AZA-1,3-BUTADIENES IN SYNTHESIS OF NITROGEN-CONTAINING SIX-MEMBERED HETEROCYCLES (REVIEW)

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We review and generalize literature data in recent years on application of heterodiene synthesis to obtain azines.

In the last decade, we have seen an increase in the importance of the [4 + 2] Diels–Alder cycloaddition reaction of aza-1,3-butadienes for synthesis of six-membered nitrogen-containing heterocycles. Many azadienes are convenient starting compounds in azine synthesis. In contrast to "classical" diene synthesis, in heterodiene synthesis in most cases cycloaddition of π-deficient dienes to π-abundant dienophiles occurs, the so-called reverse diene synthesis. This process is described by interaction of the LUMO (lowest unoccupied molecular orbital) of the diene with the HOMO (highest occupied molecular orbital) of the dienophile.

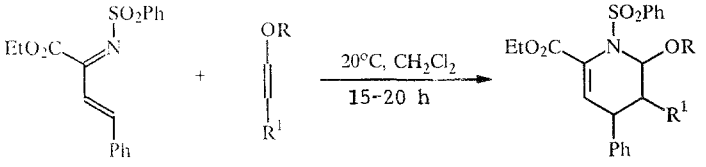
In this review, we consider papers devoted to building azine rings according to the [4 + 2] cycloaddition reaction which were not included in the fundamental reviews for 1986-1987 [1-3].

Azadienes can be both acyclic and part of nitrogen-containing heterocycles.

The material in this review is arranged according to the type of azadiene, starting with the simpler ones with respect to the number of hetero atoms.

1-AZA-1,3-BUTADIENES

Acyclic 1-aza-1,3-dienes are convenient synthons for building the pyridine ring. The presence of electron-acceptor substituents in the azadiene activates cycloaddition to π-abundant dienophiles. As a result of cycloaddition of azadiene I to vinyl ether, tetrahydropyridines II are formed in up to 85% yields [4, 5].



I II

R = Alk, CH_2Ph; R^1 = H, Me, AcO

It has been shown that the position of π-deficient substitutents in the azadiene molecule does not affect the course of the process even in reaction of azadiene III, distinguished from azadiene I by the position of the ethoxycarbonyl group; under analogous conditions, tetrahydropyridines IV were obtained, also in high yields (up to 93%) [6].

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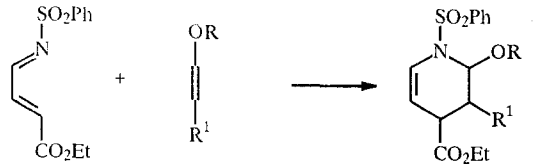
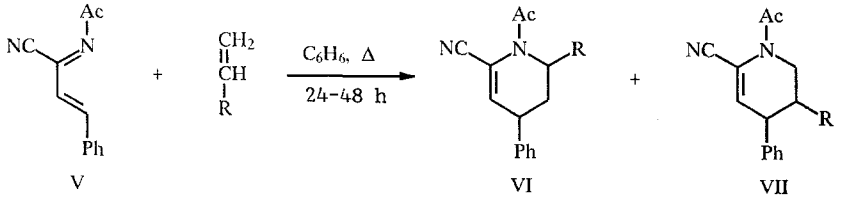


III IV

R=Et, CH_2Ph; R^1=Me, Ph, OAc

It has been found that the nature of the substituents in the dienophiles affects cycloaddition of 1-aza-1-acetyl-2-cyano-4-phenyl-1,3-butadiene (V) to olefins [7].

