PROGRESS IN HETEROCYCLIC CHEMISTRY

VOLUME 7

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HETEROCYCLIC CHEMISTRY

Volume 7

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IN

HETEROCYCLIC CHEMISTRY

Volume 7

A critical review of the 1994 literature preceded by two chapters on current heterocyclic topics

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Contents

Foreword

Progress in Heterocyclic Chemistry (PHC) Volume 7 reviews critically the heterocyclic literature published mainly in 1994. The first two chapters are traditionally review articles. Chapter 1 surveys useful synthetic routes to "Polyfunctional Pyrroles and Pyrazoles" starting from conjugated azoalkenes. This review is based on the researches of O.A. Attanasi and his school in Urbino (Italy). As last year the second review is unconventional, comprising a compilation of the "Application of Diels-Alder Cycloaddition Chemistry for Heterocyclic Synthesis". It is written by our president A. Padwa and is in an unusual format with a pertinent list of references dating back forty years in some cases. We were encouraged to include this review because of favourable comments received from readers about this type of survey in PHC Volume 6.

The remaining chapters deal with advances in the heterocyclic field, arranged in ascending order of ring size. The reference system in the text is as usual modelled on that used in *Comprehensive Heterocyclic Chemistry* (Pergamon, 1984).

We much regret that Chapter 5 Part 5 on Five-Membered Ring Systems with N & S (Se) Atoms was not submitted through unforeseen circumstances. This omission will be rectified in the next volume.

Again we had a number of unsolicited approaches from our readers offering review articles for publication in future issues, for which we are grateful. This highlights the importance attributed to PHC as a publication in the heterocyclic field.

We thank all authors for providing camera-ready scripts with clear diagrams. We ask for forbearance for lack of uniformity in the technical presentation, which is unavoidable with authors from so many countries.

We are much indebted to David Claridge of Elsevier Science for his invaluable help with the presentation of chapters.

We hope that our readers will find that PHC offers information and inspiration in a pleasurable way, helped by an index and numerous diagrams.

H. Suschitzky
E. F. V. Scriven

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1995–1996

The International Society of Heterocyclic Chemistry is pleased to announce the establishment of its home page on the World Wide Web. Access can be gained from the following locations:

for USA, Americas, Japan:
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Chapter 1

Polyfunctionalized Pyrroles and Pyrazoles from Conjugated Azoalkenes

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1.1 Introduction

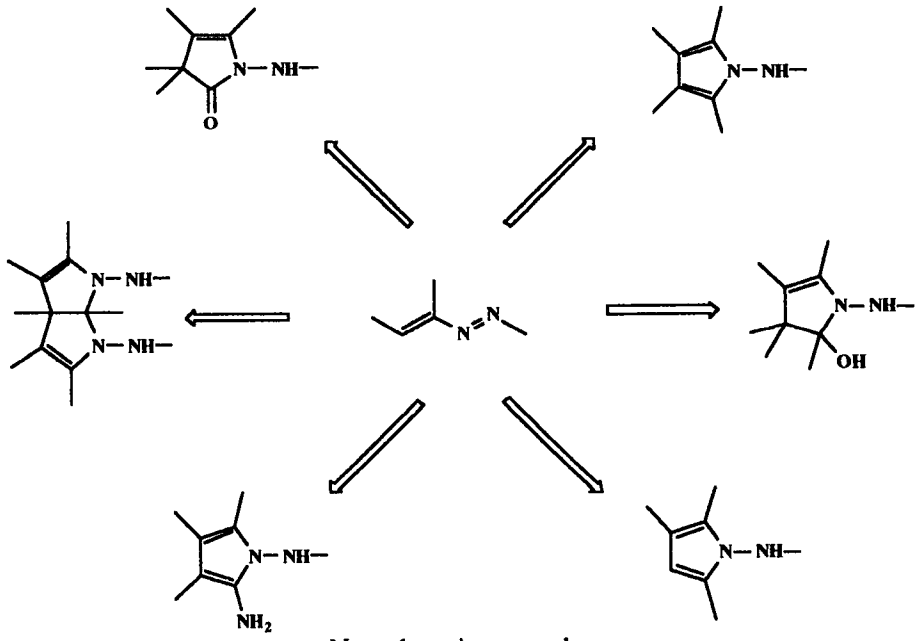
Conjugated azoalkenes, also named conjugated azoölefins or more rarely 1,2-diaza-1,3-butadienes, have been demonstrated to be valuable tools in organic synthesis both as acceptors in Michael additions and as partners in cycloaddition reactions [86OPP299]. In general, the >C=C< double bond in the heterodiene system of these substrates has been shown to be particularly reactive towards nucleophilic reagents because of the activating effect of the -N=N- group. In view of their versatility, we have frequently turned our attention to the synthesis of unknown conjugated azoalkenes [83CJC2665, 84S671, 84S873, 84S874, 85OPP385, 85JHC1341, 85H867, 87SC555, 88OPP408]. Some differences related to the presence of electron-rich (electron releasing) and electron-poor (electron withdrawing) substituents, mainly located on the terminal carbon and nitrogen atoms of conjugated azoalkenes, have been described in reference to the reactivity of these compounds [91JCS(P1)3361].

