CONDENSED PYRIDAZINES AS AZADIENES IN [4+2]-CYCLOADDITION REACTIONS

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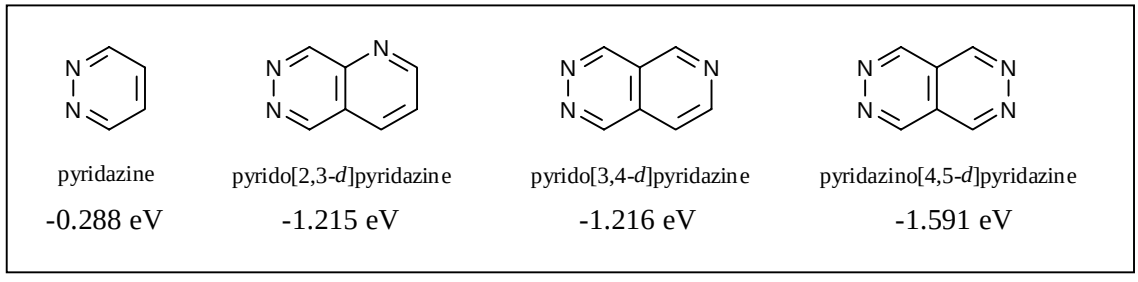
The inverse-electron-demand variant of the Diels-Alder reaction has been attracting strongly increasing interest during the past two decades. Several excellent reviews demonstrate the value of this reaction type, particularly in the field of heterocyclic chemistry.[1] Usually, such thermally induced (inter- and intramolecular) [4+2]-cycloaddition reactions result in a ring transformation of the heterocyclic educt, leading to an other heterocycle or - in certain cases - to a carbocyclic product. Many different N-heteroaromatics, such as 1,2,4,5-tetrazines,[1,2] 1,2,3-triazines,[1,3] 1,2,4-triazines,[1,4] 1,3,5-triazines,[1,5] pyridazines,[1,6] pyrimidines,[1,7] pyrazines,[1,8] and pyridines[1,9] have been employed as azadienes in cycloaddition reactions with electron-rich dienophiles like enamines, ynamines, enol ethers, alkenes, alkynes, ketene acetals, and so on. Until now, however, there are considerably less reports dealing with inverse-electron-demand Diels-Alder reactions of annelated N-heteroaromatic systems like benzo-, pyrimido-, benzofuro-, and benzothieno-fused 1,2,4-triazines,[10-13] a few phthalazines[14] and isoquinolines,[15] 1,2,3-triazolo[4,5-*d*]pyridazines,[16] and imidazo[4,5-*d*]pyridazines.[17] In the following, an overview will be given about the recent work carried out in the author's laboratory, which has been devoted to the investigation of the reaction behavior of heterocycle-annelated pyridazines, such as pyridazino[4,5-*d*]pyridazines,[18-20] pyrido[2,3-*d*]pyridazines,[21] pyrido[3,4-*d*]pyridazines,[22-24] and pyridazino[4,5-*b*]indoles[25] in inverse-electron-demand Diels-Alder reactions and to the synthetic exploitation of this reaction type for the construction of various polycyclic systems.

Inverse-electron-demand Diels-Alder reactions, in general, can be characterized by an interaction of the highest occupied molecular orbital (HOMO) of a dienophile (the 2π component) and the lowest unoccupied molecular orbital (LUMO) of a diene (the 4π

component), leading to the formation of two new σ bonds at the expense of two π bonds. The magnitude of the $HOMO_{dienophile}/LUMO_{diene}$ energy gap plays a key role in the rate-determing cycloaddition step. As the annelation of a six-membered π-deficient heteroaromatic ring to the [*d*] edge of the pyridazine nucleus leads to a considerable decrease of the LUMO energy (comparable to the introduction of electron-withdrawing substituents), this results in a pronounced azadiene reactivity of the bicyclic system. For illustration, the LUMO energies for some fused pyridazines and for the monocyclic parent compound are listed in Table 1.



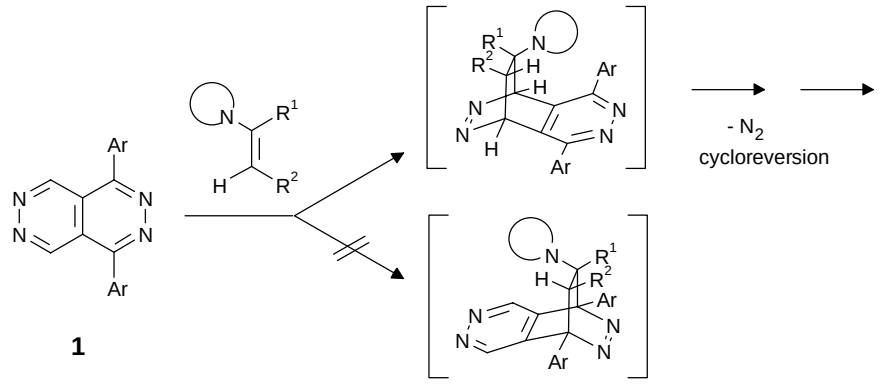
pyridazine	pyrido[2,3-*d*]pyridazine	pyrido[3,4-*d*]pyridazine	pyridazino[4,5-*d*]pyridazine
-0.288 eV	-1.215 eV	-1.216 eV	-1.591 eV