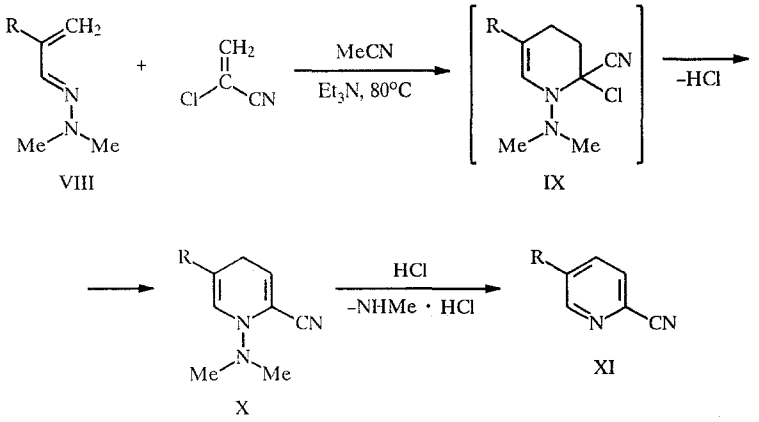


V VI VII

R=Ph, OEt, CO_2Me

The yields of the regioisomers VI and VII are respectively: R = Ph 13%, 79%; R = OEt 69%, 0%; R = CO_2Me 0%, 92%. The reactions mainly occur regioselectively. Thus if R = OEt, only isomer VI is formed; with an electron-acceptor substituent R = CO_2Me, only isomer VII is formed. It has been determined that the latter reaction contradicts the conditions for the reverse Diels–Alder synthesis: reaction of π-deficient dienes with π-abundant dienophiles. Obviously this is explained by the fact that the cyano group increases the π-deficiency of the azadiene V so much that the LUMO-diene–HOMO-dienophile ratio is preserved.

In contrast to the reactions presented above, the "classical" cycloaddition of electron-abundant 1-aza-1,3-butadienes to an electron-deficient dienophile is described by the scheme of the reverse Diels–Alder diene synthesis [8]. Upon reaction of N, N-dimethylhydrazones of α, β-unsaturated aldehydes VIII with chloroacrylonitrile, the unstable adducts IX are formed which in the presence of bases are converted to the dihydropyridines X.

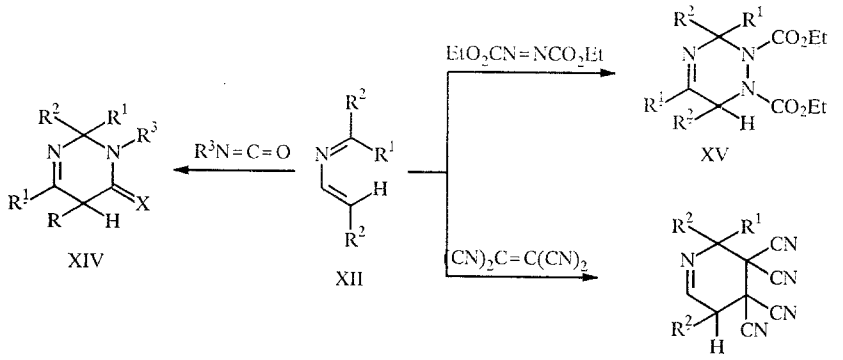


VIII IX X XI

The latter are easily aromaticized with liberation of dimethylamine and formation of nitriles of the difficult-to-synthesize alkyl-2-pyridine-carboxylic acids XI (70-75%).

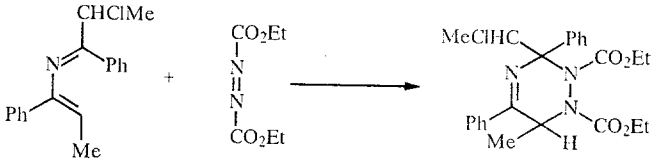
The reactions occur strictly regioselectively, obviously due to the optimal HOMO–LUMO interaction.

Unactivated 2-aza-1,3-dienes XII, as a result of cycloaddition to a π-deficient dienophile (tetracyanoethylene, heterocumulene, azodicarboxylate) upon heating in benzene or THF form the hydrated derivatives of pyridine XIII, pyrimidine XIV, and 1,2,4-triazine XV in 50-90% yields [9-11].

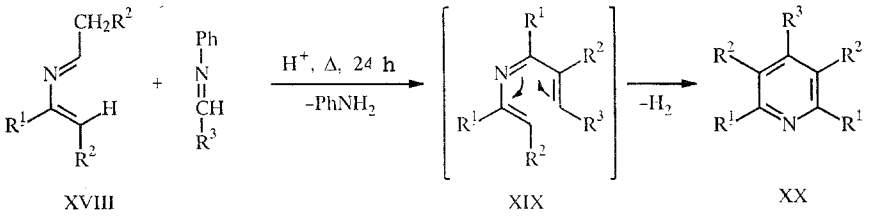


$R^1 = R^3 = Ph, Ar; R^2 = Alk; X = O, S$

In [12], a method is given for obtaining the 2-azadiene XVI, which is a modified azadiene XII, containing a bulky substituent in the side chain. However, this did not affect the results: Cycloaddition of azadiene XVI to dimethylazodicarboxylate led to tetrahydro-1,2,4-triazine XVII in good yields.