The azo-ene system of conjugated azoalkenes undergoes various nucleophilic attacks, frequently with high yield and under very mild reaction conditions, producing hydrazone derivatives by 1,4-conjugated addition (Michael-type). It is noteworthy that the hydrazones generated are often useful intermediates, giving rise to spontaneous reactions (i.e. eliminations, substitutions, internal nucleophilic attack with or without further elimination, heterocyclizations). In fact, in the presence of a good leaving group on the nucleophilic agents we have observed olefination

processes of the hydrazonic intermediate adducts, giving functionalized α,β-unsaturated hydrazones [88TL5787, 90T5685, 91JCR(S)252, 93T7027, 94S372, 94OPP485].

Based on our studies of conjugated azoalkenes over nearly twenty years, these starting materials have been shown to represent useful building blocks for the construction of uncommon polyfunctionally substituted pyrrole [93MI461] or pyrazole heterocycles.

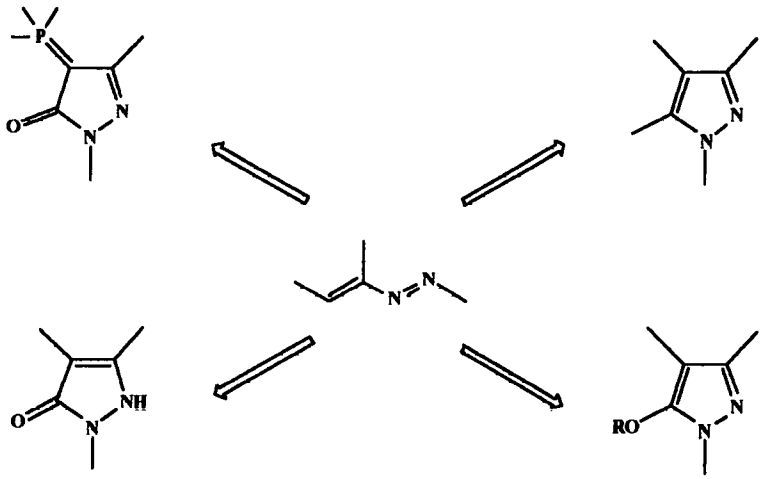
Using the above-mentioned hydrazone intermediates, derived from attack of nucleophilic species bearing carbonyl, cyano or carboxylate functions in α-position, many widely functionalized 1-aminopyrroles have been obtained (i.e. 3-substituted-1-aminopyrroles, 1-amino-2,3-dihydropyrrol-2-ols, 1,2-diaminopyrroles, pyrrolo[2,3-*b*]pyrroles, 1-amino-1*H*-pyrrol-2(3*H*)-ones, and 3-unsubstituted-1-aminopyrroles). The reaction pathway indicates an intramolecular interaction between the >C=N-NH- nitrogen atom and one of the above-mentioned functional groups followed by an appropriate molecular rearrangement and/or elimination, leading to the heterocyclization process. Scheme 1 shows the type of new pyrroles synthesized in our laboratory.



New 1-aminopyrroles

Scheme 1

In the case of the hydrazone intermediates from the nucleophilic attack of reagents possessing none of the above functions, the closure to give highly substituted pyrazole rings becomes possible. This is due to the internal attack by the >C=N-NH- nitrogen atom on the carboxylate group present in the azoalkene residue with loss of a suitable molecule yielding interesting 4-phosphoranylidene-1*H*-pyrazol-5(4*H*)-ones, 5-alkoxypyrazoles, and 1*H*-pyrazol-5(2*H*)-ones. 5-Substituted-pyrazoles derive from a slightly different reaction pathway. Schemes 2 shows the type of new pyrazoles synthesized in our laboratory.