Table 1. LUMO energies, calculated with the AM1 method[26]

We started our investigations with 1,4-diarylpyridazino[4,5-*d*]pyridazines (**1**), as these compounds are readily available in two steps from pyridazine (according to ref.[27]) and as they should be very reactive towards electron-rich dienophiles like enamines. Compounds **1** (Ar = phenyl, 4-methoxyphenyl), indeed, were found to react smoothly with cycloalkanone-derived enamines in boiling ethanol with immediately noticeable N_2 evolution. Reaction times (ranging from 10 minutes to several hours) depend on the ring size of the cyclic enamine (1-pyrrolidino-1-cyclopentene reacts faster than the six-membered analog) as well as on the electronic effect of substituents attached to the phenyl moieties (methoxy groups lead to a decreased reaction rate).

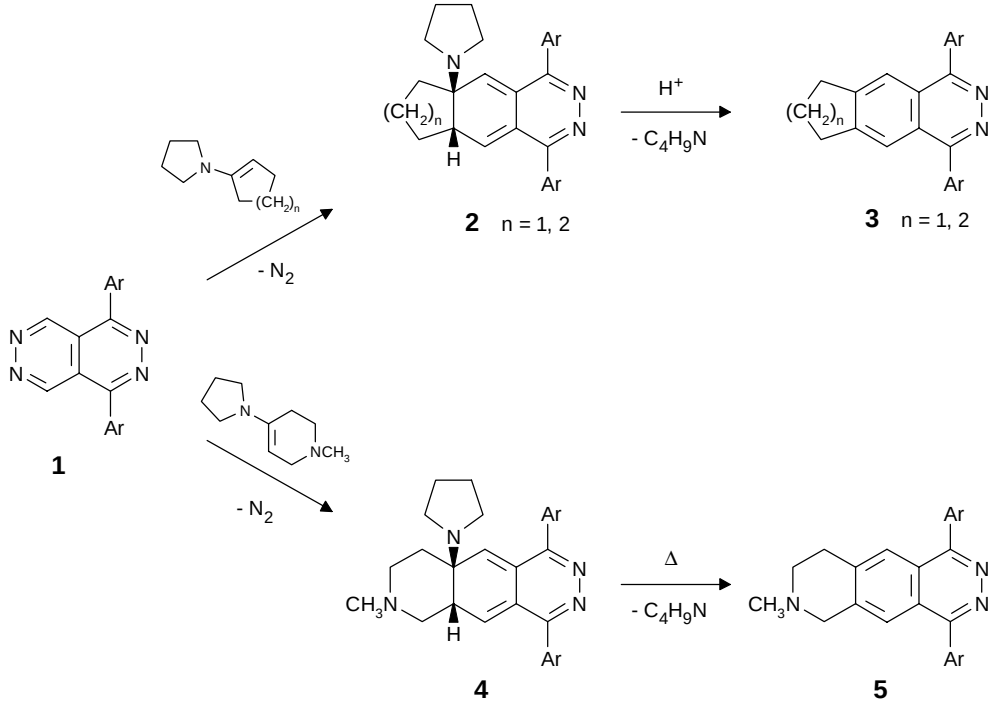
Although there are two potentially reactive azadiene substructures present in compounds of type **1**, one might expect - for steric reasons - addition of the dienophile across C-5/C-8 to predominate compared to addition across C-1/C-4 (Scheme 1). Indeed, in all instances only reaction products resulting from attack on the less hindered pyridazine ring were isolated.