In [13], a novel, simple, and regiospecific synthesis is described for obtaining substituted pyridines from 2-azadienes XVIII and azomethines. The reactions were performed in THF in the presence of catalytic amounts of trifluoroacetic acid. Instead of the expected product of the Diels–Alder reaction (pyrimidine or pyrazine), the pyridines XX were obtained in 75-90% yields.

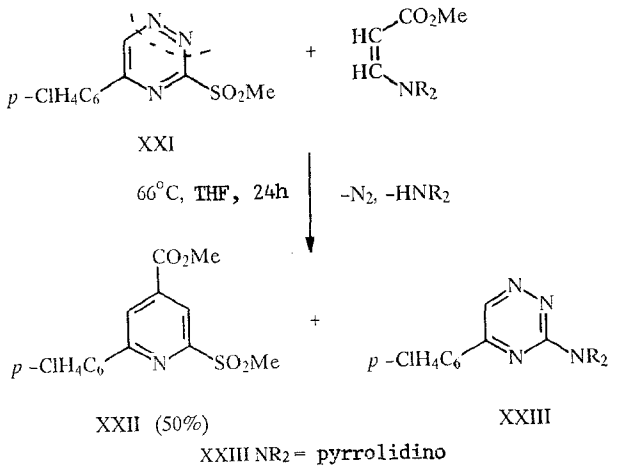


$R^1, R^3 = Ph, Ar; R^2 = Me$

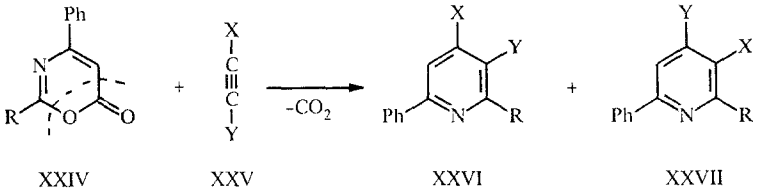
In the first step of the reaction, the intermediate azatrienes XIX are formed with liberation of amine; these intermediates upon cyclization and aromatization are converted to the substituted pyridines XX. Elimination of hydrogen, according to the data in [14], is explained by transfer of hydrogen to the multiple bond of one of the starting materials.

Along with the acyclic 2-aza-1,3-dienes, heterocycles containing the 2-azadiene moiety in the ring also participate in the Diels–Alder cycloaddition reaction.

Upon reaction of 3-methylsulfonyl-1,2,4-triazine XXI with 3-pyrrolidinoacrylate, the 2-methylsulfonyl-4-methoxycarbonylpyridines XXII were obtained; and as the product of the competing reaction of nucleophilic substitution of the sulfonyl group, 1,2,4-triazine XXIII was obtained [15, 16].



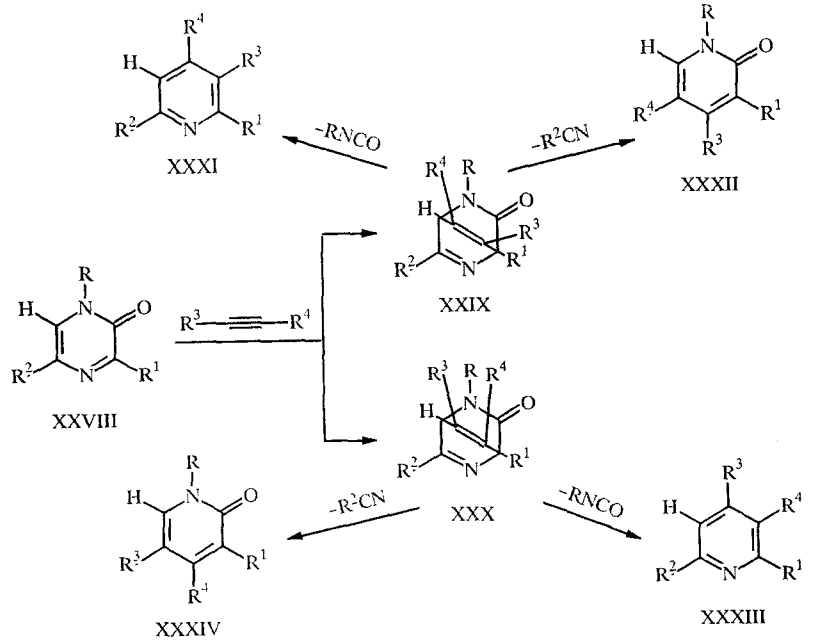
The use of the heterodiene synthesis reaction makes it possible to synthesize the practically unobtainable organotin and organosilicon derivatives of pyridine [17]. As a result of cycloaddition of the 2-azadiene fragment of 1,3-oxazin-6-ones XXIV to organometallic derivatives of acetylene XXV, the organotin and organosilicon derivatives of pyridine XXVI, XXVII were obtained.



