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Introduction.

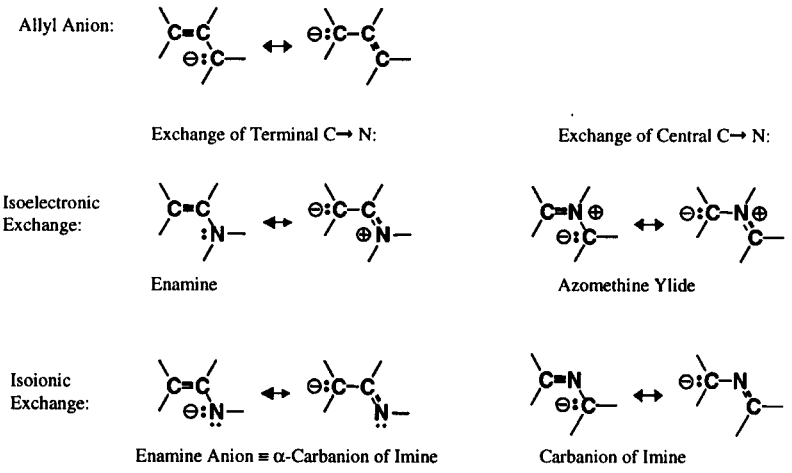
The allyl anion is characterized by 4 π-electrons distributed over three carbon atoms. The allyl anion is the parent system of a number of important and interesting functional groups which are derived from it by gradually replacing carbon atoms with hetero atoms. The formal exchange of carbon atoms by nitrogen can be achieved in two manners. The electronic situation at the site of the exchange is preserved, *i.e.* the number of bonds extended from this site including the number of nonbonding electron pairs has not changed. This so-called isoelectronic exchange applied to one terminal carbon atom of the allyl anion is represented by the enamine function (Scheme 1).

The isoelectronic exchange of the central carbon atom of the allyl anion by nitrogen gives rise to the azomethine ylide function. This system cannot be represented without separated charges as long as the octet rule is obeyed; this is a characteristic of so-called 1,3-dipolar species.

Retaining the charge at each position of the allyl anion in the course of the formal replacement of a carbon atom constitutes an isoionic exchange. The replacement of any single carbon atom of the allyl anion with a nitrogen atom gives rise to imine anions, their reactivity is mainly determined by the negative charge (Scheme 1).

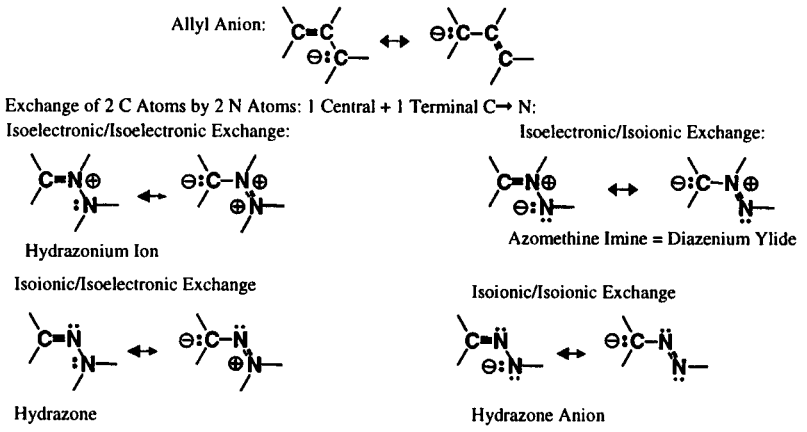
Scheme 1

Hetero Allyl Anion Equivalents: 4π-Electrons/3 Atoms (CCN, CNC)



Scheme 2

Hetero Allyl Anion Equivalents: 4π-Electrons/3 Atoms (CNN)



Replacing the central and one of the terminal carbon atoms of the allyl anion with two nitrogen atoms gives rise to charged species if both exchanges are either isoelectronic or isoionic resulting in the hydrazonium ion and the hydrazine anion, respectively (Scheme 2).

Isoionic exchange of the central atom and isoelectronic exchange of the terminal atom leads to the hydrazone function. The inverse order of both exchanges gives rise to a 1,3-polar functional group as represented by two resonance structures representing an azomethine imine or diazenium ylide (Scheme 2).

Results and Discussion.

