

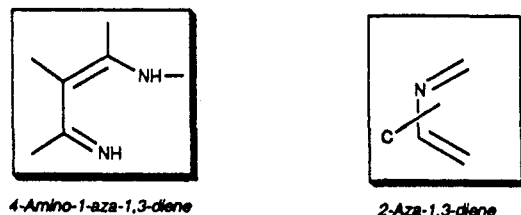
New perspectives of carbo- and hetero-1,3-dienes in organic synthesis

José Barluenga*, Fernando Aznar, Santos Fustero, and Miguel Tomás.
Departamento de Química Organometálica, Universidad de Oviedo.
33071 Oviedo, Spain.

Abstract. The preparation and reactivity of 4-amino-1-azadienes and electronically neutral 2-azadienes is reported. The suitability of the 1-azadiene system for the synthesis of five-, six-, seven-, and eight-membered as well as the synthetic utility of 2-azadienes through [4+2] cycloadditions is presented.

For some years the azadiene derivatives have attracted our attention due to their utility as synthetic intermediates. In this lecture we are going to give you some recent achievements in synthesis of nitrogen-containing cyclic and acyclic compounds starting from 4-amino-1-aza- and 2-aza-1,3-dienes (Figure 1).

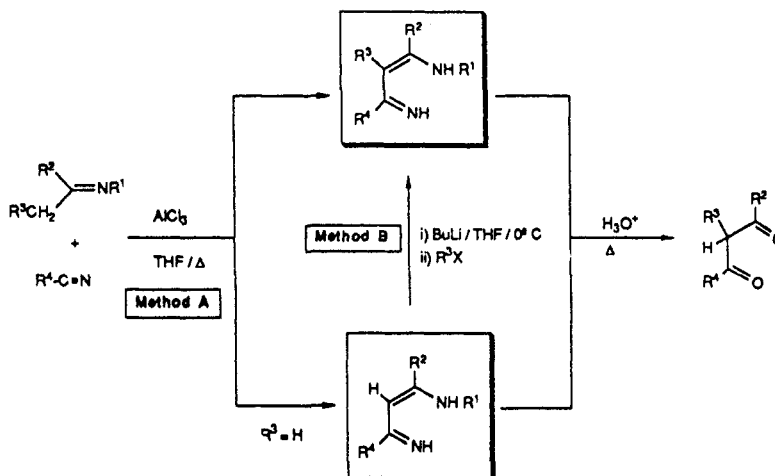
Figure 1



4-amino-1-azabutadienes

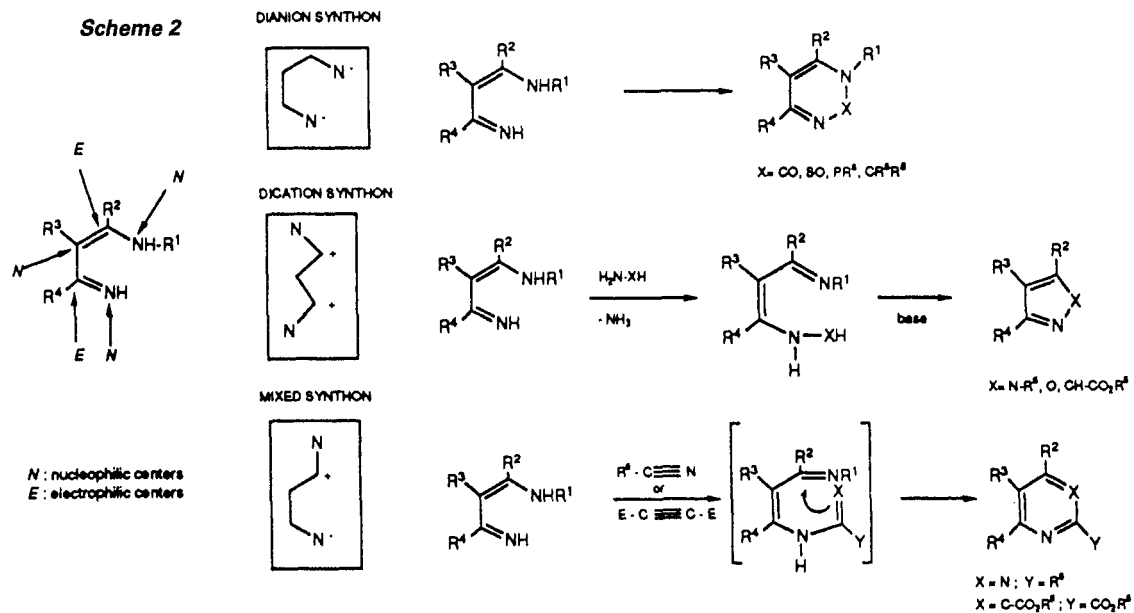
These systems are prepared in quantitative yields by heating at 60° C a THF mixture of ketimine, saturated nitrile, and aluminium chloride, as outlined in Scheme 1 (ref. 1). Azadienes derived from aldimines ($R^2=H$) are synthesized using LDA, as reported by Wittig (ref. 2). Hydrolysis of both imine and enamine groups leads cleanly to C-substituted 1,3-diketones (ref. 3).

