

CYCLOADDITION REACTIONS OF CONJUGATED AZOALKENES

Américo Lemos

CIQA, Departamento de Química e Farmácia, FCT, Universidade do Algarve, Campus Gambelas,
P-8005-139 Faro, Portugal (e-mail: alemos@ualg.pt)

Abstract: Cycloaddition reactions of conjugated azoalkenes, also named 1,2-diaza-1,3-butadienes, leading to the synthesis of six-, five-, four- and three-membered heterocycles, are overviewed. Main emphasis on [4+2] cycloadditions is given, but [3+2], [4+1], [2+2] and [2+1] cycloadditions are also discussed.

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1. Introduction

Over the past decades, conjugated azoalkenes have emerged as powerful intermediates for the preparation of an impressive number of new heterocyclic systems, when used either as Michael-type acceptors in conjugate 1,4-additions or in cycloaddition reactions, with a wide range of olefinic and heterocyclic partners. The adducts and cycloadducts so formed have proved to be of great value and importance, not only due to their pharmacological properties and/or biological activity, but also as building blocks or key intermediates in organic synthesis.

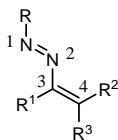


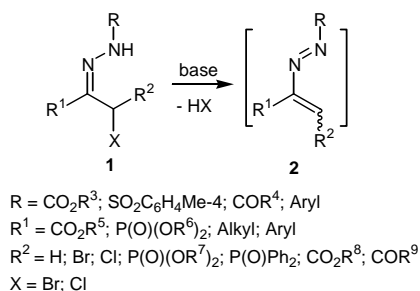
Figure 1. Numbering and possible substitution pattern on azoalkenes.

Despite their considerable interest and numerous synthetic applications, conjugate additions of azoalkenes, which have been recently reviewed,¹ fall beyond of the scope of this overview. General methods

for the synthesis or generation of azoalkenes are described briefly but most of the review is devoted to their use in cycloaddition reactions.

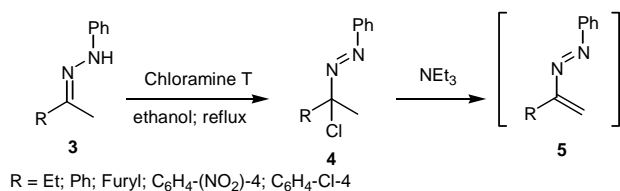
2. Synthesis or generation of azoalkenes

Conjugated azoalkenes are usually very reactive species. Their properties are profoundly modulated by the electron-withdrawing or releasing ability of substituents. Their stability is also directly associated with the substitution pattern. Electron-deficient 4-unsubstituted azoalkenes are very unstable species that are usually generated and intercepted *in situ*. Depending on the nature of their substituents, 1,3,4-substituted-azoalkenes are very often stable enough to be isolated or even to be purified by column chromatography. Whether they are isolated or generated *in situ*, by far the most common and general method for the preparation of azoalkenes is a base induced 1,4-dehydrohalogenation of α -halo-hydrazones¹⁻⁷ carrying a wide variety of substituents, the most representative of which are carboxyl, carbonyl, phosphonyl, phosphinyl, heterocyclic, aryl and alkyl groups (Scheme 1).



Scheme 1

Recently, dehydrohalogenation has also been used to promote the generation of azoalkenes. This was not the habitual 1,4- but an 1,2-dehydrochlorination, mediated by triethylamine, of chloro-azo compounds **4** derived from Chloramine T oxidized aromatic or alkyl *N*-phenylhydrazones **3** possessing an α -methyl group⁸ (Scheme 2). Other methods with less relevancy or impact like oxidation with I₂⁹ or HgO^{9,10} MnO₂¹⁰ or Cu(I)¹¹ and thermolysis¹² of hydrazones have also been occasionally used.



Scheme 2

3. Cycloaddition reactions of azoalkenes

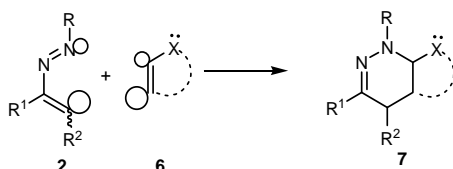
3.1. [4+2] Cycloadditions

Cycloadditions in which azoalkenes behave as conjugated heterodienes are the most representative and significant reactions and have been the basis of much of the new chemistry of these compounds in recent decades.

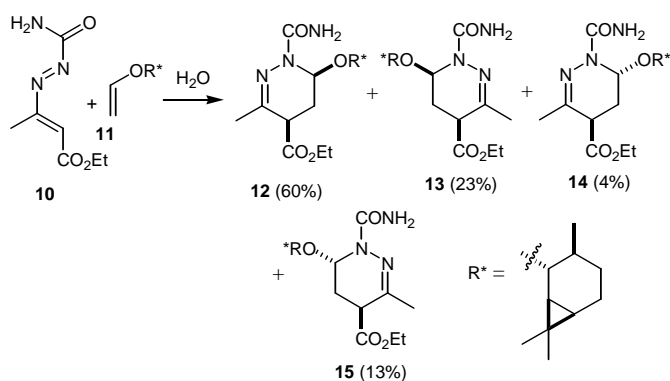
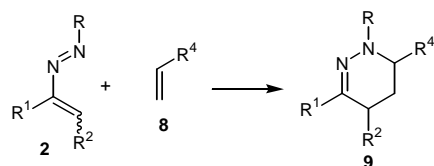
3.1.1. With electron-rich C=C bonds and heterocycles

Due to the presence of the two nitrogen atoms, more electronegative than carbon, combined with one or, more often, with two electron-withdrawing substituents, these azoalkenes possess strong electrophilic character and therefore their cycloadditions are predominantly with electron-rich double bonds and heterocycles in a Diels-Alder process with 'inverse electron demand'.