Hydrazones derived from monosubstituted hydrazines and azomethine imines can be considered to coexist in an acid induced equilibrium [1].

It has been found that ketohydrazones react with protic heterocumulenes such as the *in situ* generated isocyanic acid and isothiocyanic acid affording the respective triazolidine derivatives in an apparent [3 + 2] cycloaddition reaction (Scheme 3) [2].

A remarkable feature of these heterocyclic compounds is the facile oxidation under concomitant ring opening and the formation of diazenylalkyl-substituted heterocumulenes.

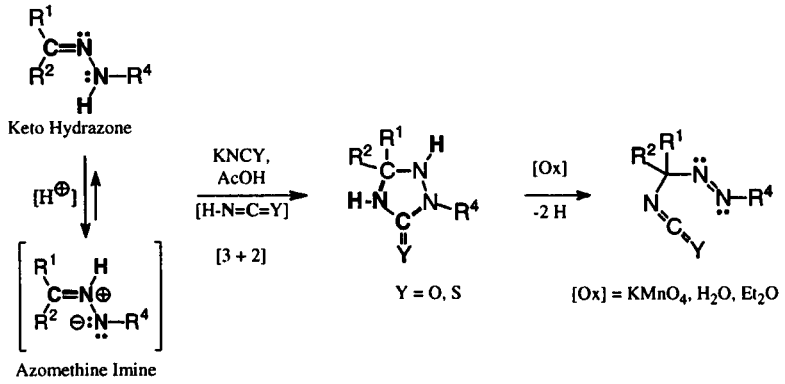
These compounds, in turn, react partly as expected: With heteroatom nucleophiles the isocyanate and isothiocyanate functions are transformed into the respective carbamic acid derivatives (Scheme 4) [3].

However, some reactions can be better rationalized by the cyclic valence isomer structure (the zwitterionic triazoliumide), which is not spectroscopically evident but can be trapped - for instance - by the addition of acid giving rise to the isolable, crystalline triazolium salt [4].

Depending on the nature of the ring substituents both the diazenylalkyl heterocumulenes (presumably in the form of the cyclic valence isomer) and the triazolium salt undergo a thermally induced rearrangement reaction, a [1,2]shift of one of the *gem* carbon substituents to the neighboring electron-deficient nitrogen atom resulting in the formation of triazolinones and triazolinethiones [4,5,6].

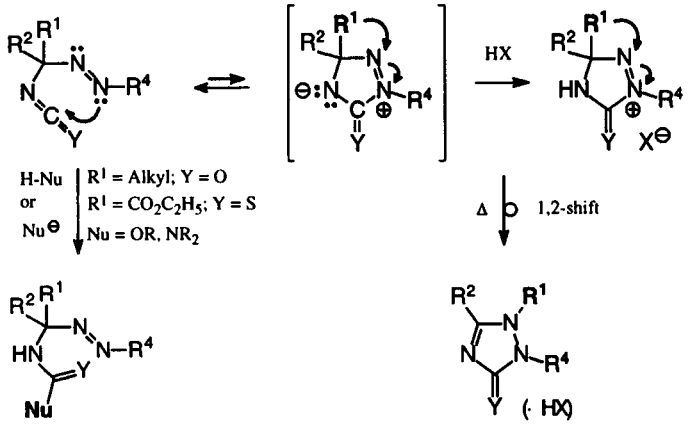
Scheme 3

[3 + 2] Cycloaddition Reaction of Ketohydrazones. Oxidation of [1,2,4]Triazolidin-3-ones and 3-Thiones



Scheme 4

Reactions of 1-(1-Diazenyl-1-alkyl)-1-heterocumulenes

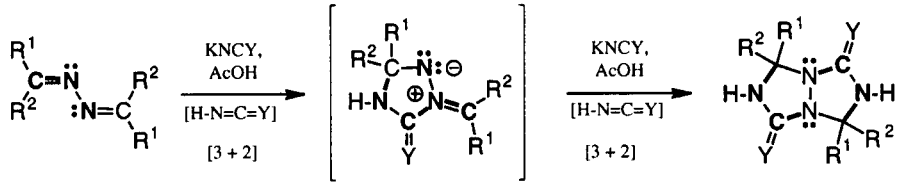


Azines, *e.g.* aldazines also react with protic heterocumulenes affording [1,2,4]triazolo[1,2-*a*][1,2,4]triazoles (Scheme 5). This reaction is envisaged as a tandem [3 + 2] cycloaddition reaction. In the first step one of the two hydrazone moieties forms a monocyclic intermediate with an azomethine imine function, which, in turn, triggers a subsequent [3 + 2] cycloaddition reaction to yield the bicyclic products. This reaction sequence is known as the "Criss-Cross" reaction [7,8].

