggish, requires high temperatures (115°C) and gives a mixture of all four possible isomers. The salt obtained upon $O$-ethylation of (S)-(−)-p-tolyl vinyl sulfoxide, 66, however, reacts with cyclopentadiene at low temperature (−78°C) to give (after hydrolytic dealkylation of oxygen) only the endo isomer in 62% yield, with >99% de (Scheme 18). Reaction of the same salt with furan at −20°C gives the corresponding oxobicycle with poorer endo/exo selectivity (59:41) but again with >98% de for each isomer. The ketene equivalence is unmasked by the conversion of the endo isomer 67 into (+)-oxanorbomenone with 100% ee.

Reagents: a) cyclopentadiene, BCl\textsubscript{3}, −78°C, 5h, CH\textsubscript{2}Cl\textsubscript{2}, 77%

Scheme 17

Reagents: a) Et\textsubscript{3}O$^+$BF\textsubscript{4}⁻; b) i) −78 °C, 36h, ii) NaOH, 62%, (2 steps); c) i) −20°, 30 h, ii) NaOH, 35% (2 steps); d) i) POCl\textsubscript{3}, py, PhH; ii) NaOH; iii) NCS; iv) Cu(II).

Scheme 18
This method was used\(^5\) to prepare the bicyclic ketone \(68\) which is an important intermediate in the synthesis of prostaglandins (Scheme 19).\(^5\)

\[
\begin{align*}
\text{Reagents:} & \quad \text{a) } \text{Et}_3\text{O}^+\text{BF}_4^-; \quad \text{b) i) } -30^\circ\text{C, DCM, 50 h, ii) } \text{NaOH, 60\% (2 steps)}; \quad \text{c) 3 Steps, 32\%} \\
& \quad \text{Scheme 19}
\end{align*}
\]

5) Sulfones and Sulfonates.

The demonstration by Little\(^6\) that anions derived from cyclic sulfones undergo oxidation to ketones, either with molecular oxygen (\textit{CAUTION} the authors report a "moderate" explosion), or oxodiperoxymolybdenum (pyridine)(hexamethylphosphoric triamide) (MoOPH)\(^6\) allows us to regard vinyl sulfones as dienophiles which act as ketene equivalents. Little applied this technology to a small range of dienes and 2-alkylidene-1,3-diyls. However, the wealth of examples of vinyl sulfones acting as dienophiles\(^6\) imply that this methodology could prove valuable.

De Lucchi \textit{et al.}\(^6\) considered a number of aryl substituted ketenedithioacetal tetroxidas as potential dienophiles. These include dienophiles \(69\) and \(70\) which are atropisomeric chiral molecules, but the levels of diastereoselectivity were disappointingly modest (endo-71:exo-72 1.5:1) (Scheme 20).

\[
\begin{align*}
& \quad \text{Reagents: a) toluene, cyclopentadiene, reflux, 12h, 95\% (endo/exo 1.5:1)} \\
& \quad \text{Scheme 20}
\end{align*}
\]

Metz \textit{et al.}\(^6\) described the use of vinylsulfonyl chloride\(^6\) in reaction with dienol 73, to give an intermediate vinyl sulfonate which readily cyclises to the corresponding sultone 74 in good yield and excellent diastereoselectivity. The sultones are degraded to hydroxy ketones 75 (formalising the ketene equivalency) via a deprotonation-borylation-oxidation hydrolysis sequence (Scheme 21).
The high level of regio- and stereocontrol of this method was contrasted with the Diels-Alder reaction of the same cyclopentadiene 73 with the standard ketene equivalent, 2-acetoxyacrylonitrile, which gave a mixture of ten isomers, and subsequent basic hydrolysis yielded a mixture of 75 with virtually all of its regio- and stereoisomers.

6) Vinyl Sulfoximines

In addition to the reactions of vinyl sulfones, a small number of aryl vinyl sulfoximines, which have a potential advantage over sulfones in that they are intrinsically chiral, have been prepared in both racemic and optically pure form and their Diels-Alder reactions investigated. While the endo/exo selectivities in these reactions are good, little or no diastereoselectivity has been observed. Fortunately, the diastereoisomers are separable by HPLC, so that the use of homochiral vinyl sulfoximines potentially provides access to homochiral products of the formal addition of ketenes to dienes [the ketone is revealed in the same manner as for sulfones, i.e. via deprotonation-oxidation (with MoOPH)] (Scheme 22).

N-tosyl sulfoximines seem to be more reactive dienophiles than the analogous sulfones, reacting with a range of cyclic and acyclic dienes in good yields. This reactivity, taken along with their ease of cleavage and the possibility of access to enantiomerically pure products (albeit via diastereoseparation) makes them a promising, if underexploited, addition to the field of ketene equivalents.