Scheme 1



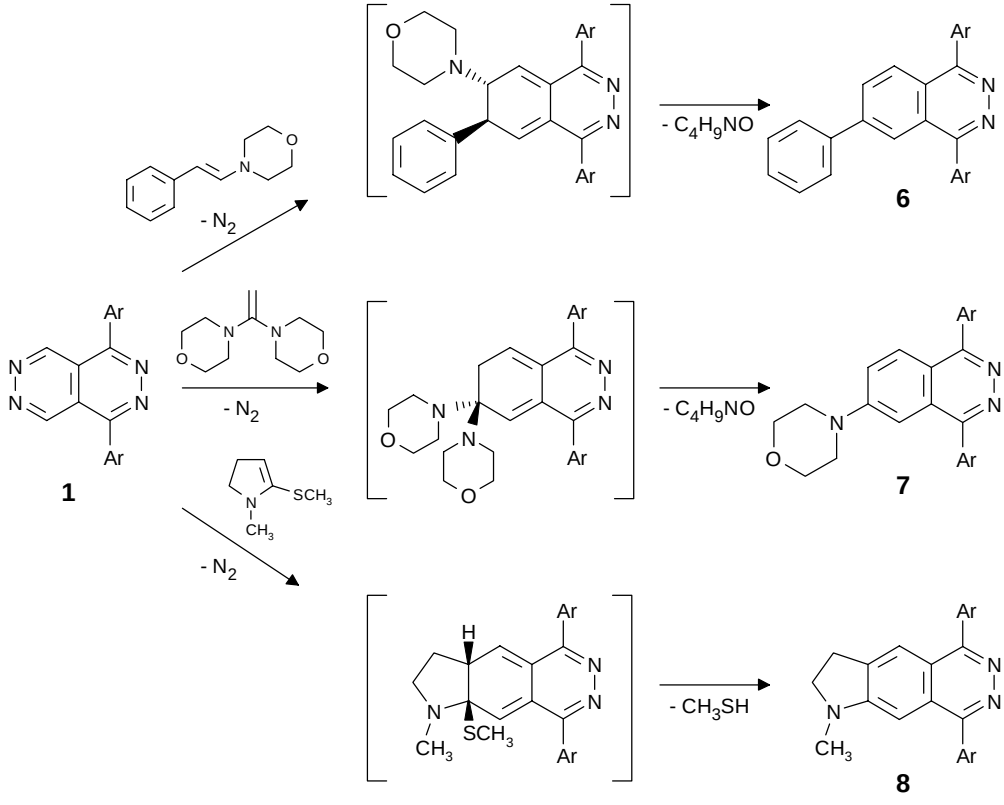
Bridged cycloadducts as displayed in Scheme 1 (other possible endo/exo isomers and enantiomers were omitted for the sake of clarity) are generally accepted as intermediates in this reaction type although they could not be detected. Obviously, these highly strained cycloadducts immediately eliminate molecular nitrogen to afford cycloamino-substituted (condensed) dihydrophthalazine derivatives (see Scheme 2). The latter are surprisingly stable, although aromatization can be accomplished under acidic conditions or simply by heating.

Scheme 2



Employment of an open-chain enamine (N-styrylmorpholine) as well as of ketene-acetal-type reagents (1,1-dimorpholinoethene or 1-methyl-2-methylthio-2-pyrroline, respectively) directly leads to (aromatic) phthalazine derivatives in good yields (see Scheme 3), thus further demonstrating the scope of this reaction type.

Scheme 3

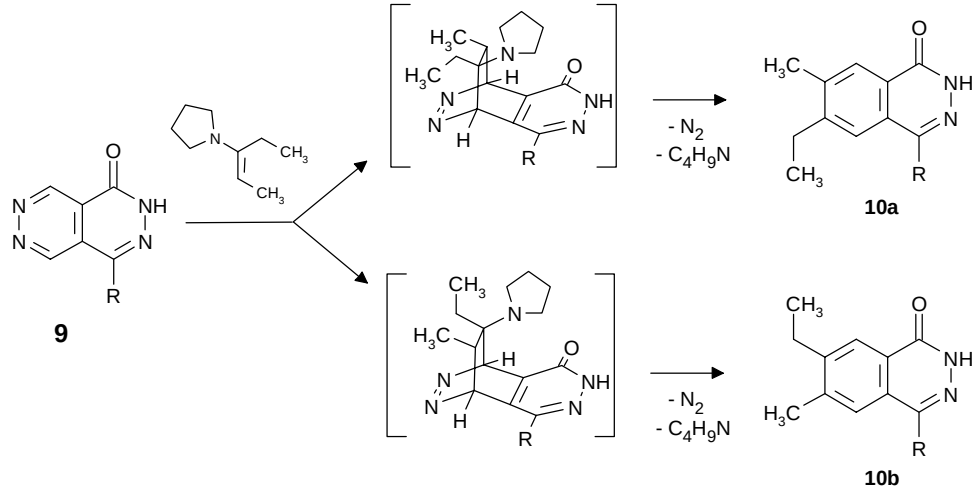


In all the transformations described above, the cycloaddition/cycloreversion sequence, followed by an elimination step (loss of an amine in most cases), leads to a single aromatic phthalazine derivative, as a consequence of the symmetrical substitution pattern of the starting azadiene. As soon as "unsymmetrical" azadienes are used, the regiochemistry of the [4+2]-cycloaddition reaction becomes an interesting issue, as will be discussed in the following examples.

Pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones (**9**) bearing a substituent at C-4 (R = ethyl, phenyl) are conveniently available from 4-pyridazinecarboxylic acid[28] and now also were found to exhibit pronounced azadiene reactivity on treatment with a variety of enamines in boiling 1,4-dioxane. Initial experiments with the "unsymmetrical" enamine,

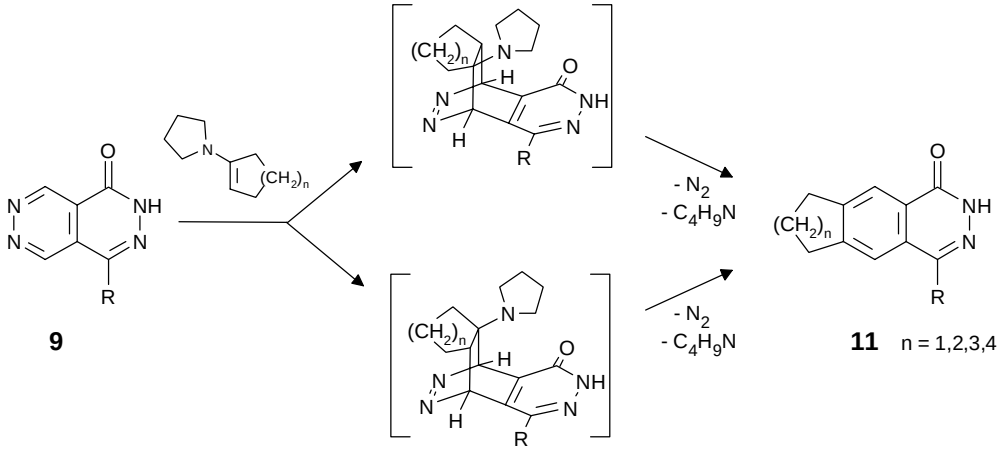
3-pyrrolidino-2-pentene, showed that both possible regioisomeric reaction products (**10a**, **10b**) are formed in a ratio of about 2 : 1 (cf. Scheme 4).

Scheme 4



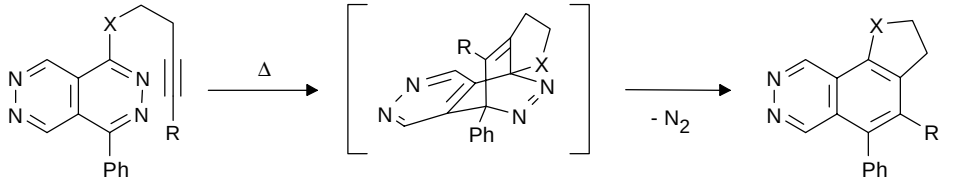
From a preparative point of view, employment of "symmetrical" dienophiles such as simple cycloalkanone-derived enamines proved to be particularly useful, as both pathways lead to a single product (after aromatization). Using this procedure, a series of cycloalkene-annelated 4-substituted phthalazin-1(2*H*)-ones (**11**; R = ethyl, phenyl) was prepared (cf. Scheme 5) with yields typically in the range of 70-90%. These compounds are required in the course of a program aimed at the study of structure-activity relationships of phthalazine-derived drug molecules.

Scheme 5



As shown so far, it has always been the *unsubstituted* pyridazine ring of the bicyclic system which acts as an azadiene. This situation changes when the [4+2]-cycloaddition reaction is performed in an *intra*molecular fashion, as outlined in Scheme 6. In these examples, an alkyne acts as a dienophile which is tethered to C-1 of the tetraazanaphthalene system *via* a hetero atom (X = O, S). Although acetylenes generally have to be considered as poor dienophiles in inverse-electron-demand Diels-Alder reactions, here the entropic assistance which results from linkage of the two reaction partners provides a significant benefit which permits such a cycloaddition process to take place under reasonable conditions.

Scheme 6



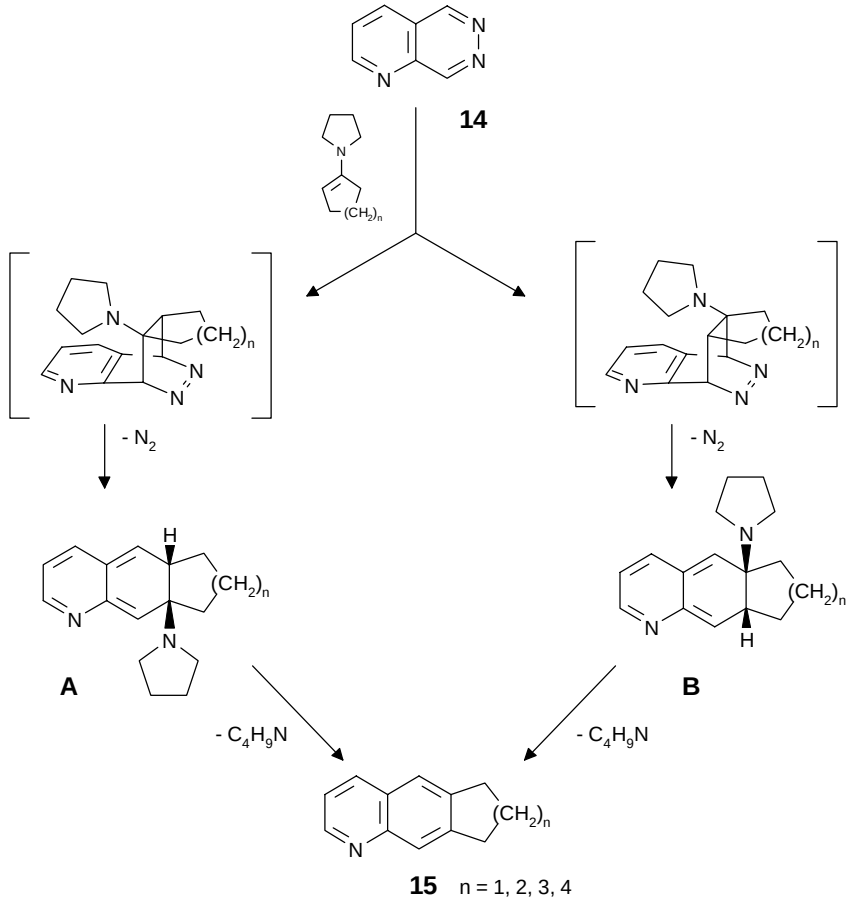
12 X = O, R = H
X = O, R = CH_3
X = S, R = H