Scheme 1



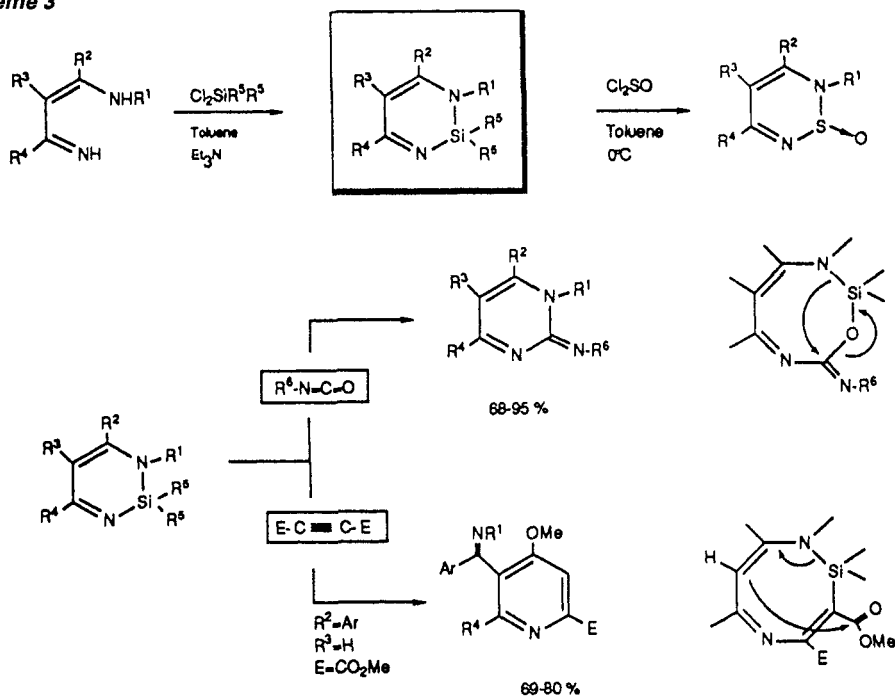
The high degree of functionalization allows these compounds to react through all positions. Several representative examples leading to heterocyclic compounds are shown in Scheme 2. Thus, both nitrogen atoms (dianion synthon) are involved in the condensation reaction with electrophilic species ($ClCO_2Et$, R^5R^6CO , Cl_2SO , Cl_2PR^5 , etc) to furnish pyrimidine (ref. 4), 1,2,6-thiadiazine (ref. 5), and 1,3,2-diazaphosphorine (ref. 6) derivatives; reaction of the azadiene system through both electrophilic imine and C α -enamine carbon atoms (dication synthon) occurs when treated in pyridine with nucleophiles, like hydrazine (ref. 7), hydroxylamine (ref. 8), and glycine methyl ester (ref. 9),

yielding five-membered heterocycles (pyrazoles, isoxazoles, and pyrroles, respectively). The azadiene behaves as a mixed synthon in its reaction with esters of acetylenedicarboxylic acid (ref. 10) and nitriles (ref. 11); this reaction allows the preparation of highly substituted pyridines and pyrimidines.

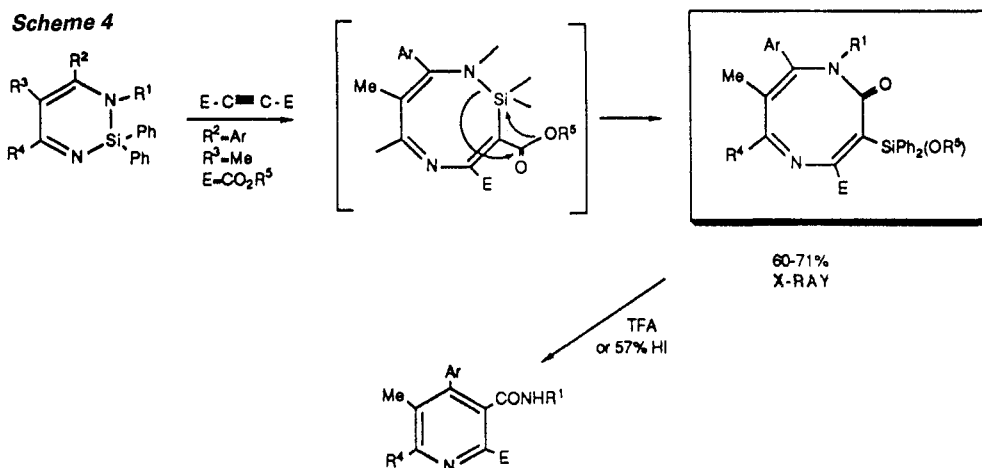


At this point, we realized that the reactivity of 4-amino-1-azadienes might be changed with the assistance of silicon. Thus, treatment of azadienes with dichlorosilanes gives quantitatively the corresponding diazasilines (ref. 12), which on reaction with thionyl chloride leads to 1,2,6-thiadiazine *S*-oxides, as expected. The reactivity of diazasilines was first tested towards heterocumulenes and esters of acetylenedicarboxylic acid and found that the reaction products are different than those formed from free azadiene; thus, treatment of diazasilines with isocyanates and of diazasilines having no substitution at the C-5 carbon ($R^3=H$) with dimethyl acetylenedicarboxylate yields 2-iminopyrimidines (ref. 13) and 4-methoxypyridines, respectively. Both reactions are assumed to occur through the insertion of the nitrogen-silicon bond into the electrophilic substrate followed by rearrangement involving either the enamine nitrogen or the C β -enamine carbon as depicted in Scheme 3.