7) Allenes

As it can be envisaged that the double bond which would remain after an allene had participated in a Diels-Alder reaction could be oxidatively cleaved to a ketone, it is surprising that there exist only a few examples of the use of allenes as ketene equivalents in organic synthesis. Kozikowski reported the cycloadditions of 1,3 diethoxycarbonyllallene 76 with a range of cyclic dienes, including cyclopentadiene and both furanyl and pyrryl
heterocyclic dienes. The yields obtained in these reactions were generally good, although the authors noted that the products were isolated as mixtures of isomers (ratios unreported). The conversion to a ketone was realised (after other functional group manipulations) by ozonolysis, furnishing a key intermediate 77 in a projected synthesis of antibiotic C-nucleosides (Scheme 23).

\[ \text{Reagents: a) PhH, 40°C, 24 h, 87%; b) Final step O}_3 \]

Scheme 23

More recently Trudel\textsuperscript{171} applied the same chemistry to a formal synthesis of racemic epibatidine. Although a variety of allenic diesters were successfully subjected to cycloaddition with pyrroles, yields in the liberation of the ketone were low, so attention was turned to an allenic sulfone. Benzenesulfonyl allene 78 was found to undergo a Diels-Alder reaction with N-Boc pyrrole to give a single product 79 in 45% yield. The ketone was liberated and the product transformed into the epibatidine precursor 80 in three further high yielding steps (19% overall, four steps, Scheme 24).

\[ \text{Reagents: a) 85-90°C, neat, 16 h, 45%; b) H}_2, \text{Pd/C, MeOH, 90%; c) O}_3, \text{-76°C, C}_2\text{H}_4\text{Cl}, \text{DMS, 78%; d) Al(Hg), THF, H}_2\text{O, 60%.} \]

Scheme 24

8) Miscellaneous

a) Vinyl Boranes

Vinyl boranes have been shown to be highly reactive and endo selective dienophiles.\textsuperscript{72} In particular their synthetic potential is demonstrated in the intramolecular Diels-Alder reactions of the vinyl borane 81 obtained by either hydroboration of dienynes 82 or tin-boron exchange of dienyl vinystannanes 83.\textsuperscript{73} The Diels-Alder adduct 84 is formed as a single isomer and readily oxidised to the alcohol 85 (Scheme 25). Although the transformation to the ketone was not undertaken, this simple oxidation would allow these vinylboronic species to be regarded as ketene equivalents.
b) Selenoacetylenes

1-(Phenylseleno)-2-toluenesulfonyl ethyne \(86^{74}\) has been shown to act as a dienophile giving selenocyclohexenes \(87\) in excellent yields with a range of dienes. Subsequent oxidation to the selenoxide, followed by addition-elimination with methoxide ion gives an enol ether \(88\), which upon hydrolysis unmasks the ketone, and confirms the ketene equivalence (Scheme 26). The \(\alpha\)-tosyl group can remain (TsHC=\(\equiv\)C=O equivalent), be reductively cleaved to a methylene group (H\(_2\)C=\(\equiv\)C=O equivalent), substituted with an electrophile before reductive cleavage (RHC=\(\equiv\)C=O equivalent) or even potentially oxidised to another ketone by the methods described in the section on vinyl sulfones (O=C=\(\equiv\)C=O equivalent). These potential transformations and the high yields may offer a very versatile ketene equivalent.

\[
\begin{align*}
86 & \xrightarrow{\text{a) PhMe, 60°C, 6h, 90%}} 87 \\
\text{Ts} & \quad \text{SePh} \\
\end{align*}
\]

Reagents: a) PhMe, 60°C, 6h, 90%; b) i) mCPBA, CHCl\(_3\) ii) NaOMe/MeOH, 91%; c) HCl, THF/H\(_2\)O, 95%; d) 59 Na(Hg), Na\(_2\)HPO\(_4\), THF-MeOH, 75%.

Scheme 26

9) Ketene Equivalents in Natural Product Synthesis

Early experiments in this area were largely concerned with the total syntheses of racemic alkaloids and involved the use of simple ketene equivalents. For example, Snider and coworker have described the synthesis of \(\pm\)-nitramine \(94\) in seven steps (33% overall yield) which incorporates methyl \(\alpha\)-chloroacrylate as a ketene equivalent in an ene reaction (Scheme 27).\(^75\) Chloro ester \(89\) derived from methylene cyclohexane and methyl \(\alpha\)-chloroacrylate was converted first to the hydroxy acid \(90\) and then to the aldehyde \(91\) in 71% overall yield. Further manipulation to the nitrone \(92\) was achieved by oxime formation, reduction to the hydroxylamine and condensation with formaldehyde. Intramolecular cycloaddition of nitrone \(92\) proceeded smoothly to give \(93\) (the formation of \(93\) is favored by entropic effects in C-C bond formation of a six-membered ring) which was converted to \(\pm\)-nitramine \(94\) by hydrogenolysis (Scheme 27).
Yoshi? has utilized α-acetoxyacrylonitrile as a ketene equivalent in the synthesis of (+)-tetronomyein, a novel tetronic acid ionophore antibiotic (Scheme 28). Construction of the left-hand cyclohexane sub-unit 95 commenced with Diels-Alder reaction of diene 96, derived from 3-methoxy-5-methylbenzoic acid, with α-acetoxyacrylonitrile (Scheme 28). Treatment of the resulting cycloadduct with 1.1 equivalents of NaOMe in MeOH afforded a 4:1 mixture of bicyclic ketone 97 and its C8 epimer in 68% yield. The stereochemistry of the major product 97 presumably arises from the approach of the dienophile to the less hindered face of 96, and was confirmed by the authors. A further nine steps yielded the key cyclohexyl aldehyde subunit 95 which constitutes ring C of the natural product (Scheme 28).