New pyrazoles

Scheme 2

1.2 Pyrroles

The synthetic strategy elaborated by us for the polysubstituted title heterocycles from conjugated azoalkenes has made possible the direct preparation of pyrroles with four or five substituents, dihydropyrroles containing up to seven substituents, and fused pyrroles bearing eight substituents. In the case of pyrroles and dihydropyrroles, three substituents (one on the nitrogen and two on the ring) are from the azoolefinic substrates and the rest are derived from the nucleophilic reagents. In fused pyrroles, conjugated azoalkenes supply two equal or different substituents onto the nitrogen heteroatoms and four substituents onto the ring, while the other two substituents derive from the nucleophile

agents employed. In accordance with the general pathway of the reaction, these facts permit to program the substituents of the final molecules. The mechanism of these reactions requires the presence of at least one hydrogen atom on the terminal carbon atom of the azo-ene system, to give 3-substituted-1-aminopyrroles, while the presence of two hydrogen atoms on the same carbon atom should produce 3-unsubstituted-1-aminopyrroles [90T395, 93JCS(P1)1391].

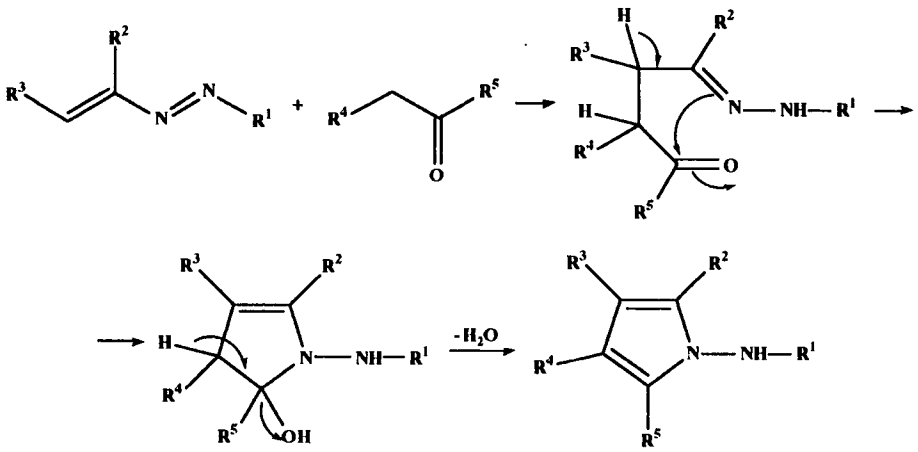
It is noteworthy that in pyrrole derivatives obtained from conjugated azoalkenes prepared by reaction of carbonyl compounds and several hydrazine derivatives (i.e. *tert*-butylcarbazate, benzoylhydrazine, *p*-toluenesulfonylhydrazine, *p*-methoxybenzensulfonyl-hydrazine, 2,4,6-trimethylbenzensulfonylhydrazine), the amino function on the nitrogen heteroatom possesses a protective group (i.e. Boc, Bz, Ts, Mbs, Mts) which is removable by well known procedures [91MI277].

In general, easier reactions are observed when methylene or methine groups in α-position to carbonyl, cyano or carboxylate functions are further activated by directly linked strong electron withdrawing groups (i.e. ketonic, ester, amidic, sulphonic, nitrilic, nitric, phosphoranic, phosponic). However, even remote activation has been found to be sufficient in some cases to bring about the expected reactions. Frequently these reactions occur with high yield in one-flask at room temperature, often without isolation of the intermediates, sometimes by metal ion or base catalysis.

1.2.1 3-Substituted-1-aminopyrroles

The activated methylene group of β-diketones or β-ketoesters [82JOC684, 83JHC1077, 85S157, 85H867, 86SC343, 86JHC25, 87T4249, 88H149, 95UP1], β-ketoamides [83S742, 84S671, 84S873, 84S874, 86OPP1, 86SC1411, 88G533], β-ketosulphones [86BCJ3332, 87S381, 88JHC1263], β-ketonitriles [92JCS(P1)1009], and β-ketophosphonates [94S181] readily attacks the heterodiene system of conjugated azoalkenes, yielding the hydrazonic 1,4-adduct intermediates followed by the 1-amino-2,3-dihydropyrrol-2-ol owing to five-membered ring formation. In this cyclization the ketonic group is clearly favoured in respect of the ester, amidic, and nitrilic groups, with preference for the aliphatic rather than aromatic carbonyl. The loss of a water molecule gives the final 3-substituted-1-aminopyrrole derivatives, as the more stable heteroaromatic rings (Scheme 3). The reaction between conjugated azoalkenes and

compounds containing a remotely activated methylene group in α-position to a keto-group proceeds in an analogous way [93JCS(P1)315].