A seemingly different but intrinsically similar reaction takes place in the course of the reaction of α-halo ketones with potassium thiocyanate in acetic acid and monosubstituted hydrazines (Scheme 7). This multistep reaction sequence is carried out as an efficient one-pot procedure and affords 1-aminoimidazoline-2-thiones. Obviously, the α-halogen atom is first displaced by the thiocyanate group. Subsequently, the corresponding hydrazone is formed, which, in turn, undergoes a 1,4-elimination reaction providing an azo-

Scheme 5

The Classical "Criss-Cross" Reaction: Tandem [3 + 2] Cycloaddition Reactions of Azines



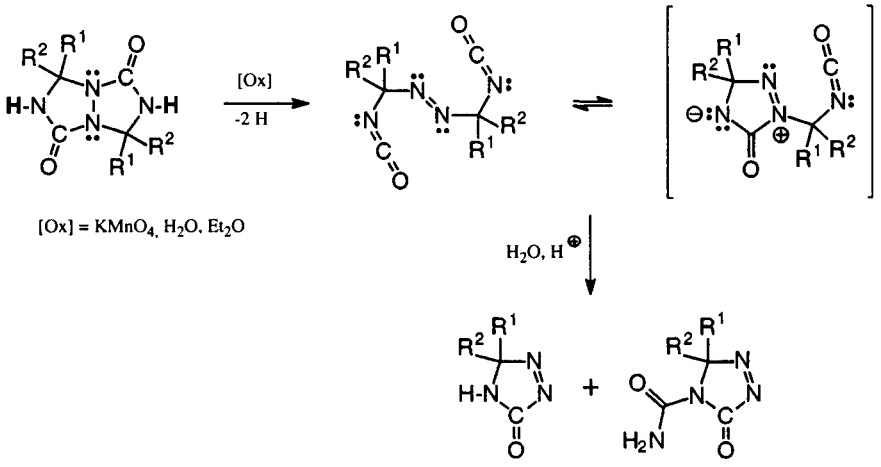
R^1 = H, R^2 = Ar; Y = O, S
R^1, R^2 = Alkyl; Y = O

The bicyclic products from the analogous reaction of ketazines with cyanic acid [8] undergo an interesting subsequent transformation. Oxidation with $KMnO_4$ gives rise to bis(isocyanatoalkyl)diazenes (Scheme 6) [10]. Also these compounds are considered to exist in an equilibrium with the cyclic zwitterionic valence isomer that nicely explains the facile formation of triazolinones upon solvolysis, in particular with aqueous acids.

alkene and thiocyanic acid. Both reaction intermediates can be supplied as reactants and afford the same final product. Apparently, the enamine moiety of the azoalkene reacts as a 4 π-electron/3 center species and undergoes a [3 + 2] cycloaddition reaction with the π-bond of thiocyanic acid resulting in an adduct containing an azomethine imine function. A subsequent and obviously rapid [1,4]shift of hydrogen from the ring position-4 to the exocyclic nitrogen atom provides the final product (Scheme 7) [11,12].

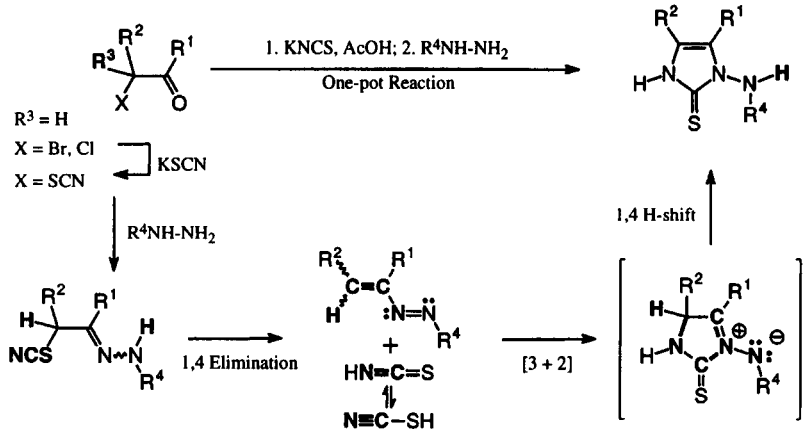
Scheme 6

Oxidation of [1,2,4]Triazolo[1,2-*a*][1,2,4]triazole-2,5-diones. Hydrolysis of 1,2-Bis(1-isocyanato-1-alkyl)diazenes