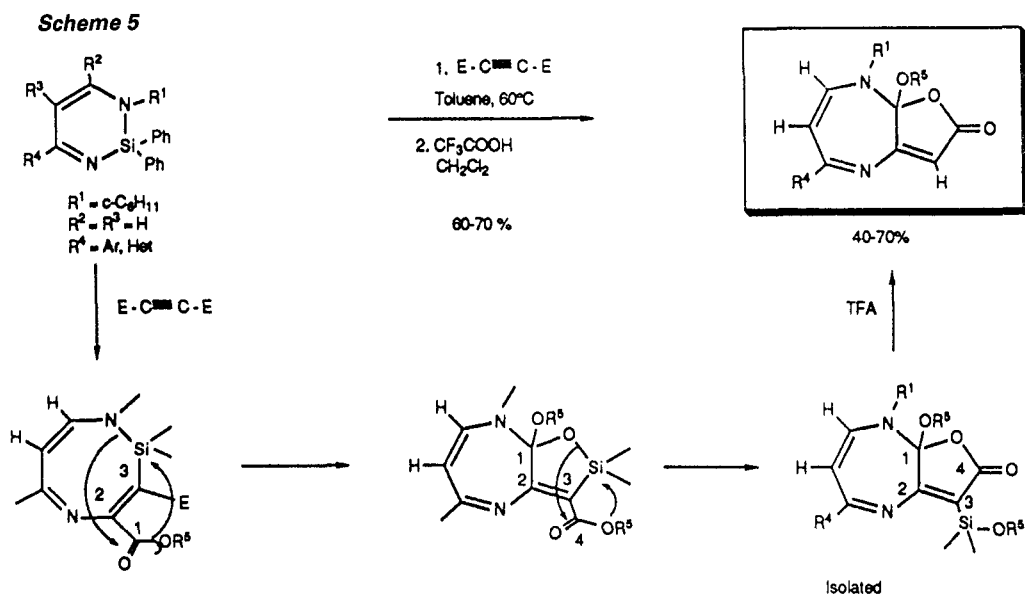
Scheme 3



Taking in mind the mechanism proposed in the case of acetylene esters, we thought that the rearrangement of the silicon-containing intermediate could be induced to involve the enamine nitrogen by simple blocking the C-5 position in the starting azadiene; in that event, medium ring heterocycles would be formed. Therefore, substituted 5-methyl-1,2-dihydro-1,3,2-diazasilines ($R^3=Me$) were reacted with esters of acetylenedicarboxylic acid and found that a new class of heterocycles -1,5-diazocin-2(1H)-ones- were obtained in good yields after stirring at 60° C (Scheme 4). All attempts to remove the silicon group by protodesilylation failed; instead, ring contraction to pyridine derivatives was observed in all instances (ref. 12).

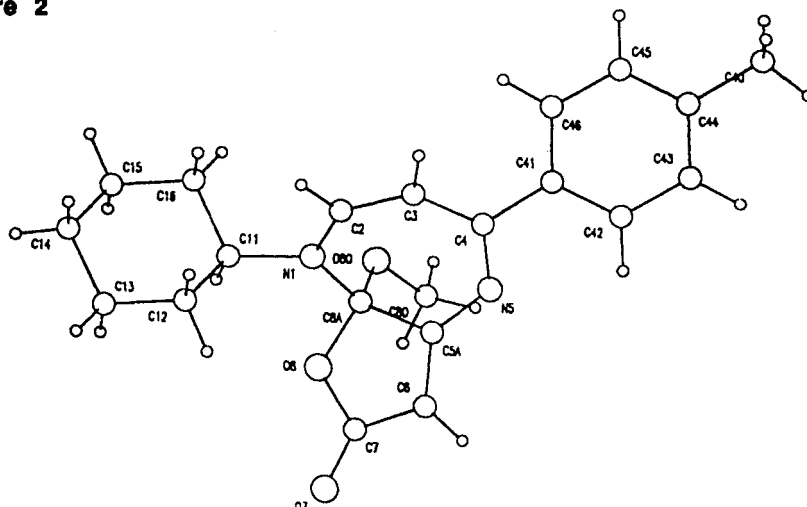


Once it was demonstrated the feasibility of diazasilines to furnish eight-membered heterocycles through rearrangement involving enamine nitrogen-carbonyl carbon bond formation, we were concerned about whether the rearrangement could take place through the other ester function. Since the intermediate leading to the diazocine ring is highly substituted, the geometry of the transition state in the rearrangement step might result primarily from steric interactions. Therefore we turned our attention to diazasilines with lesser degree of substitution in order to relieve steric hindrance in the intermediate. To this purpose, diazasilines having $R^2=R^3=H$, readily available from the corresponding azadiene, were heated in toluene at 60° C; then, aqueous work-up followed by stirring at room temperature with TFA led to heterocycles with the novel furo[2,3-b]-1,4-diazepine structure. The reaction course, which is outlined in Scheme 5, probably involves attack of the enamine nitrogen into the carbonyl C-1 (see Scheme 5) and lactone formation to give an alkoxy diphenyl substituted furo[2,3-b]-1,4-diazepine, which could be isolated or protodesilylated without purification.

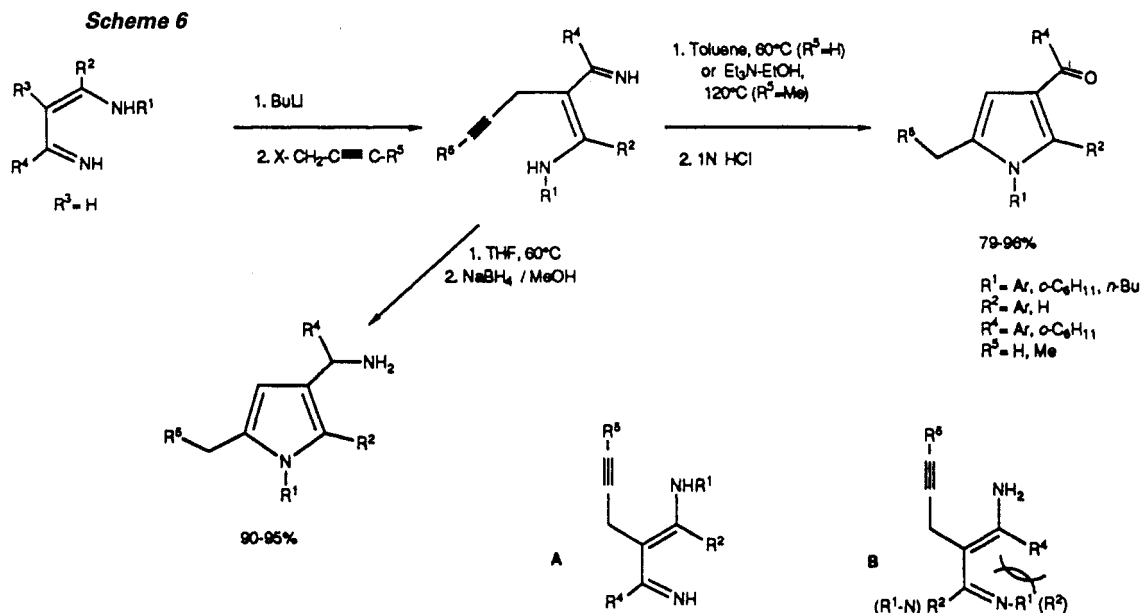


An X-ray structure was performed in order to confirm the structure. Figure 2 shows the crystal structure for the final compound ($R^1 = \text{c-C}_6\text{H}_{11}$; $R^4 = \text{p-Me-C}_6\text{H}_4$; $R^5 = \text{Me}$).