R^1=H, Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, MeOCO, EtOCO, Me_3COCO, NH_2CO, PhNHCO, $PhSO_2$, 4-$MeC_6H_4SO_2$, 2,4,6-$Me_3C_6H_2SO_2$, 4-$ClC_6H_4SO_2$, 4-$OMeC_6H_4SO_2$, MeCO, PhCO, 3-ClC_6H_4CO, 3-MeC_6H_4CO, $PhCH_2CO$, 3-NO_2-2-Pyridyl, 2-Pyrimidyl, 2-Benzothiazolyl, Ph_2PO, $(EtO)_2PO$, $(PhO)_2PO$.

R^2=Ph, $PhCH_2$, Me, 4-$NO_2C_6H_4$.

R^3=Ph, MeOCO, EtOCO, $PhCH_2OCO$.

R^2,R^3=-$(CH_2)_4$-.

R^4=Me, MeCO, Me_3CCO, PhCO, 4-BrC_6H_4CO, MeOCO, EtOCO, Me_3COCO, $PhCH_2OCO$, NH_2CO, Et_2NCO, PhNHCO, 4-$OMeC_6H_4NHCO$, 4-ClC_6H_4NHCO, $MeSO_2$, $PhSO_2$, 4-$MeC_6H_4SO_2$, CN, 4-$NO_2C_6H_4$, 2-FC_6H_4, $(MeO)_2PO$.

R^5=Me, Et, Pr, Ph, $MeOCOCH_2$, Me_3C, 4-$NO_2C_6H_4$.

R^4,R^5=-$(CH_2)_3CO$.

Scheme 3

An exception to this general reaction pathway is represented by some pyrroles derived from the reaction between conjugated azoalkenes and compounds containing active methinic groups. In this case, the molecule, yields the pyrrole ring, as terminal reaction product [89G631].

All the intermediates mentioned have been isolated, characterized, and then converted into subsequent intermediates or products. Particular difficulties were encountered in the isolation and characterization of the supposed 1-amino-2,3-dihydropyrrol-2-ol intermediate which was isolated for the first time after many years of investigations [87T4249]. These difficulties were ascribed to the poor stability of this intermediate due to the facile loss of water, as well as methanol or acetic acid [89G631], with

production of a five-membered aromatic heterocycle. Therefore, these reactions often occur with high yields in one-flask at room temperature, in the presence of catalytic amounts of copper(II) chloride.

The relatively little-known and quite controversial ^{13}C-NMR chemical shift assignments for several of these compounds have been studied in detail [85MRC383, 88MRC714, 88G533]. In view of the wrong structural assignment by previous authors, the crystal structure of some of these molecules was unambiguously determined by X-ray diffraction studies [82JOC684, 85AX(C)450, 87T4249, 88G533].

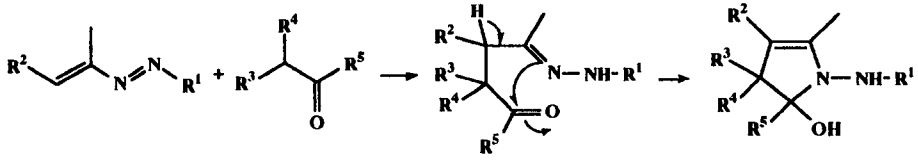
1.2.2 1-Amino-2,3-dihydropyrrol-2-ols

1-Amino-2,3-dihydropyrrol-2-ols, having an hydrogen atom on the carbon atom in position 3, were isolated for the first time during the synthesis of some 3-substituted-1-aminopyrroles, as moderately stable intermediates because of the elimination of a water molecule with consequent aromatization of the pyrrole ring [87T4249].

The structure of one of these intermediates was unequivocally confirmed by X-ray diffraction investigation [87T4249].

Several derivatives of this type have been produced by treatment of conjugated azoalkenes with CH-substituted β-diketones, β-ketoesters, β-ketolactones, β-ketonitriles or β-nitroketones containing an activated methinic group [89G631, 92JCS(P1)3099, 93T7027].