Scheme 7

Conversion of α-Halo Ketones into 1-Aminoimidazoline-2-thiones

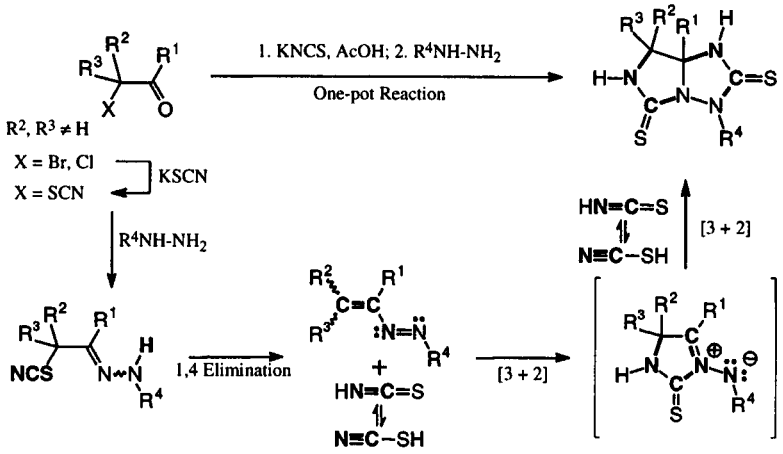


Bicyclic products, imidazo[1,5-*b*][1,2,4]triazoles are obtained from α-haloketones lacking the α-hydrogen atom at the α-carbon atom carrying the halogen atom (R^2 and $R^3 \neq H$) (Scheme 8) [13,14]. Again, the products are formed in the course of an efficient one-pot procedure. The reaction follows the same reaction path as in the previous reaction except for the last step: Again, the azoalkene and thiocyanic acid are the key intermediates that undergo a [3 + 2] cycloaddition reaction. The resultant adduct cannot undergo a [1,4]shift of hydrogen due to the lack of a hydrogen atom in the proper position 4. Therefore, the azomethine imine intermediate undergoes a [3 + 2] cycloaddition reaction with another molecule of thiocyanic acid.

This overall tandem [3 + 2] cycloaddition reaction resembles a novel facet of the classical Criss-Cross reaction (Scheme 9): The formal exchange of two atoms of the azine (the terminal carbon atom and the non-adjacent nitrogen atom), formally converts it into an azoalkene. The first [3 + 2] cycloaddition reaction occurs across the enamine moiety, and the resultant cyclic azomethine imine undergoes the second cycloaddition reaction. As in the classical Criss-Cross reaction a bicyclic product is obtained, only the regiochemistry of the second cycloaddition step is inverse.

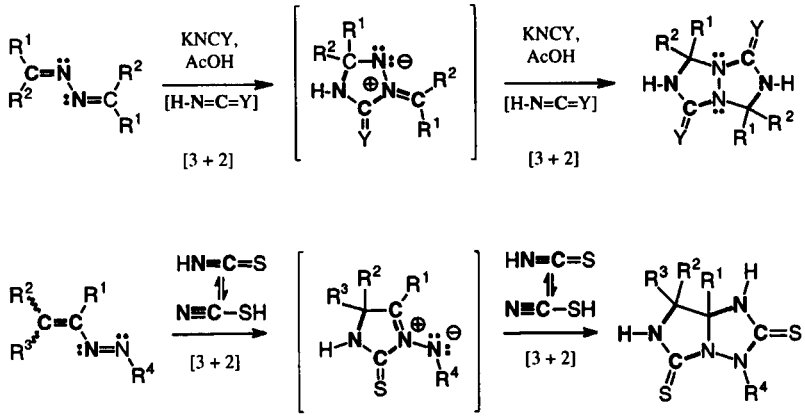
Scheme 8

Tandem [3 + 2] Cycloaddition Reactions of Azoalkenes



Scheme 9

"Criss-Cross" Reactions of Azines and Azoalkenes



The monocyclic *N*-aminoimidazoles feature some interesting properties with respect to both structure and reactivity: The thione function of the one-pot reaction product can be modified by facile and straight forward derivatization (*vide infra*).