The cycloadducts are usually obtained with a high degree of regio- and stereo-selectivity, as predicted by frontier molecular orbital interactions in which the dienophile is the donor component - HOMO controlled- and the diene is the acceptor - LUMO controlled. Consequently, the major regioisomer is the result of the interaction of the terminal atom of the electron-rich alkene or heterocycle bearing the higher HOMO coefficient with the terminal carbon atom of the azoalkene, which in the LUMO bears the higher orbital coefficient (Scheme 3).

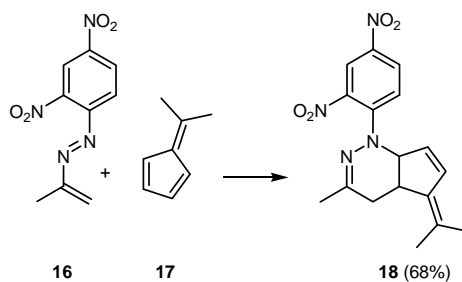


The reaction with carbon dienophiles^{12b,13,14} produces 2,3,4,5-tetrahydropyridazines (Scheme 4) and follows the pattern of the donor-acceptor relationship, *i.e.*, as more electron-rich or donor is the 2π partner and the more electron-deficient or acceptor is the azoalkene, the efficiency and selectivity of the reaction increase. Thus, for example, vinyl ethers are much more efficient reaction partners than simple alkenes. In some cases, and especially with 4-unsubstituted azoalkenes ($R^2=H$), a proper balance between electrophilicity/reactivity and stability must be attained in order to obtain better yields and clean reactions.



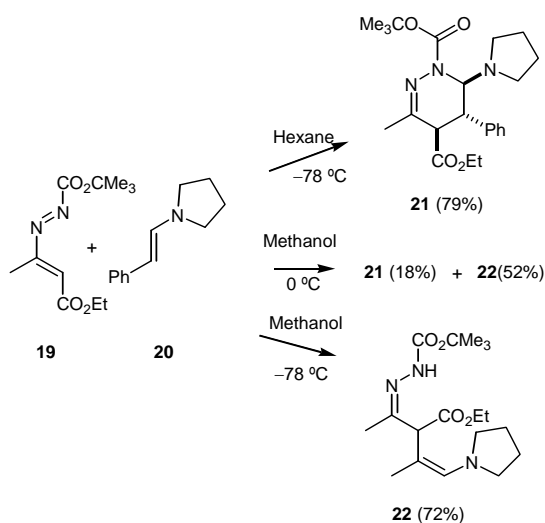
The vast majority of these reactions have been carried in a great variety of organic solvents, but often water is a better solvent and has been proved to be particularly suitable for asymmetric inverse-electron demand Diels-Alder reaction of azoalkenes¹⁵ (Scheme 5).

Cyclic and acyclic carbodienes such cyclopentadiene, 6,6-dimethylfulvene and 1,3-dimethyl-1,3-butadiene also participate, as dienophiles, in cycloaddition reactions with azoalkenes,^{10,13h,j,16} although occasionally diverse reactivity has been observed¹⁷(Scheme 6).



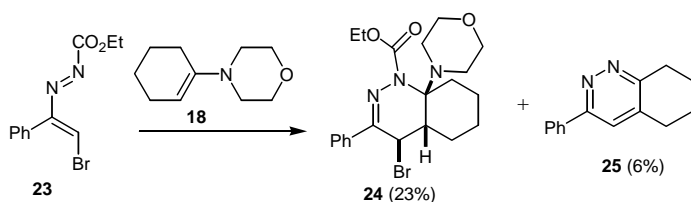
Scheme 6

When compared with other alkenes, reactions with highly activated dienophiles, such as enol ethers carrying extra donor substituents or enamines, are sometimes less straightforward. For example, reactions with enamines have been shown to be solvent and temperature dependent¹⁸ (Scheme 7).



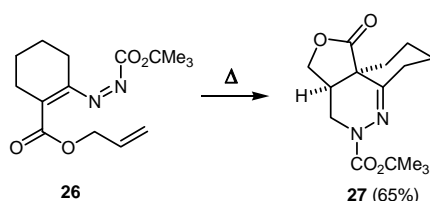
Scheme 7

In an investigation searching for possible anti-influenza virus, tetrahydropyridazines have been obtained as the sole reaction products in reactions of azoalkenes with enamines¹⁹ but 4-chloro- or 4-bromo-azodienes²⁰ produced tetrahydropyridazines and aromatized pyridazines (Scheme 8). Quite often the reactions of azoalkenes with enamines are on the borderline between [4+2] and [3+2] cycloadditions or between these and conjugate addition,^{18,20,21} and small structural or reaction conditions changes can drive the reactions to follow different mechanisms or even different mechanisms operating in the same reaction.



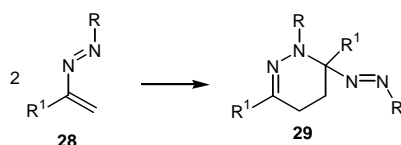
Scheme 8

Intramolecular [4+2] cycloadditions of azoalkenes have also been successfully reported as reliable synthetic strategies to diverse fused polyheterocycles.²² An illustrative example is shown in Scheme 9.



Scheme 9

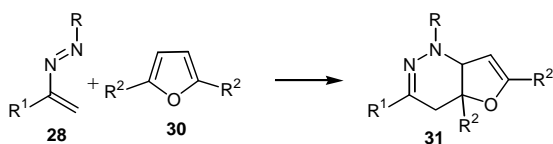
In the absence, or in the presence of a very inefficient dienophile, azoalkenes bearing no substituent at the 4-position show the tendency to self-condense giving cyclic dimers^{16,23} (Scheme 10).