Figure 2



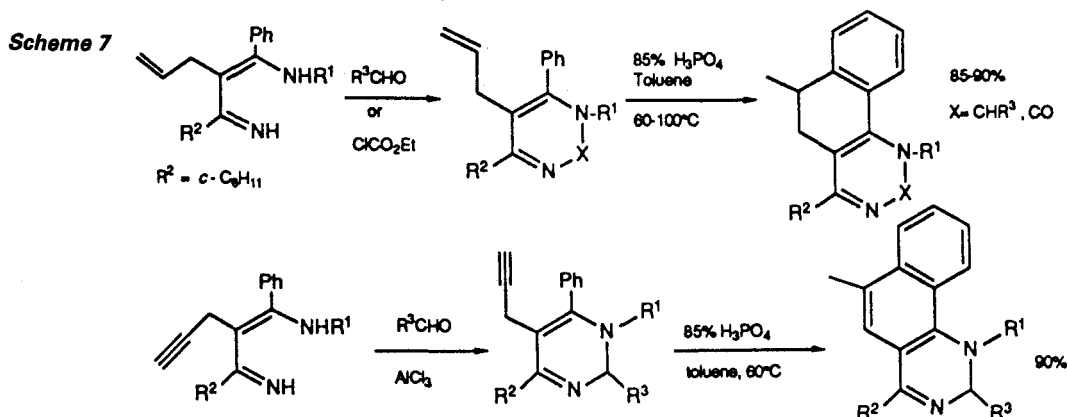
Now, we want to show some applications of 4-amino-1-azadienes having propenyl or propargyl appendages at the $C\beta$ -enamine carbon atom; the preparation of these systems is easily achieved from the corresponding unsubstituted azadienes ($R^3 = \text{H}$), butyl lithium and propargyl or allyl halides (ref. 3). Thus, the propargyl derivatives were found to smoothly undergo intramolecular cycloamination leading, after acid hydrolysis, to 3-acylpyrroles (ref. 14), which are not easily available according to known procedures (ref. 15). On the other hand, the imine pyrrole intermediate can be reduced *in situ* with sodium borohydride in THF-MeOH (Scheme 6).



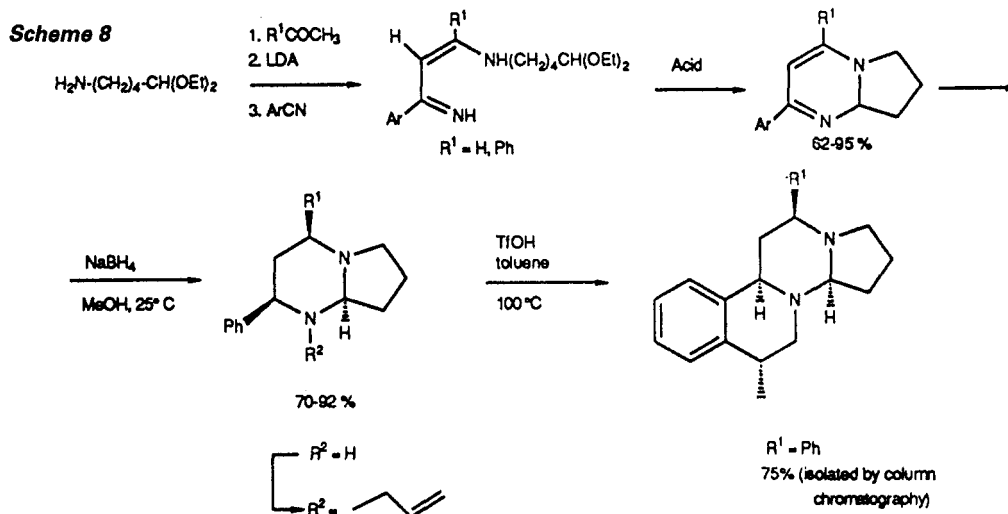
This cycloamination process involves the substituted nitrogen, unlike the behaviour found for 4-amino-1-azadienes; this fact reveals that the course of the reaction must be controlled by conformational effects. At present, it is assumed that conformation A is more stable than B in the coplanar cycloamination because of less steric requirements of the unsubstituted nitrogen (Scheme 6)

The potential demonstrated by 4-amino-1-azabutadienes in the regioselective synthesis of heterocycles along with the availability of these C-functionalized azadienes prompted us to investigate

the synthesis of nitrogen-containing heteropolycyclic compounds having the phenanthrene skeleton by intramolecular Friedel-Crafts annulation (Scheme 7) (ref. 16). Thus 5-allyl-1,2-dihydropyrimidines ($X=CHR^3$) and 5-allylpuridin-2(1H)-ones ($X=CO$), readily available by described procedures (ref. 4), underwent clean cyclization when stirred with phosphoric acid under mild reaction conditions allowing the isolation of tetrahydrobenzo[h]quinazolines in excellent yields. Moreover, the carbon-carbon triple bond did demonstrate its ability to participate in this Friedel-Crafts cyclization leading to high yield of the corresponding dihydrobenzoquinazoline.



