SYNTHESIS OF NITROGEN HETEROCYCLES
BY (4 + 2)π-CYCLOADDITION FROM NITROGEN-CONTAINING
HETERODIENES ("AZADIENE SYNTHESIS")
(REVIEW)

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The review is devoted to the (4 + 2)π-cycloaddition with conjugated nitrogen-containing
dienes. The participation in the synthesis of 1-azadienes, 2-azadienes (Schiff bases,
oxazoles, and the acridinium ion), 1,4-diazaazadienes (dehydroindigo, etc.), 2,3-diaza-
dienes (tetrazines, 4H-pyrazoles, and triazines), α,β-unsaturated azo compounds, 5,6-di-
ydrotriazines, formazans, and azadienes containing more than one heteroatom in the
conjugation chain is examined. The azadiene synthesis is a method for the preparation
of pyridines, quinolines, pyridazines, oxazines, oxadiazines with different degrees of
saturation, and several other heterocycles.

(4 + 2)π-Cycloaddition, where the components contain at least one nitrogen atom, is a universal method
for the synthesis of six-membered nitrogen heterocycles.

Variants of the reactions with the application of heterodienophiles (with C=N, N=N, N=O, N=S and
other bonds) have been discussed in detail [1-4] and are therefore not considered in this review. The sub-
ject of this review is the Diels-Alder reaction with the participation of azadiene systems. 1,4-Cycloaddi-
tion for heterocumulenes (a=b=c and a=b=c=d=e) is not included here, since, first, this problem has al-
ready been examined [5], and, second, heterocumulenes react as 1,2- or 1,4-dipoles [6], and the reaction
with them is consequently not (4 + 2)π-cycloaddition.*

In spite of the previously formulated opinion regarding the low reactivity of 1,3-azadienes in 1,4-
cycloaddition [10], more and more attention is currently being extended to both the theoretical and practical
aspects of the azadiene synthesis. In discussing the problem, one should take into account a number of gen-
eral assumptions that are characteristic for the Diels-Alder reaction as a whole.

First, it is necessary to consider the compliance of the synthesis with specific steric principles (con-
formational requirements for the reaction components, steric factors, etc.) [11].

Second, in accordance with the Woodward-Hoffman rule [12], this reaction is a thermally allowed
(4s + 2s) process, as a consequence of which it is highly stereospecific (cis principle and endo rule) [11].

Third, the azadiene components should have low 1,4-localization energies (E_{1,4}) [13], and it should
therefore be expected that heterocyclic systems with strongly expressed aromatic character are passive
in the azadiene synthesis.

* See also [7-9] for individual interesting examples of reactions with heterocumulenes.

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Fourth, the introduction of nitrogen atoms into the conjugated system should lead to an increase in the role of polar factors for the unsymmetrical azadiene components and, in extreme cases, to a polar two-step mechanism. The character of the azadiene component may change appreciably under the influence of acidic agents, and the appearance of acid catalysis is therefore possible during the reaction.

Fifth, donor-acceptor relationships for the diene and dienophile are essential. The introduction of nitrogen atoms into a conjugated system should lower its nucleophilicity and consequently suppress the reactivity with respect to the usual electron-acceptor dienophiles (tetracyanoethylene, maleic anhydride, etc.). However, two different variants should be distinguished. In terminal azadiene components (1-aza and 1,4-diaza-1,3-dienes), at least one of the ends of the conjugated chain retains nucleophilic character (C = N) when their nucleophilicity is lowered as a whole. Consequently, one should expect low activity in 1,4-cycloaddition reactions for such systems. On the other hand, the nucleophilicity of both the entire system and its ends is reduced for 2-aza- and 2,3-diaza-1,3-dienes. The manifestation of reactivity in condensations with electron-donor dienophiles (inversion of the diene synthesis) is more likely for these azadiene components.

**Terminal Azadienes**

1-Aza-1,3-dienes. 1,4-Cycloaddition reactions are unknown for noncyclic derivatives, i.e., α,β-un-saturated imines and Schiff bases. The products of the addition of them to maleic anhydride are apparently molecular complexes [14].

1-Styryl-6,7-dimethoxy-3,4-dihydroisoquinoline (I) reacts with maleic anhydride [15] in the same way as 1-(1-cyclohexenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline [16].

![Image]

Isoxazoles and pyrazoles [17] are inactive in the diene synthesis because of their strongly expressed aromatic properties (high E14 value). However, anthranil (II) gives 1,4-cycloaddition products with maleic anhydride [18], maleimidimide [19], and some acetylenes [20], and the latter reaction is a method for the synthesis of 2,3-disubstituted quinolines.

![Image]

1,4-Diaza-1,3-dienes. Dinitriles and dioximes of α-dicarbonyl compounds do not react via the scheme of the Diels–Alder reaction, with the exception of the bis(4-dimethylaminocinnil) of glyoxal (III) in the reaction with p-benzoquinone [21].

![Image]

The electron-donor effect of the dimethylamino group, which increases the nucleophilicity of the 1 and 4 positions of the conjugated chain, is probably exerted here.

The opposite effect is observed when electron-acceptor substituents are introduced into the 2 and 3 positions of the diene component. Because of this, dehydroindigo (IV) reacts with the dienophiles with nucleophilic character – styrene, safrole, isosafrole, and isoeugenol methyl ester [22].