Scheme 10

3.1.2. With electron-rich aromatic heterocycles

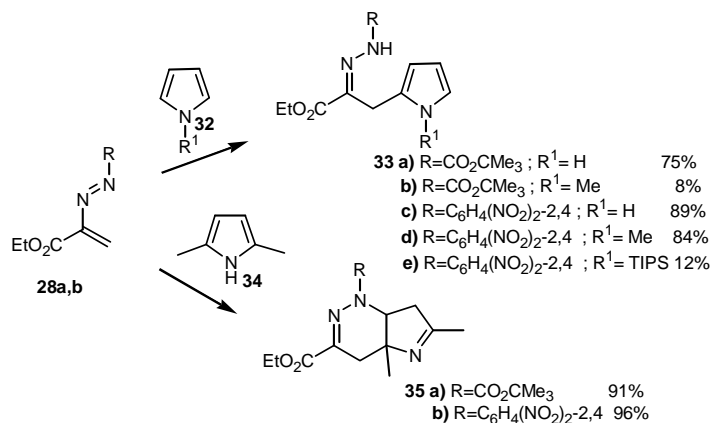
The most commonly reported cycloadditions with this class of compounds are with 5-membered rings, π -excessive heteroaromatics such as furans, pyrroles and indoles. Furan and 2,5-dimethylfuran have proved to be particularly good dienophiles in reactions with highly electrophilic azoalkenes bearing no substituent at C-4^{13b,h,16} (Scheme 11). However, when azoalkenes carrying 1- and/or 3-substituents possessing lower electron-withdrawing capacity were used, the reaction efficiency was lower and the yields inferior. No adducts were isolated when an ethoxycarbonyl group was present at the C-4 position.¹⁶



- a) R = CO₂CMe₃; R¹ = CO₂Et; R² = H 100%
- b) R = C₆H₄(NO)₂-2,4; R¹ = CO₂Et; R² = H 73%
- c) R = C₆H₄(NO)₂-2,4; R¹ = Ph; R² = H 89%
- d) R = C₆H₄(NO)₂-2,4; R¹ = Me; R² = H 22%
- e) R = C₆H₄(NO)₂-2,4; R¹ = Ph; R² = Me 87%

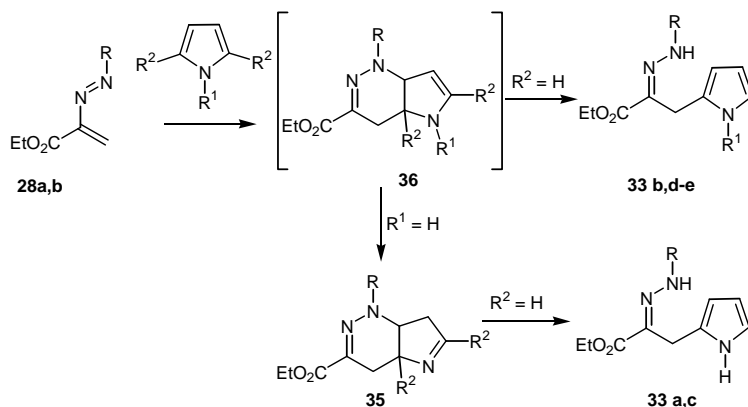
Scheme 11

With pyrrole^{13a,c,24} and *N*-methyl pyrrole²⁴ the open chain hydrazones **33** were isolated as single *anti* stereoisomers, but with 2,5-dimethylpyrrole **34** bicyclic pyridazines **35** were obtained²⁴ (Scheme 12).



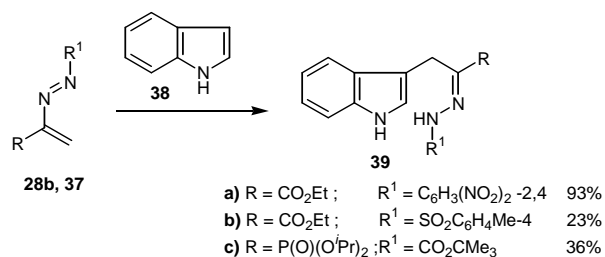
Scheme 12

With 1,2,5-trisubstituted pyrroles no adducts or cycloadducts were isolated, but only degradation products were detected. Taking into account all the above observations, the authors postulate that these reactions are all Diels-Alder cycloadditions with inverse electron demand. Cycloadducts **36** are proposed as the primary products of the reactions, but if no 2,5-substituents are present (R²=H), the six-membered heterocycles open to the corresponding hydrazones with the concomitant rearomatization to the thermodynamically more favorable pyrrole ring. With 2,5-disubstituted pyrroles, the primary cycloadducts **36** tautomerize to the imines such **35**; with 1,2,3-trisubstituted pyrroles this enamine-imine tautomerization is blocked and likely further additions (with the very reactive enamine double bond of **36**) can occur producing complicated mixtures of products²⁴ (Scheme 13).



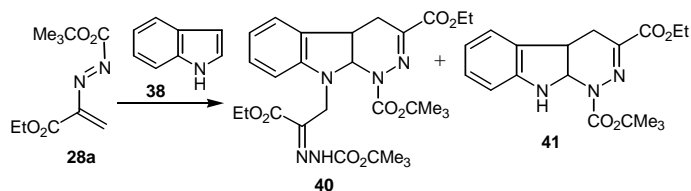
Scheme 13

Generally, for the reaction of azoalkenes with indole, the open chain hydrazones **39** are isolated as result of the rearrangement of primarily formed cycloadducts^{13c} (Scheme 14).