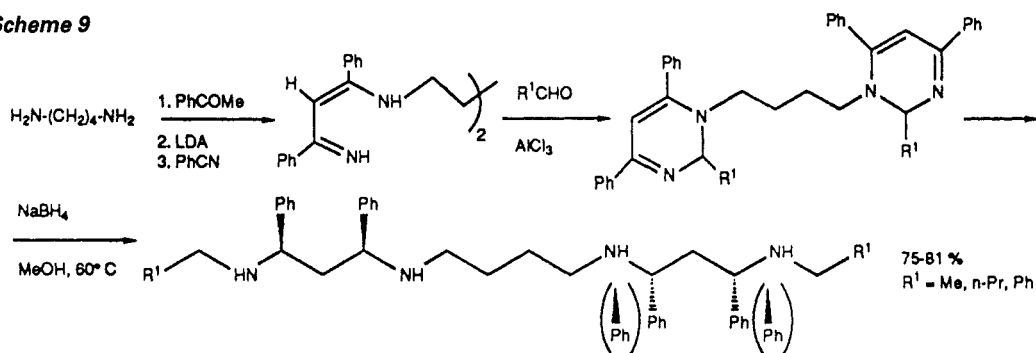
Finally, owing to the considerable interest and biological activity of azasteroids, we became interested in devising a route to diazasteroids based on this strategy (Scheme 8). Thus, tetrahydropyrrole [1,2-a]pyrimidines, prepared in one step from aromatic nitriles and imines derived from 4-aminobutyraldehyde diethyl acetal (ref. 17), were reduced with sodium borohydride at room temperature to yield octahydropyrrolo[1,2-a]pyrimidine in a stereoselective fashion (d.e. > 98%); this heterocycle was N-allylated and then subjected to intramolecular cyclization at 100°C in the presence of triflic acid to yield a 86:14 mixture of diastereoisomers in 86% yield; the mayor isomer shown in Scheme 8 was easily separated and isolated in 75% overall yield from the allylated pyrrole[1,2-a]pyrimidine by column chromatography (ref. 16).



As stated above, the reaction sequence leading to diazasteroids involves a stereoselective reduction of the pyrimidine ring (Scheme 8). In connection with this reaction, we found that the reduction of the parent monocyclic pyrimidines does not occur so, but carbon-nitrogen bond cleavage leading to 1,3-diamines takes place. With this idea in mind, now we wish to show the synthesis of compounds of great interest, i.e. polyamines (ref. 18), as an example of the applicability of 4-amino-1-azadienes in the synthesis of acyclic compounds (Scheme 9).

Thus, bis-azadienes were readily prepared from putrescine (1,4-diaminobutane) using standard procedures and treated with aliphatic and aromatic aldehydes to produce the expected bis-pyrimidines in yields around 90%. Further reduction with sodium borohydride in methanol at 60°C provided spermine derivatives, as a sole diastereoisomer; studies directed to ascertain the correct stereochemistry are currently underway.

Scheme 9



2-Aza-1,3-dienes

Regarding the 2-aza-1,3-diene system, we focussed our attention into electronically neutral 2-aza-1,3-dienes, whose reactivity was unknown a few years ago. These compounds were obtained in high yields by thermal dimerization of imines, in the presence of catalytic amounts of trifluoroacetic acid (ref. 19); the 2-aza-1,3-dienes were isolated as a sole isomer (Scheme 10).

Scheme 10

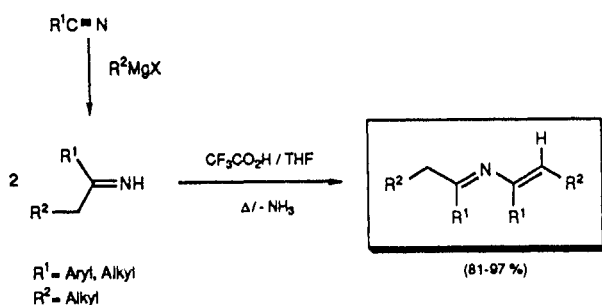
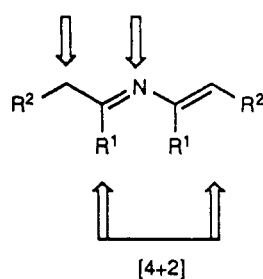


Figure 3

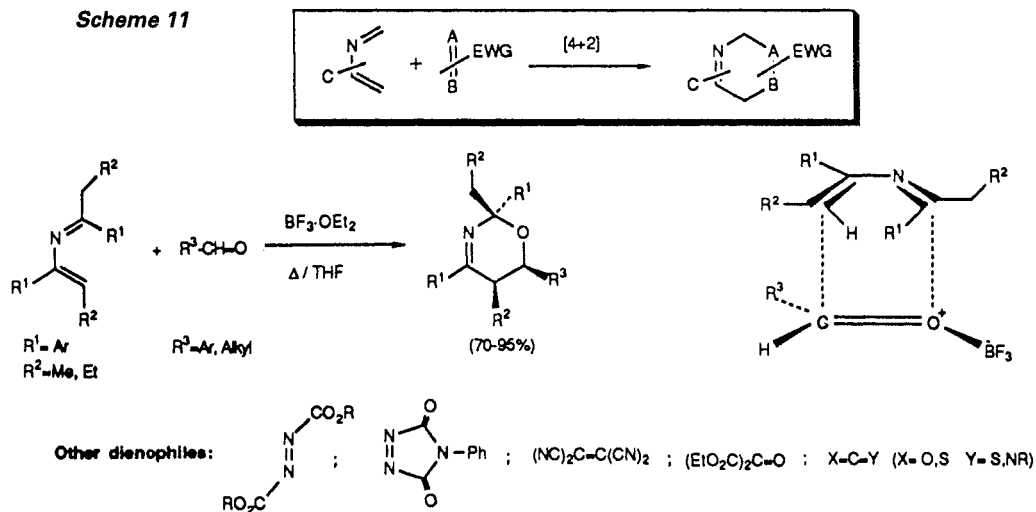


In relation with this structure, the general reactivity (ref. 20) of 2-aza-1,3-dienes can be summarized as follows (Figure 3):

- participation in [4+2]-cycloaddition reactions as heterodiene,
- reactions through the nitrogen atom
- reactions involving the carbon α -hydrogens.