13 X = O, R = H
X = O, R = CH_3
X = S, R = H

The cyclization, giving [*f*]-annelated phthalazines (**13**) in good to high yields, usually is carried out by heating the precursor (**12**) in an inert solvent like bromobenzene; the progress of the reaction can be conveniently monitored by ^{1}H-NMR spectroscopy. For steric reasons, the presence of a terminal methyl substituent at the acetylenic substructure leads to a marked decrease in the reaction rate, elongation of the spacer chain by one CH_2 unit leads to complete loss of reactivity.

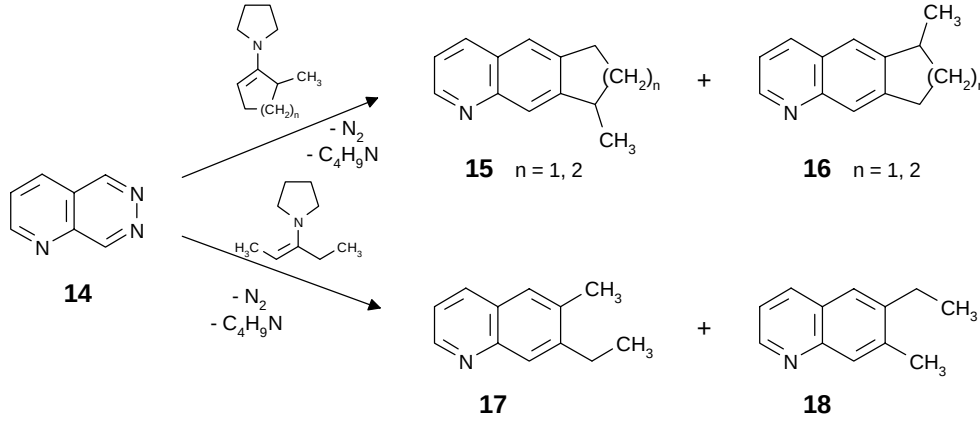
Anellation of a pyridine ring to the pyridazine nucleus can be anticipated to result in a similar activating effect on the azadiene reactivity of the 1,2-diazine system as that observed in the case of the pyridazino[4,5-*d*]pyridazines (see above), albeit somewhat less pronounced (cf. Table 1 for a comparison of the LUMO energies of the parent systems). This was found to be true when the triazanaphthalene **14**[29] was treated with various cyclic enamines in boiling 1,4-dioxane. A series of [*g*]-annelated quinolines was prepared in this manner (yields: 31-67%), as outlined in Scheme 7. Again, marked differences in the reaction rates were observed with respect to the ring size of the employed dienophile, with the six-membered enamine showing the lowest reactivity.