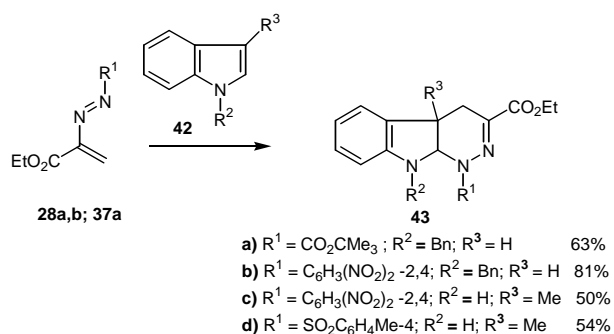
Scheme 14

The reaction of a large excess of indole with azoalkene **28a**^{13g} was more complicated. Two products were isolated, but neither of them was the expected open chain hydrazone. One, **40** (47%) was formed from one molecule of indole and two of the azoalkene; the other one was the 1:1 cycloadduct **41** (41%). If one equivalent of indole was used, only the 2:1 adduct **40** was isolated in 78% yield (Scheme 15).



Scheme 15

When an *N*-substituted indole such as 1-benzylindole was reacted with azoalkenes **28a** and **37a**, the 1:1 adducts **43a,b** were isolated. In contrast, this strategy was not necessary in the reactions of 3-methylindole and this latter proved to be a good heterodienophile. The cycloadducts **43c-d** were the sole isolated products^{13h} (Scheme 16).



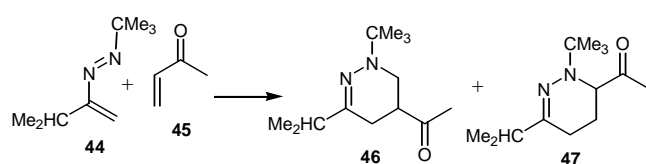
Scheme 16

Reactions between 1,3-dimethylindole and 1,3,4-trisubstituted azoalkenes were troublesome,^{21b} leading to complicate mixture of products arising from [4+2] or [3+2] cycloadditions.

3.1.3. With electron-deficient dienophiles

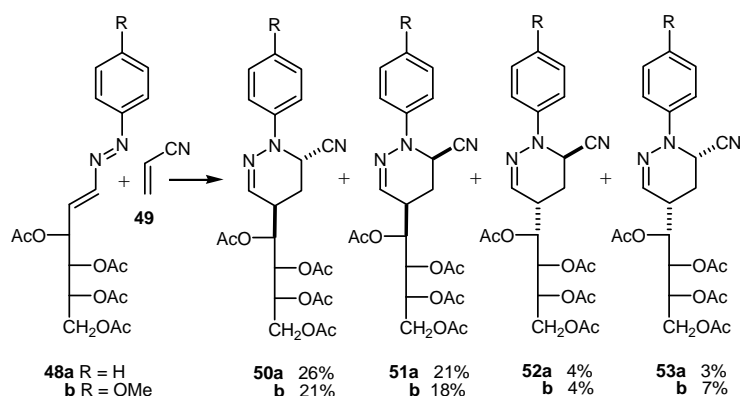
Although fewer examples are found, conjugated azoalkenes carrying no electron-withdrawing substituents, *i.e.*, possessing neutral or electron-releasing properties, can also efficiently participate, as

heterodienes, in normal electron demand Diels-Alder reactions with a large variety of electron-deficient 2π partners. Symmetrical dienophiles, such as tetracyanoethylene,²⁵ *N*-phenylmaleimide,²⁵ 4-phenyl-4*H*-1,2,4-triazole-3,5-dione,^{12a} maleic anhydride,²⁶ maleimide,²⁶ dimethyl fumarate²⁶ and diethyl azodicarboxylate (DEAD)²⁷ have been satisfactorily used. Methyl vinyl ketone^{23c,26} proved to be a very efficient dienophile for azoalkene **44**, since a quantitative yield was obtained, but the reaction lacked in regioselectivity since a 39/61 mixture of structural isomers of 5- and 6-acetyltetrahydropyridazines **46** and **47** were obtained, respectively (Scheme 17). Reactions of chiral carbohydrate-derived azoalkenes with 1,4-benzoquinone, 1,4-napthoquinone and also diethyl azodicarboxylate²⁸ occurred with high facial stereoselectivity. The reaction with DEAD was greatly improved by the use of microwave induction.²⁹



Scheme 17

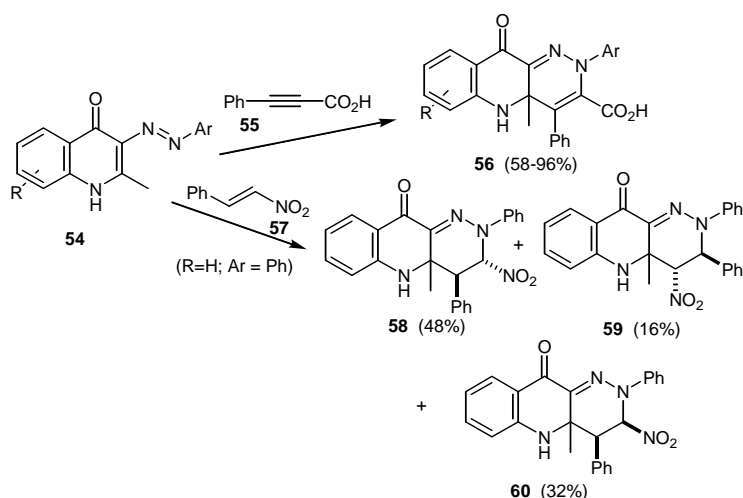
In order to shed some light on the regio- and diastereo-selectivity, the behaviour of chiral azoalkenes **48** with the unsymmetrical dienophile acrylonitrile **49** was experimentally and theoretically investigated³⁰ (Scheme 18).