These *N*-aminoimidazole derivatives can be viewed also as tri- and tetrasubstituted hydrazine derivatives (Scheme 10). A common feature of these compounds is the mostly restricted rotation about the N,N-bond inducing axial chirality at ambient temperature. This can be observed in the ^{1}H nmr spectra of these compounds by monitoring the signals of the diastereotopic methylene protons of a benzyl substituent. The rotation is strongly affected by the substituents at the exocyclic nitrogen atom and at the neighboring ring positions [11].

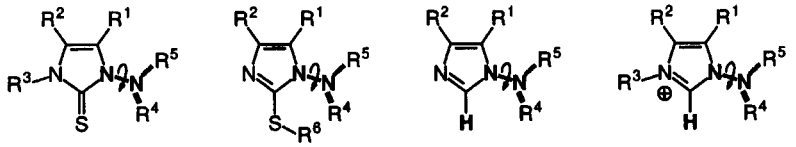
As an illustration the ^{1}H nmr spectrum of the 1-(*p*-nitroanilino)imidazole-2-thione derivative exhibits an AB quartet for the methylene group at room temperature (Scheme 11). The coalescence temperature at 75° C allows the evaluation of the rotational barrier with 72.1 kJ/mol [11].

Oxidative reduction of 1-aminoimidazoline-2-thiones with hydrogen peroxide in acetic acid replaces the sulfur function by hydrogen, and the resultant 1-aminoimidazole derivatives can be converted into imidazolium salts (Scheme 12) [11,12].

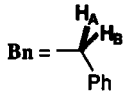
The 2-unsubstituted imidazolium ions undergo various reactions: Imidazole derivatives with 2-substituents are obtained upon the reaction with nucleophiles. Apparently, the addition across the charged C=N double bond is followed by the elimination of the amine substituent (Scheme 13) [12].

Scheme 10

Restricted Rotation About N-N-Bonds

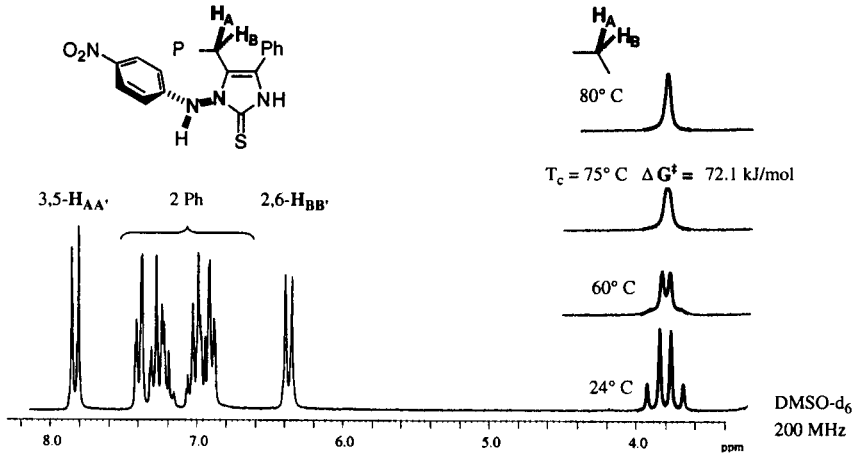


R^1, R^2 = H, alkyl, aryl;
R^3 = H, alkyl; **Bn**
R^4 = alkyl, aryl;
R^5 = H, alkyl, Ac
R^6 = H, alkyl; **Bn**