Scheme 7



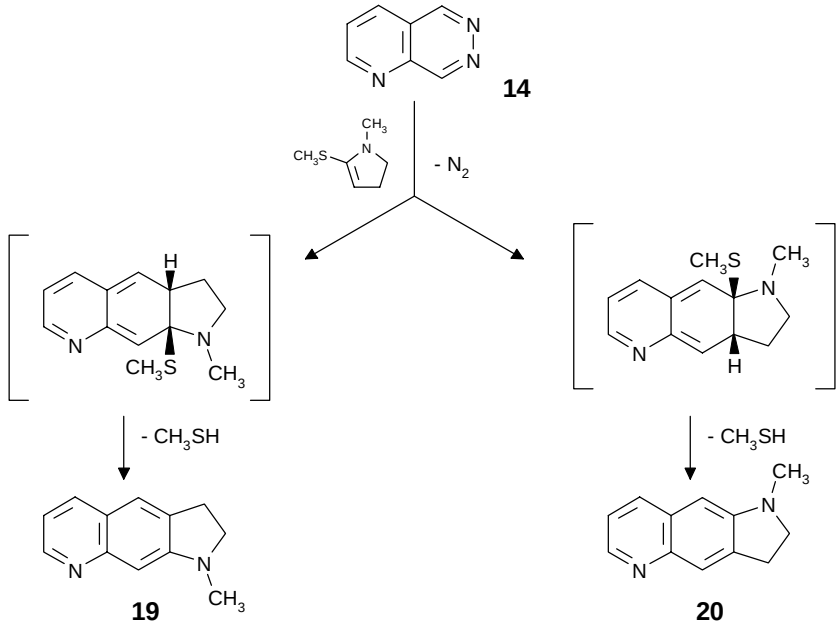
In analogy to the formation of the cycloalkene-annelated phthalazinones **11**, both possible diene/dienophile orientations finally lead to a single aromatic product (**15**) *via* the regiosisomeric intermediates **A** and **B**. When **14** is reacted with "unsymmetrical" enamines as dienophiles, mixtures of isomeric quinoline derivatives (one component clearly dominating in each case) are obtained (see Scheme 8).

Scheme 8



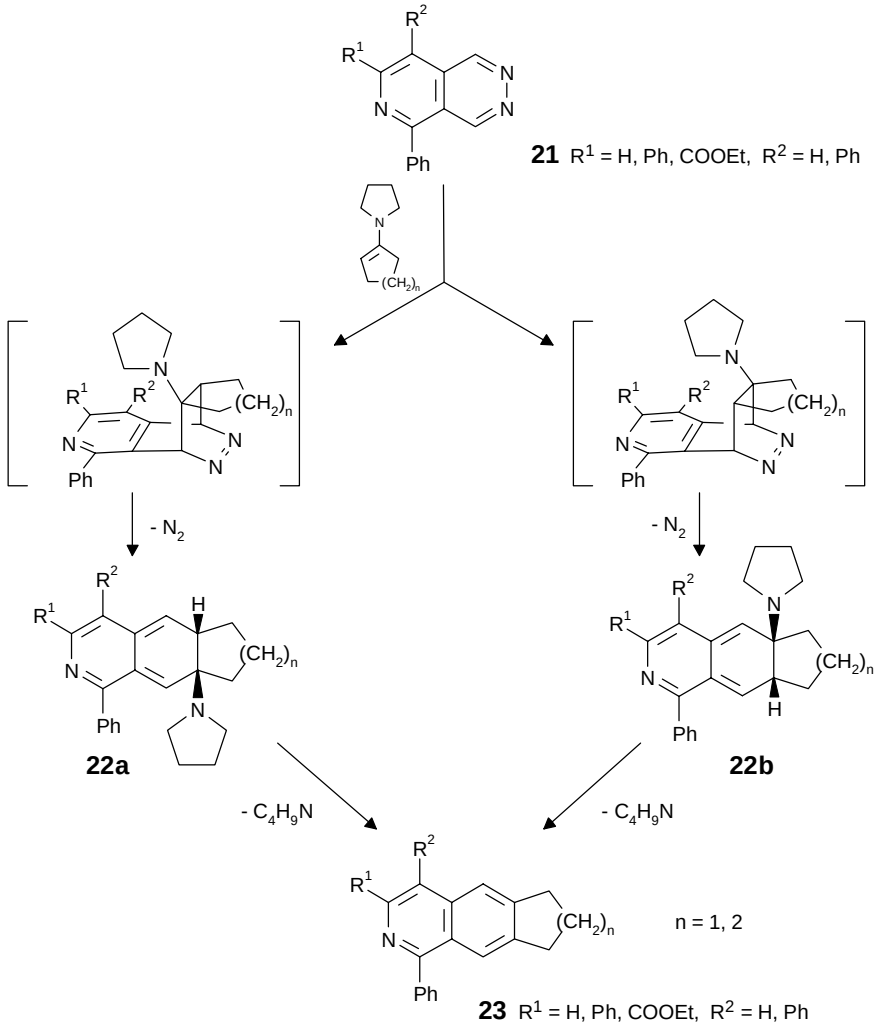
In general, preferential attack of an enamine dienophile on the azadiene takes place in an orientation which leads (after expulsion of N_2 from an initially formed bridged cycloadduct) to an intermediate of type **A** (cf. Scheme 7), which means that the more electron-rich enamine carbon atom shows a higher affinity to the C-5 position of the azadiene than to C-8. Interestingly, this situation is reversed when a cyclic ketene N,S-acetal (1-methyl-2-methylthio-2-pyrroline) is employed as a C=C dienophile. Loss of N_2 from the cycloadduct and subsequent elimination of methyl mercaptane gives rise to the formation of two isomeric pyrroloquinoline derivatives **19** and **20** in a ratio of 1 : 1.7.