Scheme 18

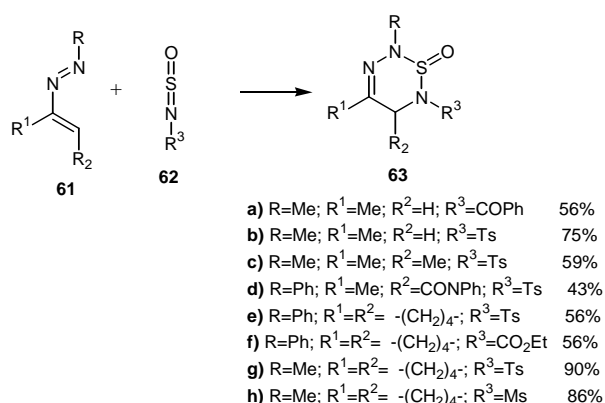
Reactions were found to be completely regioselective and the observed diastereoselection was consistent with a preferred attack to the *Re* face of the heterodiene unit. The stereochemistry of the major cycloadduct **50a** has been definitely established by X-ray crystallography, revealing in addition a conformation in which the cyano group was in axial position. The theoretical calculations, on a reduced model, correctly predicted the regiochemistry experimentally observed and also indicated that the axial orientation of the cyano group can be rationalized in terms of a stabilizing anomeric effect.

Quinolone based azoalkenes have been reported³¹ to produce pyridazines regioselectively when intercepted by phenylpropionic acid; β -nitrostyrene was also an efficient dienophile, but in this case, tetrahydropyridazinequinolone cycloadducts were obtained with lower selectivity (Scheme 19).



Scheme 19

In addition to electron-deficient C=C and N=N bonds, also N=S bonds of sulphinylamines³² (Scheme 20) and C=S bonds of fluorene-thione and fluorene-thione *S*-oxide (sulphine) have been used as hetero-dienophiles in reactions with azoalkenes (Scheme 21).³³ However, diarylsulphines and diarylthiones failed to react.



Scheme 20

Thus, cycloadditions of azoalkene **64** with thione **65** were found to be completely regioselective, leading to the corresponding *6H*-1,3,4-thiadiazine **66** but with sulphine **67**, smaller selectivity was observed, with the formation of regioisomeric mixtures of *2H*-1,2,3- and *6H*-1,3,4-thiadiazine-1-oxides **68** and **69**, even though the latter in a much smaller amount.

Diels-Alder cycloaddition reactions between electron-rich dienes and electron-rich dienophiles or *vice-versa*, between electron-deficient dienes and electron-poor dienophiles are uncommon. Recently unprecedented cycloaddition reactions between azoalkenes carrying electron-withdrawing substituents and electron-deficient dienophiles were reported,³⁴ conducting to novel tetrahydropyridazines **72** with a high degree of regio- and stereo-selectivity (Table 1).

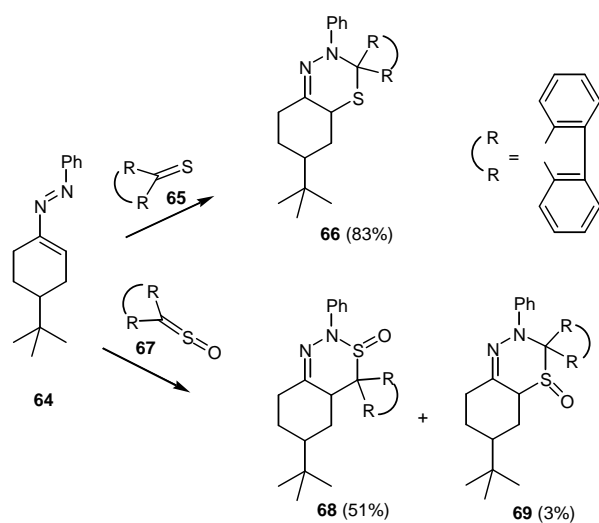


Table 1. Diels-Alder reactions of electron-deficient azoalkenes **70** with electron-deficient acrylate esters **71**.

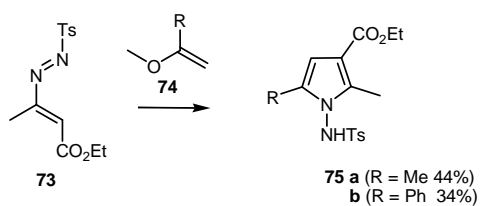
Entry	R	R ¹	R ²	R ³	R ⁴	yield %
1	H	Me	OEt	Me	H	65
1	H	Et	OMe	Me	H	78
1	Ph	Me	OMe	Me	H	52
1	Ph	Me	NMe ₂	Me	H	-
1	H	Me	NMe ₂	Me	H	-
1	H	Me	OEt	H	H	48
1	Ph	Me	OEt	H	Me	64

The authors postulate that these are Diels-Alder reactions with inverse electronic demand. The interaction between similar size coefficients of the LUMO and HOMO orbitals of azoalkene and of dienophile, respectively, will account for the observed selectivity.

3.2. [3+2] Cycloadditions

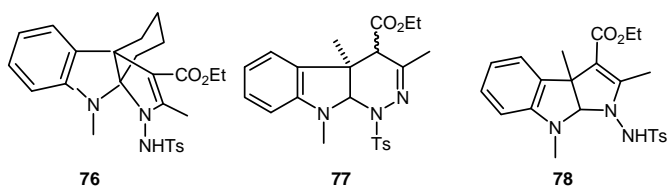
As previously mentioned, there are several examples in the literature where this type of reaction competes with the [4+2] cycloaddition.^{18,21}

The [3+2] reaction is predominant, or exclusive, when highly substituted enamines^{35,36} and highly substituted vinyl ethers,^{21b} further activated by the inclusion of electron-donor substituents, are used. Ethers such **74a** gave predominantly pyrroles by this type of reaction with tosyl azoalkene **73**^{21b} (Scheme 22).