R=H, Me, Ph, CO_2Et; X=Y=Me_3Sn, Bu_3Sn, Me_3Si; X-same, Y=H

The reactions were carried out with boiling in dibutyl ether or decalin for 3-120 h; yield of pyridines XXVI, 20-88%. The compounds XXVII are formed when Y = H, in 4-17% yields. Better results were obtained if R = H in the starting oxazines, since less bulky terminal groups in the diene facilitate the cycloaddition reaction.

2-(1H)-Pyrazinones, like 2-azadienes, are starting materials for synthesis of pyridines and pyridones [18]. Upon reaction of pyrazinones XXVIII with different acetylene derivatives, two series of pyridines XXXI, XXXIII and pyridones XXXII, XXXIV are formed.



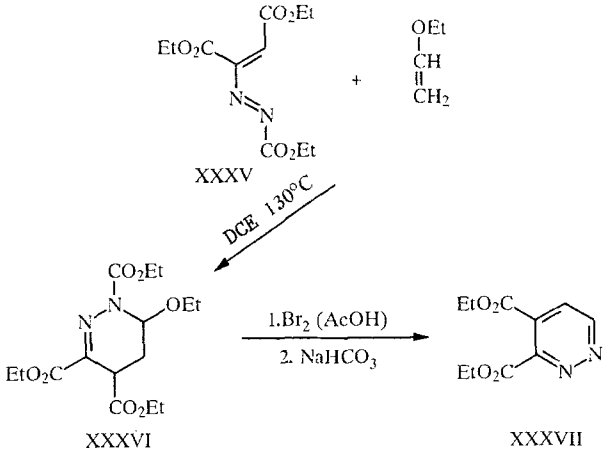
R = Me, Ph; R^1 = Cl, O, Me, CN; R^2 = Cl; R^3 = R^4 = CO_2Me; R^3 = CO_2Et, Ph; R^4 = H

The cycloaddition reaction does not occur regioselectively. Therefore we obtain two intermediates XXIX and XXX, which differ in the position of the substituents on the acetylene residue. Pyridines and pyridones are formed as a result of two competing retro Diels–Alder reactions of the intermediates (adducts) with liberation of RNCO and R^2CN. Based on data from 43 experiments, the pyridine–pyridone ratio is 97:3-0:100; total yield, 7-92%. The reactions were carried out with heating in an excess of the starting pyrazinone.

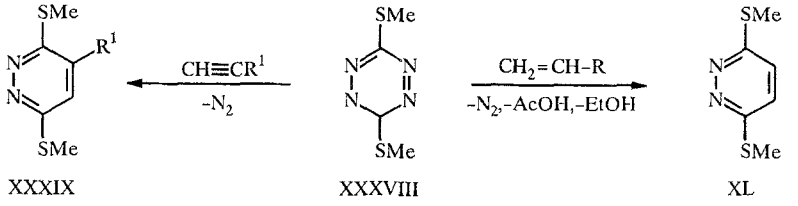
1,2-DIAZA-1,3-BUTADIENES

1,2-Diaza-1,3-butadienes have been used as starting materials in syntheses of pyridazines [19-21].