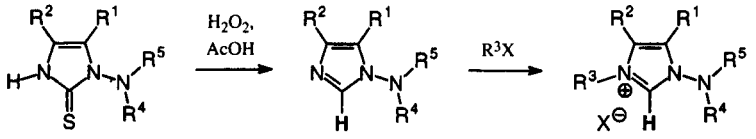
Scheme 11

^{1}H-nmr Monitoring of Restricted N,N-Bond Rotation



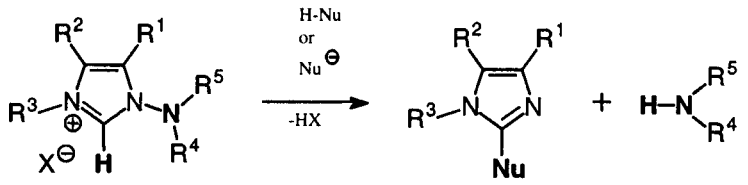
Scheme 12

2-Unsubstituted 1-Aminoimidazolium Ions. Preparation



Scheme 13

2-Substituted Imidazoles Derived from Nucleophiles



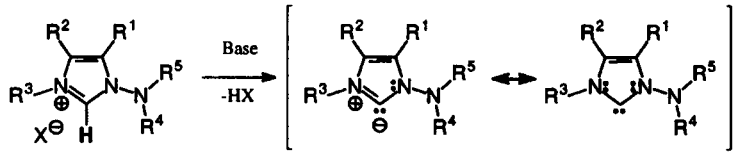
Nu = OR, NR_2, $CR_3^{\ominus}$

On the other hand, aroyl groups are introduced in position-2 upon treatment of the 2-unsubstituted imidazolium salts with base in the presence of aromatic aldehydes again at the expense of the amino side chain that is lost in the course of this reaction (Scheme 14) [12].

As shown before, the bicyclic products are available only as thione derivatives. Both thione functions can be converted into carbonyl groups upon reaction with alkaline hydrogen peroxide (Scheme 16) [14].

Scheme 14

2-Unsubstituted 1-Aminoimidazolium Ions. Reaction with Base: Transient Nucleophilic Carbenes

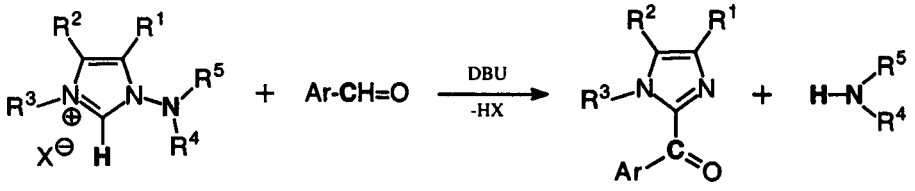


Presumably, the treatment with base gives rise to the formation of a nucleophilic carbene as a transient species. There are more examples available indicating the intermediacy of nucleophilic carbenes (Scheme 15) [12].

Treatment of the bicyclic compounds with base induces the cycloelimination of one of the two thiocyanic acid moieties. With a methyl group at the angular position the isolated elimination product is the ene hydrazine isomer

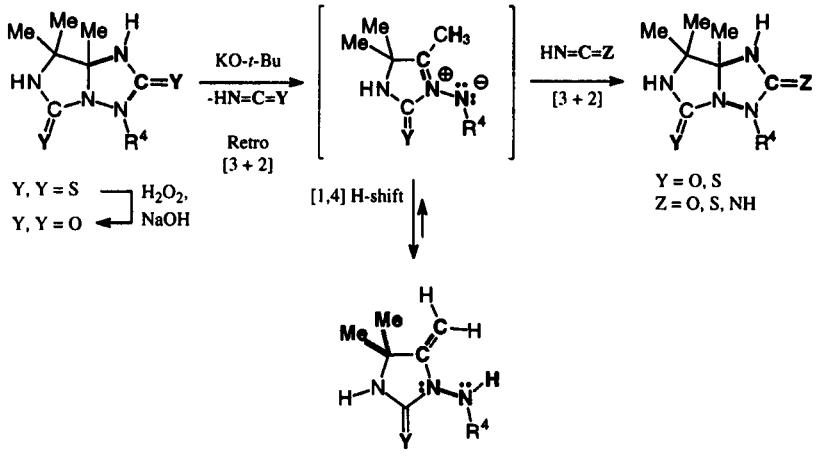
Scheme 15

2-Substituted Imidazoles Derived from Electrophiles (*e.g.* Aromatic Aldehydes) *via* Nucleophilic Carbenes



Scheme 16

Equilibrium Azomethine Imine - Ene Hydrazine



resulting from a [1,4]shift of hydrogen of the expected monocyclic azomethine derivative [14] (Scheme 16). However, the reactivity is determined by either of the two structures, the azomethine imine and the enamine (ene hydrazine).