It has been observed that the heterocyclization process of the hydrazonic 1,4-adduct occurs selectively on the keto group and the absence of a proton on the carbon atom in α-position allows the preparation of unknown stable 1-amino-2,3-dihydropyrrol-2-ols in good



R^1=MeOCO, Me_3COCO, NH_2CO, PhNHCO, PhCO, 3-ClC_6H_4CO, 3-MeC_6H_4CO, $PhCH_2CO$.
R^2=MeOCO, EtOCO.
R^3=Me, MeCO, PhCO, EtOCO, CN, NO_2.
R^4=H, Me, Ph.
R^3,R^4=-$(CH_2)_2OCO$.
R^5=Me, Ph, 4-$NO_2C_6H_4$.
R^4,R^5=-$(CH_2)_3$-, -$(CH_2)_3CO$, 2-C_6H_4CO.

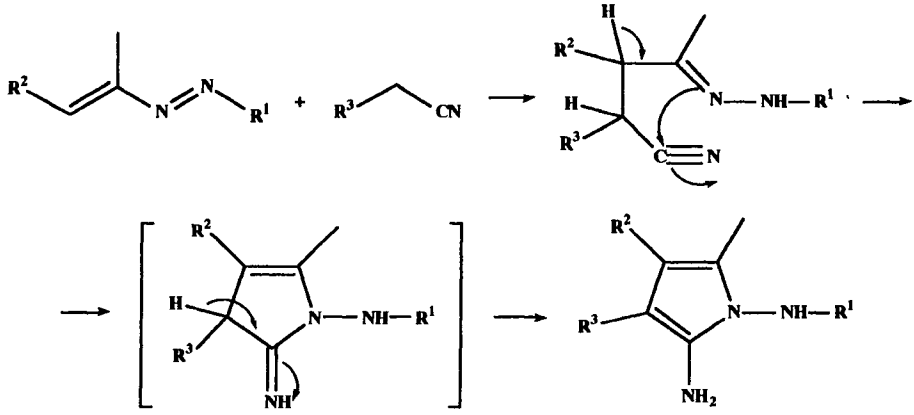
Scheme 4

yields (Scheme 4).

1.2.3 1,2-Diaminopyrroles

The ready reaction of conjugated azoalkenes with a molar excess of nitriles containing activated methylene groups (e.g. malononitrile, β-cyanoamides, β-phosphononitriles or remotely activated nitriles) has been examined.

This reaction afforded the preliminary equimolecular conjugate adducts by nucleophilic attack of these reagents on the azo-ene system of the azoölefin substrates. An intramolecular nucleophilic attack from the >C=N-NH- nitrogen atom on the carbon atom of the cyano group brings about the five-membered ring closure leading to the 2-iminopyrroline intermediates that readily tautomerize into novel 1,2-diaminopyrroles (Scheme 5).



R^1=H, MeOCO, EtOCO, Me_3CO, $CONH_2CO$, PhNHCO.
R^2=MeOCO, EtOCO.
R^3=CN, 4-$NO_2C_6H_4$, 2-Benzoimidazolyl, PiperidineNCO, $(EtO)_2PO$.

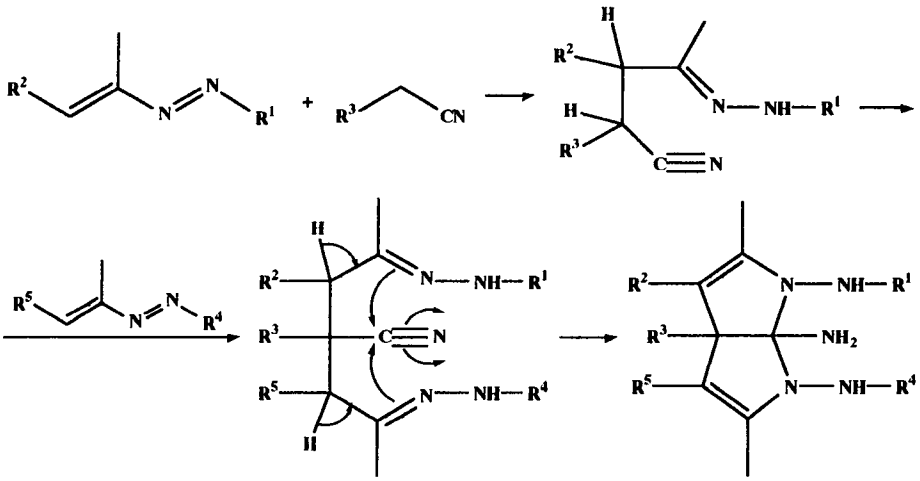
Scheme 5

These reactions often proceed with good yields in one flask at room temperature [90JCS(P1)1669, 92JCS(P1)1009, 93JCS(P1)315, 94S181].