Tabacchi and coworker? have also utilized α-acetoxyacrylonitrile in the stereoselective synthesis of the novel allenic cyclohexanoid epoxide 98 produced by the fungus Eutypa lata. Reaction between the diene 99 and α-acetoxyacrylonitrile gave the cycloadducts 100a and 100b (ca. 8:1). The major isomer 100a obtained in 50-65% yield by recrystallisation, was transformed over three steps to the epoxy ketone 101 and then to the desired allenic cyclohexanoid epoxide 98 over a further three steps (seven steps in total, 7.4% overall yield) (Scheme 29).
Vogel has utilized his chiral ketene equivalent technology in the asymmetric syntheses of (+)-6-deoxycastanospermine and (+)-6-deoxy-6-fluorocastanospermine. Both syntheses rely on the "naked sugar" (-)-(1S,4S)-7-oxabicyclo[2.2.1]hept-5-en-2-one (-)-22 referred to earlier in the section on chiral α-acyloxyacrylonitriles. Naked sugar (-)-22 allows ready access (via its dibenzoyl ketal 99) to epoxy lactam 102 in four steps (Scheme 30), a further two steps affords the indolizidine alkaloid 6-deoxycastanospermine (+)-103. Epoxy lactam 102 is also an intermediate for 6-deoxy-6-fluorocastanospermine (+)-104 (Scheme 30).

Reagents: a) 110°, 4 days; b) (i) mCPBA, (ii) NaBH₄, (iii) CrO₃·py₂; c) 6 steps, 7.4% overall.

Scheme 29

10) Conclusions

Ever since the discovery by Staudinger in the early 1910s that ketenes do not undergo [4+2] Diels-Alder cycloadditions, the development of new ketene equivalents has inspired many researchers around the world. From the early use of α-acetoxyacrylonitrile and α-chloroacrylonitrile through to the use of enantiomerically pure dienophiles as ketene equivalents many ingenious methods of circumventing the failure of ketene to react as desired have been developed. With the continued emphasis on homochiral synthesis set to continue well into the new millennium there is little doubt that the development of new chiral ketene equivalents will continue to attract great interest.

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References and Notes


9. See sections 4) and 5) of reference 8 and references cited therein.


12. GAUSSIAN 92 was used for calculations. Frisch, M.J.; Trucks, G.W.; Head-Gordon, M.; Gill, P.M.W.; Wong, M.W.; Foresman, J.B.; Johnson, B.G.; Schlegel, H.B.; Robb, M.A.; Replogle, E.S.; Gomperts, R.; Andres, J.L.; Raghavachari, K.; Binkley, J.S.; Gonzalez, C.; Martin, R.L.; Fox, D.J.; DeFrees, D.J.; Baker, J.; Stewart, J.J.P.; Pople, J.A. GAUSSIAN 92, Revision C; Gaussian, Inc.: Pittsburgh, PA, 1992.


Biographical sketch

Varinder K. Aggarwal

Amjad Ali

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Varinder Aggarwal was born in Kalianpur in the northern state of Punjab in India in 1961 and in 1963 his family emigrated to England. He received his BA in 1983 and PhD in 1986 from Cambridge University under the guidance of Stuart Warren. He then carried out post-doctoral research with Professor Gilbert Stork at Columbia University as a Harkness Fellow and returned to a lectureship at Bath University in 1988. In 1991 he moved to Sheffield University where, in 1997, he was promoted to Professor in Organic Chemistry.

Amjad Ali received his first degree from the University of Hertfordshire (Hatfield, UK) in 1986. He then moved to the University of Nottingham to read for his Ph.D. under the direction of Professor Gerald Pattenden where he investigated the development of novel cascade cyclization processes mediated by organocobalt reagents. Having successfully completed his Ph.D. in 1993 he moved to Austin, Texas (USA) as a Fulbright Postdoctoral Fellow to collaborate with Professor Stephen F. Martin on the total synthesis of the marine alkaloid, manzamine A. Two years later he returned to the UK to work with Prof. Varinder Aggarwal at the University of Sheffield, and he is currently a Senior Research Chemist at Merck Research Laboratories, Rahway, New Jersey (USA).

Mike Coogan was born in Birkenhead in 1969, graduated from Leicester University in 1990 and remained there for Ph.D. studies with Dr. R.S. Atkinson on quinazolinone based aziridinations. In 1994 he began post doctoral work with David Knight at the University of Nottingham in the area of reverse-Cope cyclisations, moving to Cardiff University upon the appointment of David Knight to the Distinguished Chair of Organic Synthesis. He returned to England in 1997 to work at Sheffield University with Prof. Varinder Aggarwal on the application of zinc carbenoids to epoxidations, and took up a Lectureship at Durham University in September 1998.