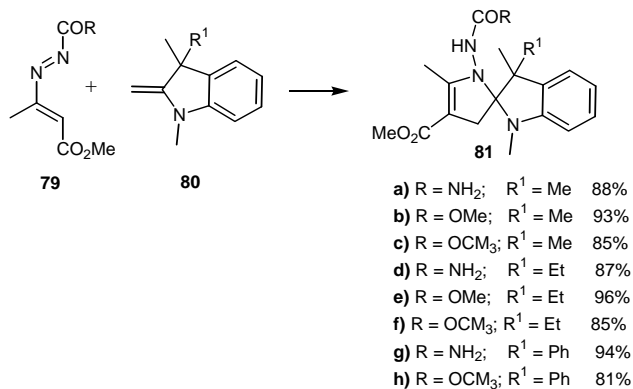
Scheme 22

Cyclic enol ethers, such as 5,6-dihydro-2-methyl-4*H*-pyran and 4,5-dihydro-2-methylfuran, produced dihydropyrroles similarly, although in an impure and inseparable mixture. This substituted dihydrofuran contrasts with unsubstituted 2,3-dihydrofuran, which gave the corresponding tetrahydropyridazine *via* a [4+2] reaction mechanism.^{21b} *N*-Methyltetrahydrocarbazole also preferably produced the corresponding dihydropyrrole **76** in 53% yield, although 1,3-dimethylindole produced a mixture of epimeric tetrahydropyridazines **77** (55%) and the corresponding dihydropyrrole **78** in 34% yield (Scheme 23).



Scheme 23

With 2-methyleneindolines, electrophilic azoalkenes such as **79** gave rise to spiro-dihydropyrroles **81**, likely resulting from a [3+2] cycloaddition process, since neither spiro-tetrahydropyridazines from a possible [4+2] cycloaddition nor Michael addition products were detected³⁷ (Scheme 24).



Scheme 24

Gilchrist *et al.*^{21b} postulated that a possible extreme zwitterionic mechanism could be operating, in which the nucleophilic olefin would add to the azoalkene, this being in a transoid conformation (and not in a *cis* conformation as required for the [4+2] cycloaddition), which then would collapse to an azomethine imide. Pyrroles and dihydropyrroles could then be formed from these by proton transfer (Figure 2). However such mechanism would be sensitive to the polarity of the solvent and this was not experimentally observed.

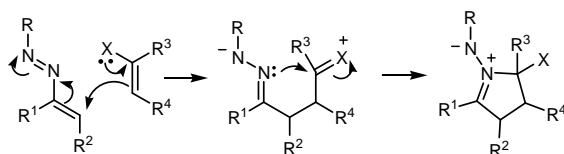


Figure 2. Eventual zwitterionic mechanism.

These observations led the authors to propose a concerted mechanism through a highly unsymmetrical transition state, in which C–C bond formation is more advanced than the C–N. The reaction could be initiated by the attack of the nucleophile on the transoid azo-olefin, but that as the reaction proceeds, the C–N–N fragment of the azo-olefin twists out of the plane, aligning the lone pair on the central nitrogen atom with the developing electrophilic centre of the α -carbon atom of the nucleophile (Figure 3).

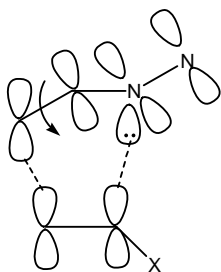
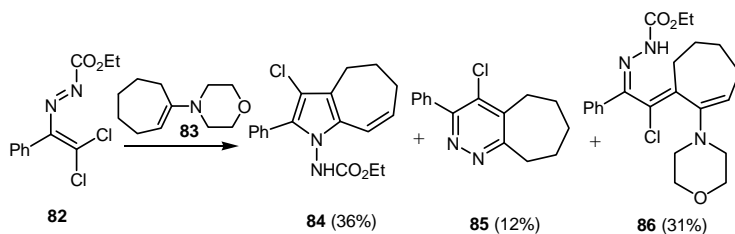


Figure 3. Proposed concerted [3+2] mechanism.

In the reactions of 4,4-dichloroazodienes **82** with enamines, pyrroles, pyridazines and hydrazones were isolated³⁸ (Scheme 25).



Scheme 25

This variety of products and the verified possibility of interconversion between some of them led to the presumption that both [3+2] and [4+2] reaction mechanisms were operating, but in a stepwise mode and not in a concerted mechanism. This would better account for the obtained results, although in clear contradiction with results encountered before with monochloroazoalkenes.^{13g}

Recently Attanasi et co-workers,³⁹ in kinetic studies aiming at the quantification of the electrophilicity of different azoalkenes in the reactions with α,β -disubstituted enamines, have isolated 1-aminopyrrole derivatives, arising from [3+2] reactions and beside the corresponding hydrazones resulting from 1,4-additions. Moreover, they found that experimental rate constants were larger than theoretically predicted and the strongest deviation was found for the reaction between the least electrophilic azoalkene with the least nucleophilic enamine. Thus this particularly high acceleration rate for the slowest reaction led the

authors to postulate a reaction mechanism with zwitterionic intermediates and transition states in which Coulombic attractions would explain the increased reactivity (Figure 4). This mechanism will accommodate the eventual addition of the enamines to both *Z*- and *E*-azoalkenes and also, as discussed above, the observations that enamines with no α -substituents gives rise to tetrahydropyridazines by [4+2] cycloaddition reactions. Although not ruling out the possibility of similar [4+2] reactions also occurring with these α,β -disubstituted enamines, the authors point out that these reactions would profit much less from Diels-Alder concertedness.