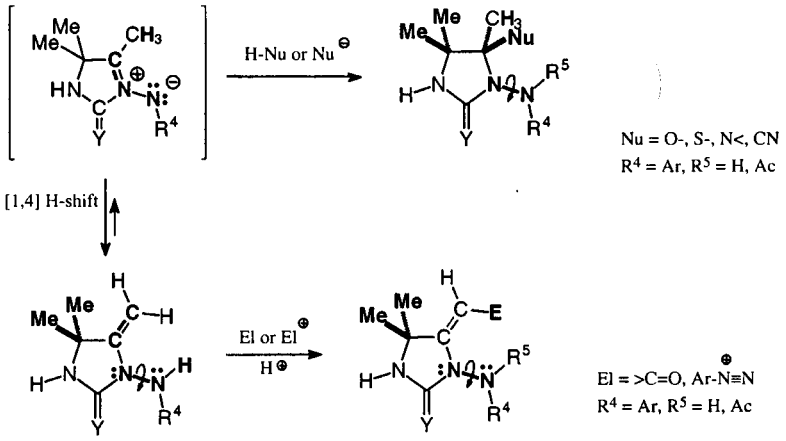
Protic heterocumulenes add across the 1,3-dipolar azomethine imine function to give bicyclic adducts (Scheme 16) [14]. Nucleophiles invariably add across the charged C=N double bond. Electrophiles (*e.g.* acid chlorides) attack the exocyclic N-atom of the ene hydrazine form (Scheme 17), but some electrophiles like activated carbonyl compounds and diazonium ions react at the terminal olefinic carbon atom to give the substituted ene hydrazine derivatives (Scheme 17) [14,15].

Subsequent oxidation with *t*-butyl hypochlorite goes along with ring-opening and provides α-diazenylalkanoyl chlorides, which upon treatment with diazomethane provide the corresponding α-diazoketones (Scheme 16) [17].

The treatment of α-diazoketones with silver benzoate or rhodium acetate afforded partly unexpected products. With silver benzoate in the presence of triethylamine and methanol the expected Wolff rearrangement of a carbene intermediate is induced as indicated by the formation of the methylester of the respective ketene precursor. In addition, a yellow crystalline product was isolated which turned out to be a 4-membered azomethine imine (Scheme 19) [17].

Scheme 17

Reactions of the Azomethine Imine/Ene Hydrazine with Nucleophiles and Electrophiles



The ene hydrazines, and their reaction products with nucleophiles and electrophiles are tri- and tetrasubstituted hydrazine derivatives, and again, the restricted rotation about the N-N single bond is observed giving rise to axial chirality which is monitored in these compounds by the ^1H nmr signals of the diastereotopic gem methyl groups [15].

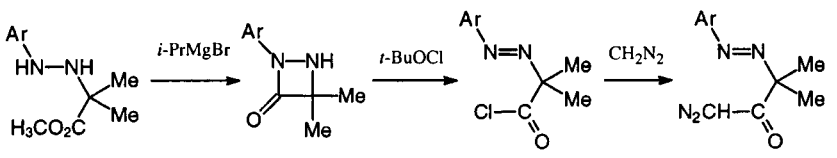
Recently, the conversion of hydrazine alkanoates into diazetidinone derivatives has been reported (Scheme 18) [16].

The same 4-membered heterocyclic product was formed in higher yield in the course of the reaction of the diazoketone with catalytic amounts of rhodium acetate. Furthermore, a minor crystalline product was isolated which was shown to be the 5-membered isomer of the former product, again containing an azomethine imine function (Scheme 19) [17].

The 4-membered azomethine imine appears to be formed in the course of a kinetically controlled reaction

Scheme 18

Preparation of 3-[(*E*)-2-Aryl-1-diazenyl]-1-diazo-3-methyl-2-butanones



The U-4CR.

Particularly in the chemical industry, the U-4CR is nowadays used very often, since their products can be prepared by minimal preparative work, and usually in very high yields and are thus easy to automate. In 1961 it was demonstrated that educts of a U-4CR can simultaneously form 10,000 substitutionally different products if all four classes of educts contain 10 different starting materials [29]. In the search for new products libraries of the U-4CR and related processes are now formed and industrially investigated very intensely [4,6,7].