Although it has been reported that electronically neutral 2-aza-1,3-dienes are reluctant to undergo Diels-Alder reactions with typical dienophiles, we succeeded in the [4+2]-cycloaddition of these azadiene derivatives with several electron-poor dienophiles. Thus, the reaction of 2-aza-1,3-dienes with aldehydes, catalyzed by boron trifluoride, gave the corresponding 1,3-oxazine adducts in excellent yields. Other dienophiles were used, e.g. diethyl ketomalonate, azodienophiles, tetracyanoethylene, and heterocumulenes (Scheme 11).

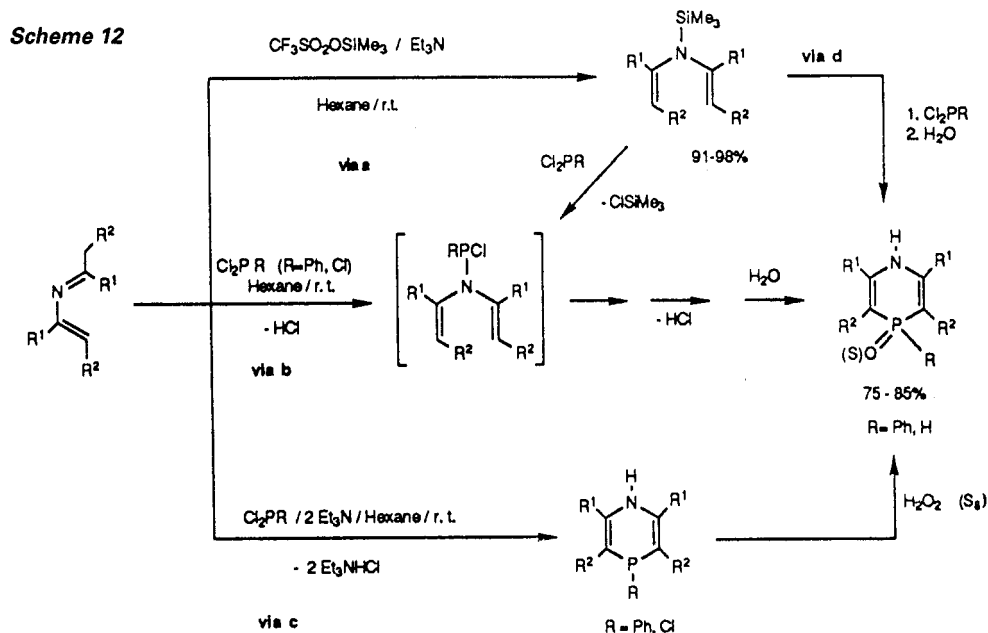
Scheme 11



All these processes are stereoselective. The structure of some of the adducts was confirmed by X-Ray structural analyses.

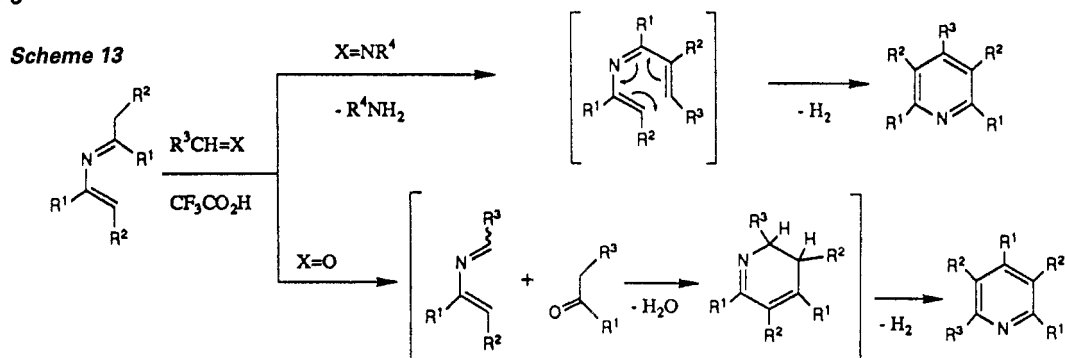
The reaction of 2-aza-1,3-diene derivatives through the nitrogen atom was found to occur in the case of halogenophosphines and silylation agents. The silylation of these systems (ref. 21) takes place exclusively at the nitrogen atom leading to *N*-silyldivinylamines with complete stereoselectivity (Scheme 12, via a). In the same way, the reaction of the 2-aza-1,3-dienes with halogenophosphines (ref. 22) yielded λ^5 -azaphosphinine derivatives in high yields (Scheme 12, via b). These λ^5 -derivatives can be also obtained by treatment of λ^3 -azaphosphinines with hydrogen peroxide or elemental sulphur. These λ^3 -azaphosphinines were in turn obtained by reaction of 2-aza-1,3-dienes with halogenophosphines, in the presence of triethylamine (Scheme 12, via c).

The formation of these phosphorous-containing heterocycles can be easily understood through the formation of nitrogen-phosphorous bond with loss of an equivalent of hydrogen chloride, followed by rearrangement and cyclocondensation. This mechanism is supported by the fact that the reaction of the *N*-silyldivinylamines (see above) with halogenophosphines gave rise to the azaphosphinine derivatives, under the same reaction conditions (Scheme 12, via d).