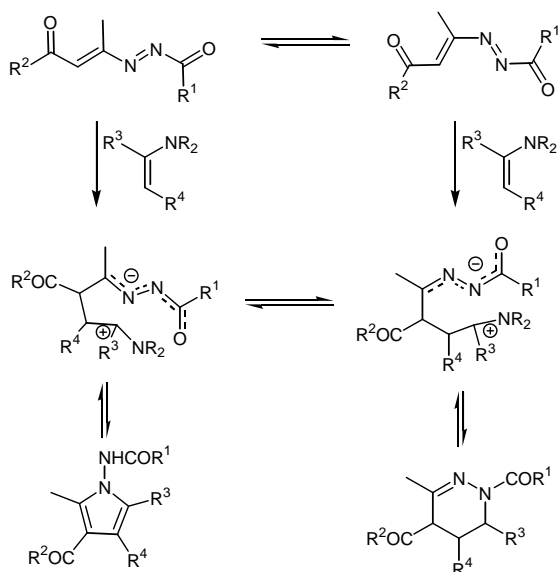
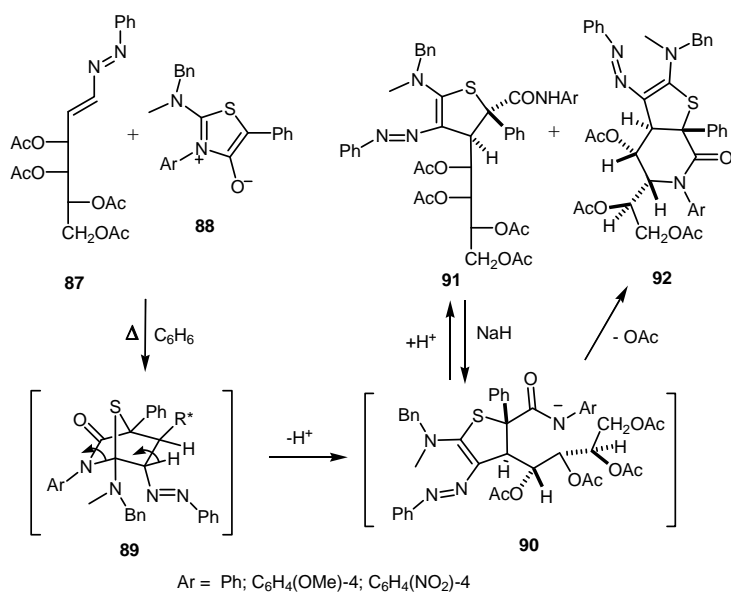


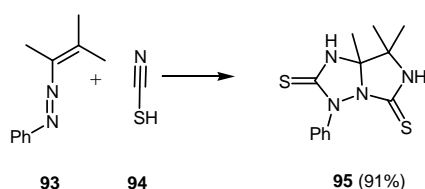
Figure 4. Postulated zwitterionic mechanism.



Scheme 26

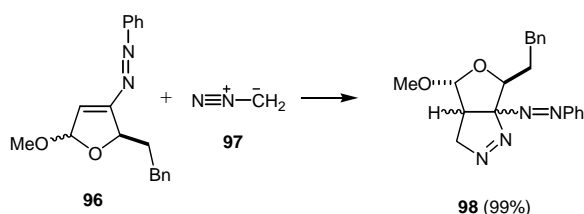
Five-membered heterocycles have also been obtained in reactions of mesoionic compounds, acting as 4π reaction partners, with azoalkenes, these now acting as the 2π components. Thioisomunchnones were utilized as starting dipoles and reacted with homochiral azoalkenes bearing an acyclic *D-arabino* carbohydrate derived side chain affording diastereomeric mixtures of 4,5-dihydrothiophenes.⁴⁰ When *D-lyxo* or *D-glycero* based carbohydrate azoalkenes were used, the primarily formed cycloadducts **89** evolved to didhydrothiophenes **91** and *trans*-fused bicyclic dihydrothieno[2,3-*c*]piperidines **92** with stereo-differentiation. These latter can also be obtained by treating those with NaH^{41} (Scheme 26). The chemoselectivity of this type of reactions should be emphasized since only the C=C double bond that was involved, therefore showing a higher electrophilicity/reactivity.

New imidazolinethiones, screened as potential inhibitors of retroviral HIV replication agents, have been synthesized *via* [3+2] cycloaddition reactions of azoalkenes with thiocyanic acid.^{42,43} This strategy was latter extended⁴⁴ when phenylazoalkene **93** was allowed to react with excess of thiocyanic acid affording 2,3,5,6,7,7a-hexahydro-7,7,7a-trimethyl-3-phenyl-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithione **95** as a result of two consecutive [3+2] cycloaddition steps (Scheme 27).



Scheme 27

Dihydro-pyrazole **98** has been obtained regioselectively when diazomethane was intercepted by azoalkene **96**⁴⁵ (Scheme 28).



Scheme 28

3.3. [4+1] Cycloadditions

In the search for a preparation of Fipronil®, a new fluorinated pyrazole with high insecticidal activity, and as well in search for anti-histaminic pyrazoles, Rhone-Poulenc (now BASF holds the patent rights for producing and selling Fipronil) researchers disclosed another type of cycloaddition reaction in which azoalkenes also participate as a 4π component, the formal [4+1] reaction of azoalkenes with isocyanides⁴⁶ (Table 2).