The π-deficient acyclic 1,2-diazadiene XXXV reacting with vinyl ether forms the adduct XXXVI in 82% yield [19]. The latter is converted upon oxidation and elimination of the ethoxycarbonyl groups to the 3,4-pyridazinedicarboxylates XXXVII (90%), which are otherwise difficult to obtain.



In [20], [4 + 2] cycloaddition reactions were described for the first time for 3,6-di(methylthio)tetrazine XXXVII as a cyclic 1,2-diazadiene.



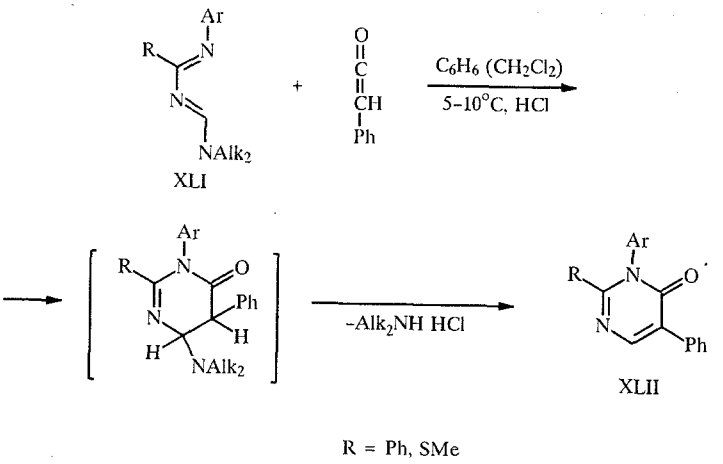
R^1 = Ph, Alk, CO_2Me; R = OEt, AcO

Upon reaction of azadiene XXXVIII with acetylene and ethylene dienophiles, the pyridazines XXXIX, XL were obtained; upon reaction with ethylene dienophiles, aromatization proceeded upon cyclization with liberation of the good leaving groups of the dienophile (OEt, AcO).

1,3-DIAZA-1,3-BUTADIENES

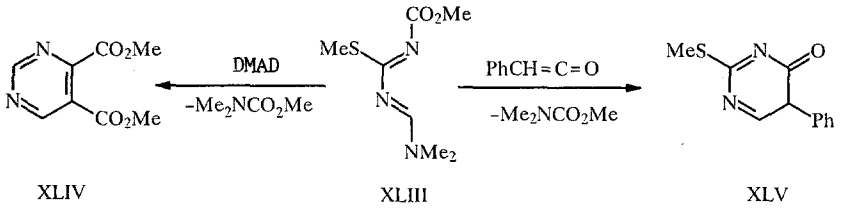
1,3-Diazadienes are convenient starting compounds for one-step syntheses of pyrimidine derivatives according to the hetero Diels–Alder reaction. When good leaving groups are present in the azadienes, aromatization of the cycloadducts occurs with formation of pyrimidine rings.

Pyrimidine-4-(3H)-ones XLII were obtained in high yields (up to 95%) upon cycloaddition of 1,3-diazadienes XLI to phenyl ketene [22-24].



R = Ph, SMe

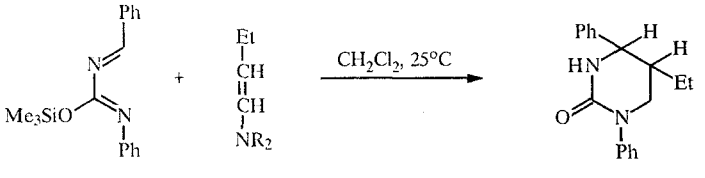
Reaction of 1-methoxycarbonyl-2-methylthio-4-dimethylamino-1,3-azabutadiene XLIII with dimethylacetylenedicarboxylate (DMAD) leads to formation of pyrimidinecarboxylate XLIV (72%) [23].



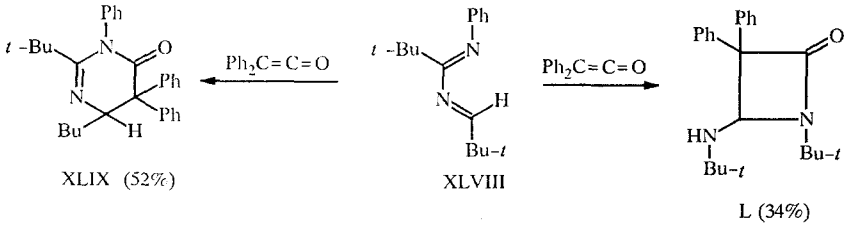
In this case, in contrast to the reverse diene synthesis, interaction of the HOMO of the diene with the LUMO of the dienophile occurs.