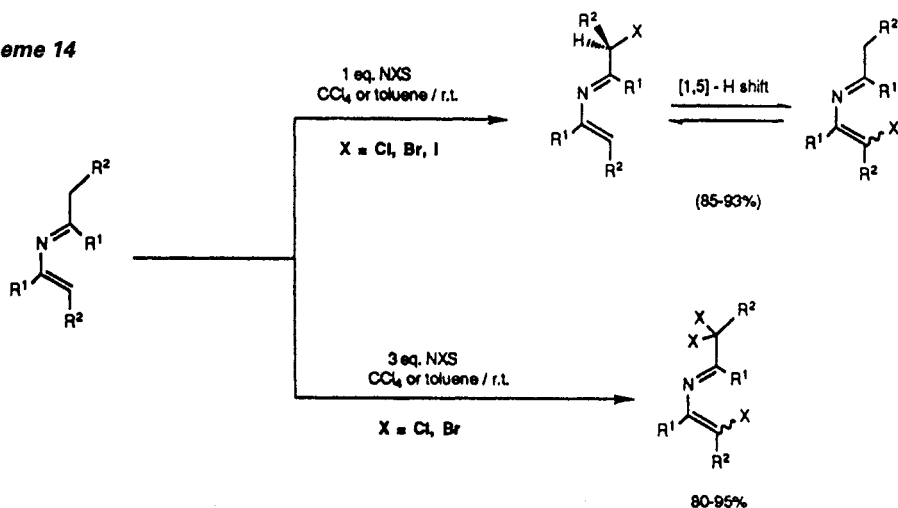
The reactivity through the carbon α -hydrogens is shown in Scheme 13, where a new synthesis of pentasubstituted pyridines (ref. 23) using carbonyl and imine derivatives is outlined.

Thus, the cyclization reaction of 2-aza-1,3-dienes with imines led to an azatriene intermediate which undergo electrocyclic ring-closure and dehydrogenation to produce symmetric pentasubstituted pyridines. On the other hand the reaction with aldehydes furnished unsymmetrical pyridines, whose formation can be probably explained as the result of a rapid ketimine-alimine exchange followed by condensation of the new 2-aza-1,3-diene with the displaced ketone and loss of hydrogen.



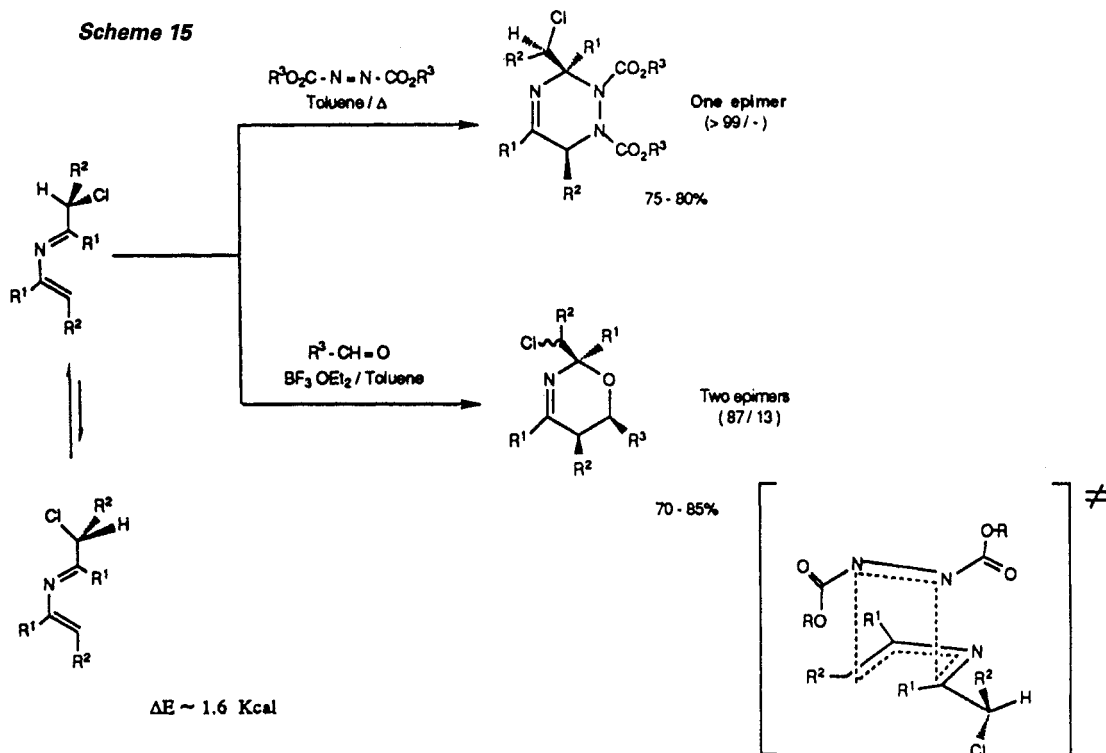
In order to functionalize these compounds, we realized that the halogenation reaction could be a simple procedure, allowing the creation of a chiral center in the molecule and increasing therefore their synthetic potential considerably. The synthesis of mono- and trihalogenated derivatives of 2-aza-1,3-dienes (ref. 24) was performed by treatment with one or three equivalents of *N*-halosuccinimide at room temperature (Scheme 14).

Scheme 14



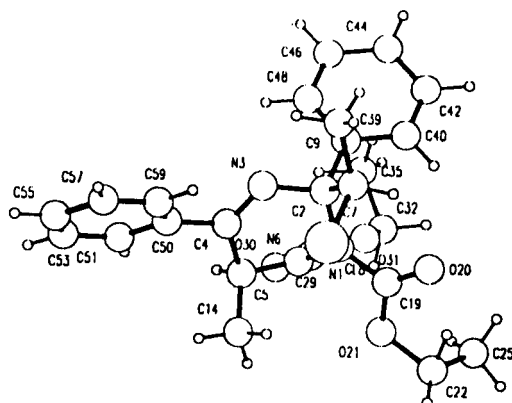
The monohalogenated 2-aza-1,3-dienes were isolated as a mixture of two tautomers, which equilibrated through [1,5]-hydrogen shifts. In all cases, R¹ should be an aryl group, since a mixture of polyhalogenated compounds were obtained when R¹ = alkyl. At this point, we carried out a study on the participation of the monohalogenated 2-aza-1,3-dienes with a chiral center in Diels-Alder reactions, in order to check the possible diastereofacial selectivity induced by the stereogenic center (Scheme 15). Thus, we tested the behaviour of the monochlorinated 2-aza-1,3-dienes towards dienophiles,