The U-4CRs form their products from amines, aldehydes or ketones, acids and isocyanides. In contrast to other reactions, the U-4CR can form a very great variety of constitutionally different types of products, whose different types of acid and amino components determine their structural features. If a U-4CR proceeds too slowly, then instead of the amine and carbonyl components, their Schiff bases or enamines are reacted with the acid and isocyanide. Under suitable reaction conditions their products are then very quickly formed, and their yields are often almost quantitative [7]. In contrast to most other chemical reactions, the U-4CR and related processes allow all combinations of their educts to form their products. These reactions proceed though their educts form products that are extremely crowded. Thus, it was recently demonstrated that even the tripeptide **9** can be formed by a U-4CR, which cannot be produced by any other reaction [30].

The *Xylocain*™ **14** of the AB Astra in Sweden was one of the most popular local anaesthetics, which was originally prepared by several different multistep procedures [31]. In January 1959 Ugi and co-workers [23] introduced a new way of producing **14** by the U-4CR. The *Xylocain*™ **14** was then the only widely used product of its type, but in the last few years more than 20 different but closely related products were derived. All of these compounds could be formed in one step by a U-4CR [7].

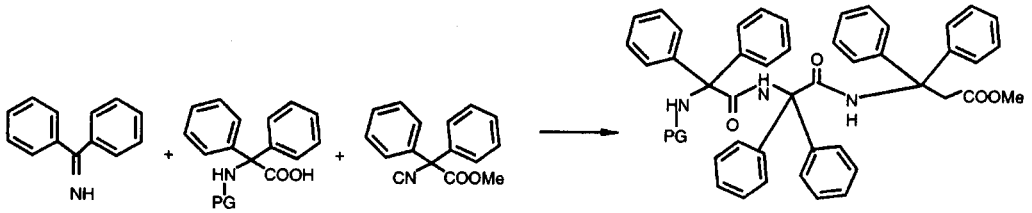
The products shown in Scheme 6 were directly formed by the U-4CR. They were thus always easier and in higher yields prepared than by any different way that consisted of some multistep syntheses [4,7].

Generally there are two ways of the formation of heterocyclic compounds by MCRs. Either the heterocycle is formed during the MCR - quasi de novo - or the heterocycle is part of a starting material and is diversified during the MCR.

Is the heterocyle synthesized during the MCR? One can distiguish between the heterocycle formation as an intrinsic consequence of a starting material (inner circle of Scheme 7) or as a consequence of a combination of functional groups of one or more classes of starting materials (outer circle of Scheme 7).

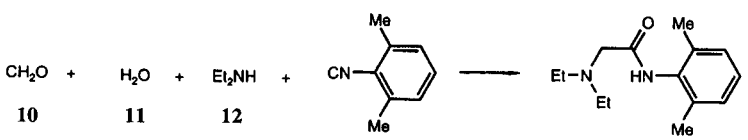
Recently the Merck Research Laboratory prepared the HIV protease inhibitor *Crixivan*™ (MK 639) **20** by a U-4CR as the central step. Thus, the number of preparative steps towards **20** could be tremendously reduced [32].

Scheme 4



6 7 8 9

Scheme 5

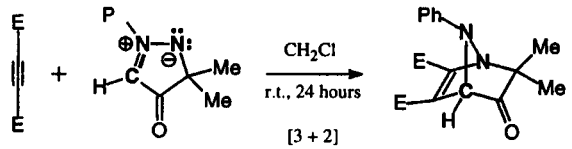


10 11 12 13 14

Contrary to the mechanistically rather complicated transformations of the 4-membered azomethine imine, the reaction of the 5-membered azomethine imine isomer with DMAD provides a single [3 + 2] cycloaddition product (Scheme 21) [18]. In this bicyclic adduct the CNN connectivity of the azomethine imine is retained.

Scheme 21

Reaction of the 4-Membered Ring Azomethine Imine with Dimethyl Acetylenedicarboxylate



$E = CO_2CH_3$ 90%

With both cyclic azomethine imine isomers further reaction have been carried out [18,19]. Furthermore, the intramolecular interaction of diazoketone-derived carbenoids or carbenes with diazenyl groups separated by a longer tether affording larger rings is under investigation [20].

Acknowledgements.

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