Upon cycloaddition of azadiene XLIII to phenyl ketene, the pyrimidine-4-one XLV was obtained (96%). Aromatization occurs with elimination of the terminal groups of the diene during cyclization in the form of N,N-dimethylcarbamate. From the work presented above, we see that phenyl ketene is an effective dienophile in heterocyclization reactions.

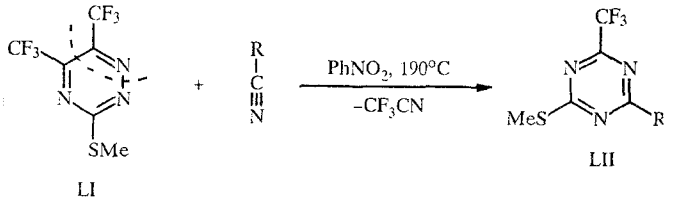
In [25], an example is given of the formation of tetrahydro-2(1H)pyrimidinone XLVII in high yield (80-96%) upon reaction of 1,3-azadiene XLVI, containing the trimethylsiloxy group, with a π-abundant enamine.



We know that the results of Diels–Alder cycloaddition are affected not only by the nature of the substituents in the diene and the dienophile, but also by steric factors. Thus upon reaction of 1,3-diazadiene XLVIII with diphenyl ketene, both [4 + 2] and [2 + 2] cycloaddition occur with formation of dihydro-4(3H)pyrimidinone XLIX and azetidinone L [26].



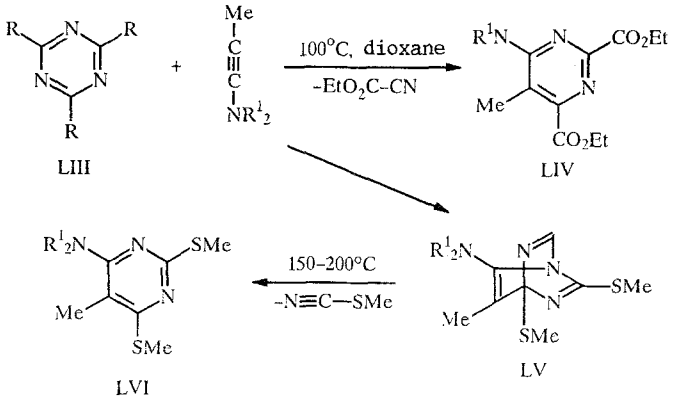
The [4 + 2] cycloaddition reaction of 1,2,4-triazines whose rings contain a 2-aza-1,3-diene moiety is described in [15]. Depending on the nature of the substituents, the 1,2,4-triazines participate in cycloaddition reactions like 1,3-diazadienes.



LI LII

R = NMe_2, pyrrolidino, morpholino, piperidino

1,2,4-Triazines form 1,3,5-triazines LII in good yields upon reaction with cyanamides, which are strong nucleophiles [27, 28]. The reactions occurs strictly regioselectively. The 1,3,5-triazines LIII form the pyrimidine rings LIV or LV by [4 + 2] cycloaddition to a π-deficient dienophile (inamine) [29]. When electron-donor substituents are present in triazines LIII, the stable adducts LV are formed, which upon heating are converted to the pyrimidines LVI. For R = CO_2Et, the pyrimidines LIV are formed immediately with liberation of ethylcyanoformate. Yields: 66-95%.



LIII LIV LV LVI

LIII R = CO_2Et, SMe; LIV-LVI R^1 = Et, CH_2Ph

In these papers, note the unique transformation of azine rings, which is possible only according to a Diels–Alder reaction.

This review confirms that heterodiene Diels–Alder synthesis has acquired an increasingly practical importance for synthesis of azines. This is explained mainly by the fact that accessible methods have been found to obtain acyclic azadienes and great success has been achieved in the use of nitrogen-containing heterocycles as synthons.

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