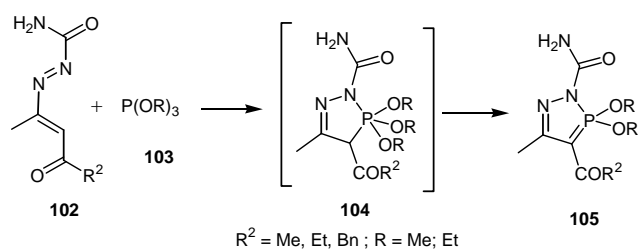
The reactions were more efficient when both R and R¹ were electron-withdrawing groups, in which cases good yields were obtained with almost equimolar amounts of reagents.

Eliminado:

Table 2. Reactions of azoalkenes with isocyanides.

$$\text{28a, 99} + \text{100} \longrightarrow \text{101}$$

Entry	R	R ¹	R ²	yield %
1	Ph	CO ₂ CMe ₃	CMe ₃	63
2	CO ₂ Et	CO ₂ CMe ₃	CMe ₃	80
3	CO ₂ Et	CO ₂ CMe ₃	o-tolyl	56
4	CO ₂ Et	CO ₂ CMe ₃	CH ₂ CO ₂ Et	57
5	CO ₂ Et	CO ₂ CMe ₃	CH ₂ CH(OMe) ₂	60
6	CO ₂ Et	2,4-dinitrophenyl	CMe ₃	96
7	CO ₂ Et	COPh	CMe ₃	0
8	Me	CO ₂ CMe ₃	CMe ₃	0
9	CO ₂ Et	CO ₂ CMe ₃	2-carbomethoxy-phenyl	50

**Scheme 29**

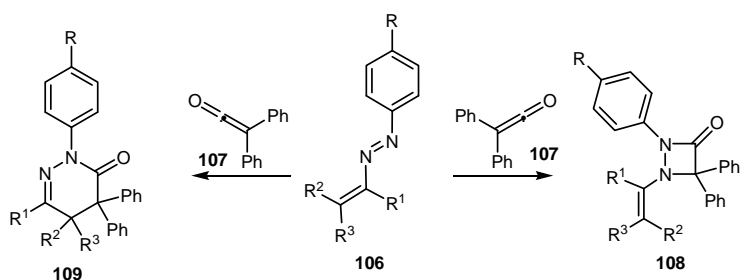
Trialkyl phosphites and electrophilic azoalkenes, *via* the same reaction mechanism and under nitrogen atmosphere, provided a general protocol for the selective preparation of alkyl 3,3-dialkoxy-2*H*-1,2,3λ⁵-diazaphosphole-4-carboxylates **105** in high yields^{47a} (Scheme 29). Similarly, 3-alkoxy-3-phenyl-2*H*-1,2,3λ⁵-diazaphospholes were obtained in reactions of azoalkenes **102** with dialkylphenylphosphonites under solvent free conditions without the need to exclude moisture.^{47b}

Diazaphosphole derivatives have also been obtained by reaction of azoalkenes with various phosphorus sources, such as dichlorophenylphosphine,⁴⁸ phosphorus trichloride⁴⁹ and fused benzothia-diphospholes.⁵⁰

3.4. [2+2] Cycloadditions

This type of cycloaddition of azoalkenes is much less common and the sole report involves the N=N bond and not the carbon-carbon double bond. (*E*)-Arylazoalkenes **106** readily react with diphenylketenes **107** providing *N*-vinyl-1,2-diazetidiones **108** and/or pyridazinones **109** by the more usual [4+2] reaction mechanism⁵¹ (Scheme 30).

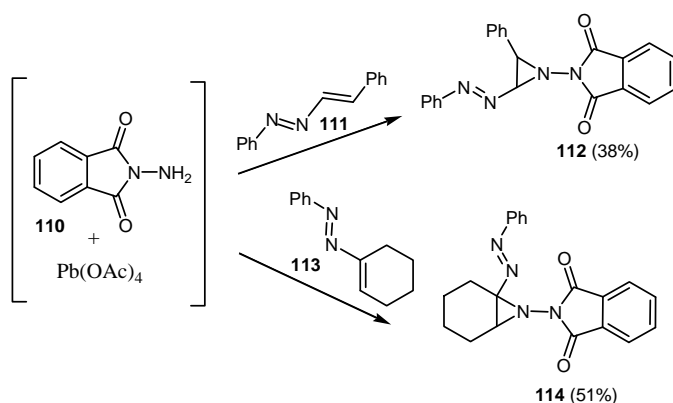
Analogous reactions involving a [4+2] and/or a [2+2] mechanism have been described between 1,3-diaza-1,3-butadienes and ketenes affording pyrimidinones and/or azetidiones.⁵²



Scheme 30

3.5. [2+1] Cycloadditions

The synthesis of three-membered ring heterocycles have been achieved *via* the reaction of *N*-amino-phthalimide with conjugated azoalkenes and lead tetraacetate.⁵³ The carbon-carbon double bond of azoalkenes **111** and **113** reacted chemoselectively producing the unknown C-azoaziridines (Scheme 31). The reaction is not general, since, by changing cyclohexene to the apparently very similar cyclopentene, dissimilarly products such as triazole derivatives were obtained.



Scheme 31

4. Final remarks

During the last three decades, the chemistry of conjugated azoalkenes has progressed amazingly. Their use either as 4 π or 2 π reaction partners in cycloaddition reactions has allowed the production of a great variety of heterocyclic compounds with interesting biological, pharmaceutical and chemical properties, using methodology based on accessible starting materials and easy scale-up. This, combined with the spectacular development of the 1,4-conjugate additions, demonstrates once again the efficiency of conjugated azoalkenes in heterocycles synthesis.

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