Scheme 9

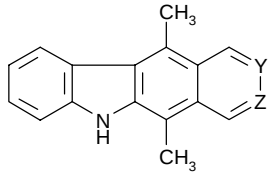


Representatives of another type of triazanaphthalene, namely pyrido[3,4-*d*]pyridazines, were also found to undergo inverse-electron-demand Diels-Alder reactions with enamines under "standard" conditions (refluxing 1,4-dioxane), as outlined in Scheme 10. Here, the reaction generally stops at the stage of a (fused) dihydroisoquinoline derivative (still bearing the pyrrolidino moiety). Aromatization requires more or less drastic conditions, depending on the ring size of the cycloalkane substructure. In all cases, mixtures of regioisomeric primary reaction products were obtained. However, only with the monophenyl-substituted compounds ($R^1 = R^2 = H$), separation and structural assignment of the components was possible (major isomer: **22b**).

Scheme 10



The most recent research efforts in the author's laboratory[23-25] have been devoted to the use of inverse-electron-demand Diels-Alder reactions for the construction of tetracyclic compounds which are structurally related to the antitumor alkaloid ellipticine and its congeners. In particular, the synthesis of fluorinated ellipticine analogs has become a major target.

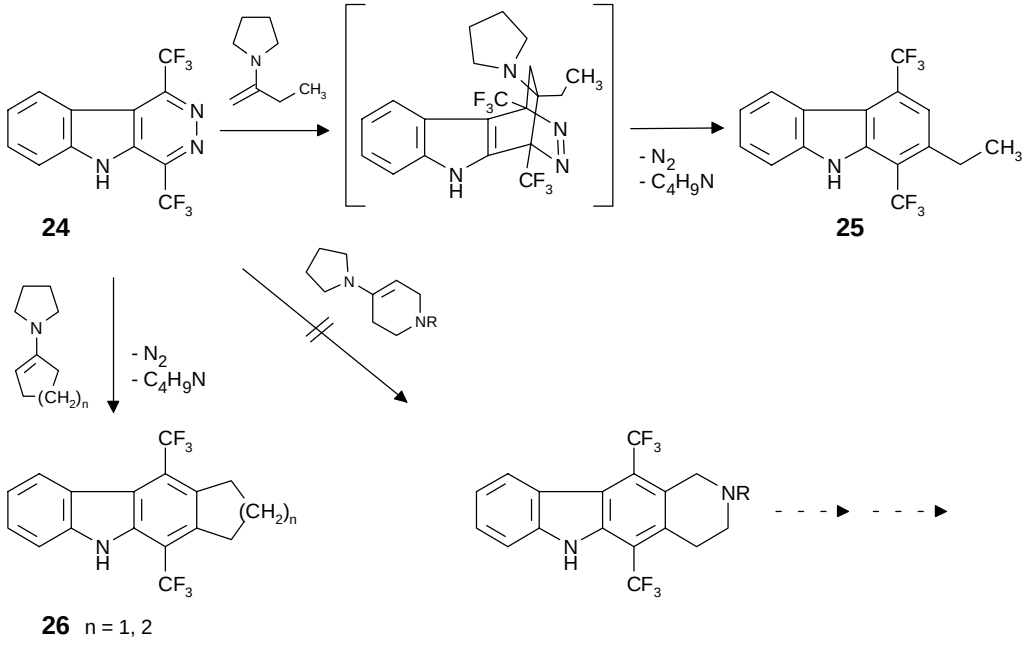


Ellipticine: Y = N, Z = CH
Isoellipticine: Y = CH, Z = N

A first approach was investigated, using the pyridazino[4,5-*b*]indole **24**[30] as an azadiene in order to build up the tetracyclic system in a "3+1 ring" fashion. Although [4+2]-cyclo-

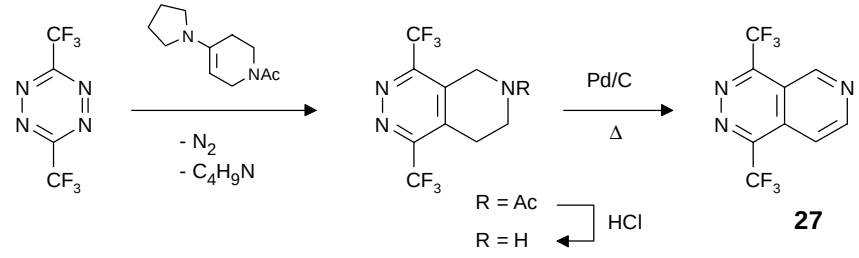
addition takes place upon treatment of **24** with 2-pyrrolidino-1-butene (affording the tri-substituted carbazole **25** as a single regioisomer) as well as with five- and six-membered cycloalkanone enamines, the desired (tetrahydro)pyridine ring annelation failed owing to the low reactivity of the 4-piperidone-derived dienophile (Scheme 11).