Scheme 15



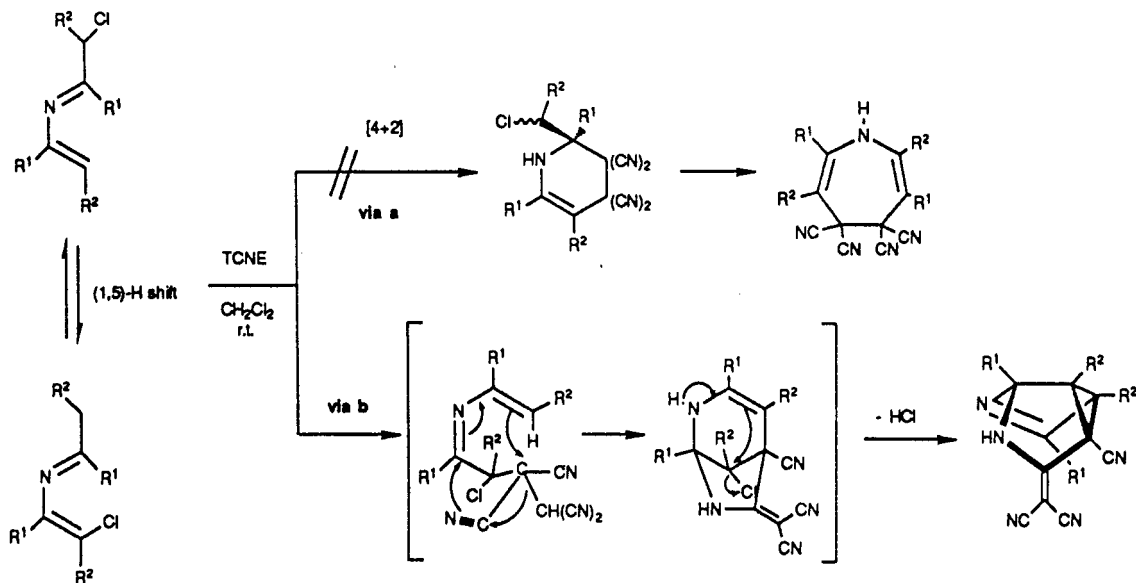
like aldehydes and dialkyl azodicarboxylates, (ref. 24) and found that, in all cases, the reactions took place through the less-substituted form of the 2-aza-1,3-diene (Scheme 15). Moreover, the diastereofacial selectivity was apparently complete, in the reaction with esters of azodicarboxylate acid and only one isomer of the cycloadduct was detected. In the case of the reaction with aldehydes an *ca* 87:13 mixture of epimers of the expected cycloadduct was obtained, showing a face selectivity in the process. In this reaction the presence of catalytic amounts of BF_3OEt_2 was found to be necessary. The formation of one epimer in the case of azoderivatives can be understood by assuming an *exo* approach of the dienophile to the diene through the opposite face of the chlorine atom in the most stable conformation (ref. 25), in order to avoid the electronic repulsions between the carboxylate grouping and the chlorine atom. The stereochemistry of the Diels-Alder adducts of chlorinated 2-aza-1,3-dienes and dialkyl azodicarboxylate was confirmed by X-Ray diffraction. (Figure 4; $\text{R}^1=\text{Ph}$, $\text{R}^2=\text{Me}$, $\text{R}^3=\text{Et}$).

Figure 4



At this point, we thought that these Diels-Alder adducts could lead to seven-membered heterocycles by a ring-closure to the aziridine ring, followed by a ring-expansion to the seven membered heterocycles (Scheme 16, via a). However, the reaction of the chlorinated 2-aza-1,3-dienes derivatives with TCNE (ref. 26) did not lead to the expected azepines or their Diels-Alder adducts, but interestingly 4,6-diazasemibullvalene derivatives were obtained in high yields (Scheme 16, via b).

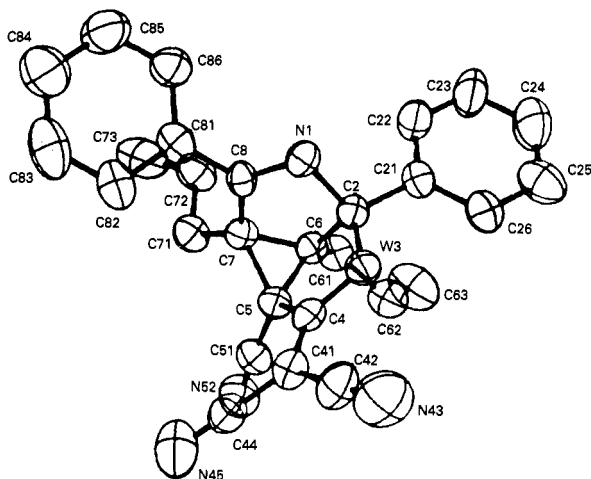
Scheme 16



The formation of the 4,6-diazasemibullvalene derivatives could be understood by assuming a four-step mechanism, as outlined in Scheme 16; thus, Michael addition of the azadiene to TCNE followed by intramolecular cyclization and migration of the dicyanomethyl group (ref. 27) would give an bicyclic intermediate, which leads to the diazasemibullvalene system by loss of one eq. of HCl . Further studies in order to provide details about the mechanism of this reaction are in progress. It must be

pointed out that this is the first one-pot synthesis of these rare systems, which starts from readily accessible starting materials. Figure 5 shows the X-Ray structure of one of these unusual compounds ($R^1=Ph$, $R^2=Pr$).

Figure 5



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