1.2.4 Pyrrolo[2,3-*b*]pyrroles

A molar excess of conjugated azoalkenes reacts with nitriles containing activated methylene groups (e.g. malononitrile, β-

cyanoketones, β-cyanoesters, β-cyanoamides or β-phosphononitriles) to give at first 1:1, and then 2:1 conjugate adducts. At times, these bis-adducts have been obtained either starting with a molar excess of the same conjugated azoalkene, or by addition of a further amount of a different conjugated azoalkene molecule to the 1:1 adducts formed.



R^1 and R^4=MeOCO, EtOCO, Me_3COCO, NH_2CO, PhNHCO.
R^2 and R^5=MeOCO, EtOCO.
R^3=MeOCO, EtOCO, Me_3COCO, PhCO, CN, PiperidineNCO, $(EtO)_2PO$.

Scheme 6

The 2:1 conjugate adduct intermediates undergo a double concerted ring formation in which one nitrile group is twice operative, most probably due to the greater reactivity of the imino function produced after the first ring closure rather than to that of other cyano or different groups present in the molecular residue. For this reason fused-type, rather than spiro-like, five-membered heterocycles have been obtained by these reactions, providing new polyfunctionally substituted 1,3a,6,6a-tetrahydropyrrolo[2,3-*b*]pyrroles (Scheme 6).

Frequently, these reactions take place smoothly with good yields at room temperature without isolation and purification of the intermediates [90JCS(P1)1669, 92JCS(P1)1009, 94S181]. The complicated molecular structure of one of these compounds has been unequivocally established by X-ray diffraction study [90JCS(P1)1669].

1.2.5 1-Amino-1*H*-pyrrol-2(3*H*)-ones

Many widely substituted 1-amino-1*H*-pyrrol-2(3*H*)-ones, which cannot be easily prepared by other procedures, have been recently prepared by treatment of conjugated azoalkenes with various activated esters or Meldrum's acid derivatives.

During many years of our investigation, only cyano or ketonic carbonyl groups proved to be operative in the pyrrole ring production from 1,4-adduct intermediates. A qualitative examination of the comparative reactivity order between these two functional groups in the closing step may be summarized as follows: CO>CN [92JCS(P1)1009, 92JCS(P1)3099]. Other activating groups, including the ester group, present in the nucleophilic agents were found to be ineffective in the cyclization process. This is mainly due to the spontaneous ability of the cyano and keto groups to undergo ring formation under very mild conditions, while the ester group generally requires more drastic conditions (i.e. strong bases).

In fact, activated esters with one active hydrogen atom (i.e. CH-substituted β-cyanoesters, β-diesters, β-esterphosphoranes or β-esterphosphonates) react rapidly with conjugated azoalkenes to produce the corresponding hydrazonic adduct intermediates, from which the required 1-amino-1*H*-pyrrol-2(3*H*)-ones are formed by ring closure onto the carboxylate group, with loss of a molecule of alcohol (Scheme 7, path A). However, in the case of the 1,4-adduct intermediates derived from the treatment of conjugated azoalkenes with CH-substituted β-cyanoesters, the ring closure onto the cyano group is more difficult because of the lower stability of the 2-iminopyrroline compared to the final 1-amino-1*H*-pyrrol-2(3*H*)-one originating from the ring closure on the ester function [90T5685, 92JCS(P1)3099, 94SC453, 94CJC2305].

The treatment of conjugated azoalkenes with β-diesters or β-esterphosphonates possessing two active hydrogen atoms produces, by means of the usual preliminary hydrazone intermediates, the unusual 3-monosubstituted 1-amino-1*H*-pyrrol-2(3*H*)-ones, as discussed above [94SC453, 94CJC2305].

These findings appear to be consistent with the following qualitative reactivity order in the closure of the heteroring: CO>CN>COOR.

The reaction between conjugated azoölefins and Meldrum's acid or its 5-substituted derivatives leads, *via* 1,4-conjugate addition, to the