Scheme 11



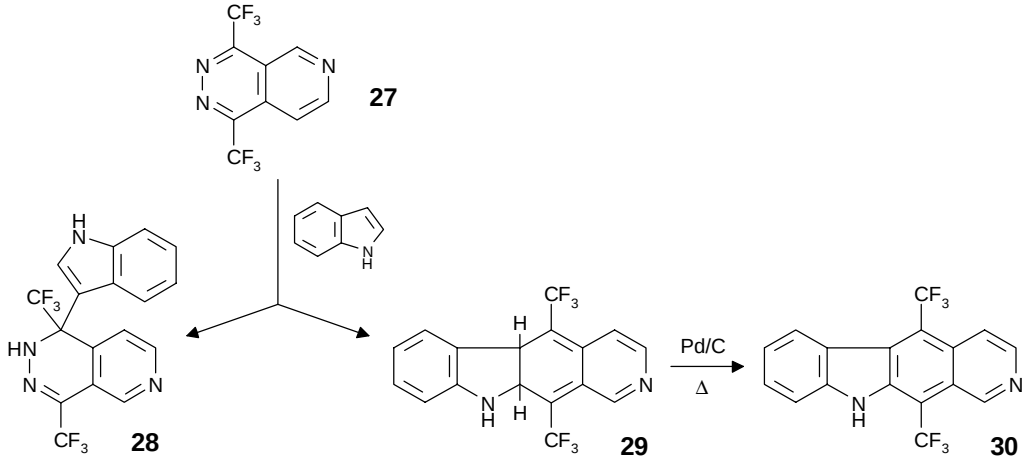
In an alternative approach, the pyrido[3,4-*d*]pyridazine **27** should be employed as an azadiene with indole (or indole derivatives) as dienophile, in order to build up the tetracyclic skeleton in a "2+2 ring" manner. A convenient synthesis for **27** was developed, starting from 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine[31] as outlined in Scheme 12.

Scheme 12

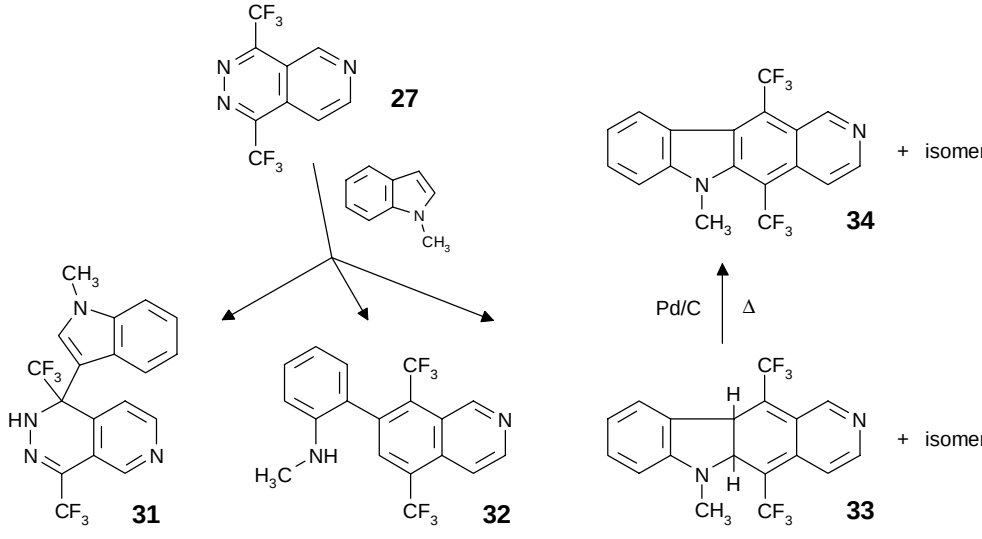


In all attempted [4+2]-cycloaddition reactions performed so far with **27** and indole-type dienophiles, complex product mixtures were obtained. Both indole and its N-methyl derivative were found to act as dienophiles as well as nucleophiles (compare ref.[32]). In the latter case, addition of the indole C-3 atom to a pyridazine carbon atom leads to compounds **28** or **31**, respectively. Cycloaddition/ cycloreversion processes give rise to the formation of the isoquinoline **32** (resulting from ring opening of a tetracyclic intermediate) and the dihydropyridocarbazoles **29** and **33**, the latter (**33**) representing an isomer mixture. In both cases, Pd-catalyzed oxidation smoothly affords the corresponding aromatic pyridocarbazoles **30** and **34**, respectively (Schemes 13, 14).

Scheme 13



Scheme 14



In conclusion of the findings shown in this overview, one may state that the ability of heterocycle-fused pyridazines, most of them easily available, to undergo thermally induced inverse-electron-demand Diels-Alder reactions with various electron-rich dienophiles represents an interesting and versatile tool for the construction of higher annelated heterocyclic ring systems.

Acknowledgement

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