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LETTERS

A novel double 'inverse electron-demand' Diels–Alder reaction of azolyldienamines and tetrazines

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Abstract

Appropriately substituted azolyldienamines were found to undergo double 'inverse electron-demand' Diels–Alder reactions with tetrazine derivatives, yielding azolylpyridazines and dihydropyridazines as products. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Diels–Alder reactions; dienamines; pyridazines; tetrazines.

Hetaryldienamines, which are easily accessible via the ring opening of condensed pyridinium salts with secondary amines, were reported[1,2] to react readily with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[3] **2**, the reaction taking place selectively on the double bond next to the amine moiety. For example tetrazolyldienamine **1a** was converted into the tetrazolylvinylpyridazine **3**[1] (Scheme 1). On the other hand, reaction of 2-methyl-1-morpholino-1,3-pentadiene **1b** with the tetrazine **2** resulted in a 'tandem' Diels–Alder reaction sequence, in which both double bonds of the dienamine reacted with a single tetrazine unit, and the strained azo-bridged compound **4** was formed in good yield[4,5] (Scheme 1). In the hope of extending the tandem 'inverse electron demand' Diels–Alder process to hetaryldienamines we hoped that introduction of a methyl group into the appropriate position of the hetaryl-dienamines would change the course of the process from a single to a tandem cycloaddition.

The required methylated hetaryldienamines **5a–c** were prepared by the ring opening of the appropriate methyl-substituted condensed heterocyclic salts with pyrrolidine and morpholine. Introduction of a methyl group into the azolopyridinium salts resulted in a marked decrease in their ring opening ability and the [1,2,4]triazolo[4,3-*a*]pyridinium system reacted only with the more nucleophilic pyrrolidine to yield a dienamine. All the dienamines were *E*,*E*-isomers, a fact that was established by NOE measurements.

The methylated dienamines **5a–c** reacted readily with the tetrazine diester **6a** (Table 1, entries 1–3), as shown by the rapid evolution of nitrogen, but after the addition of one equivalent of **6** TLC analysis of

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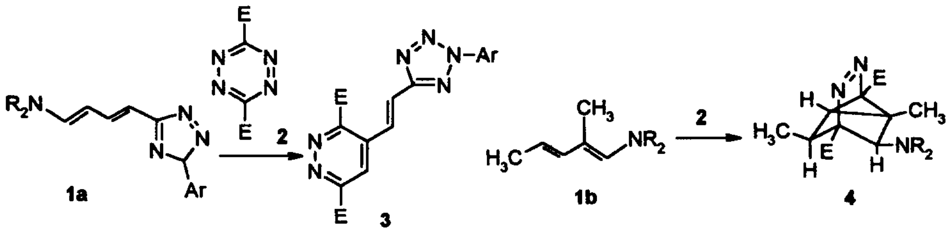
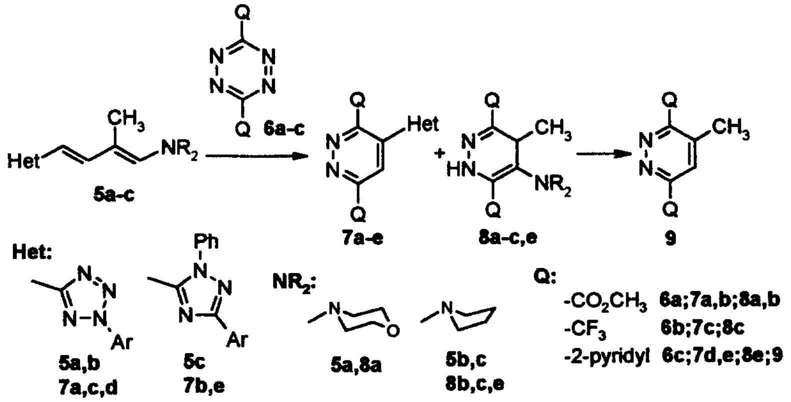


E = CO_2Me; Ar = 4-chlorophenyl; NR_2 = morpholinyl

Scheme 1.

the mixture still indicated the presence of unreacted starting material which was consumed only on the addition of another equivalent of tetrazine. The analysis of the mixture then showed the presence of two products which were isolated by column chromatography and identified as the hetarylpyridazine diester **7a,b** and the dihydropyridazine diester **8a,b** (Scheme 2), which implies that both double bonds of the dienamine reacted with a molecule of tetrazine and at some stage, fission of the C(2)–C(3) bond also took place.[6] Our attempts to identify any intermediate by following the reaction with NMR spectroscopy failed, since at any stage of the addition the mixture consisted of only the two products and starting material. This result suggests that take-up of the second tetrazine molecule is much faster than that of the first.



Scheme 2.

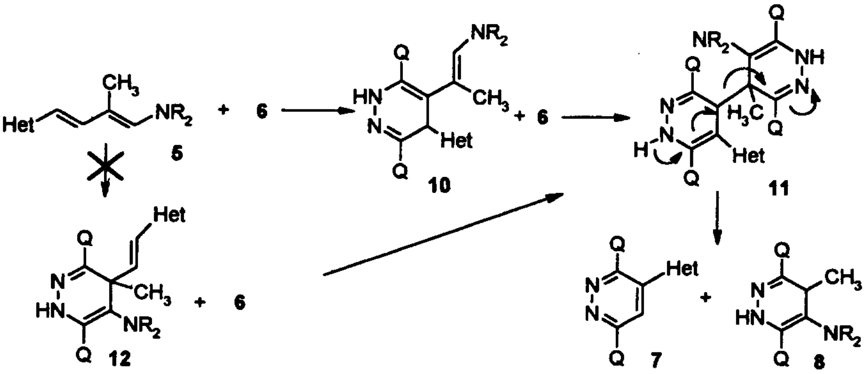
Table 1
Products obtained by the double inverse electron demand Diels–Alder reaction of hetaryldienamines with tetrazines

Entry	Dienamine	Tetrazine	Pyridazine[a]	Dihydropyridazine[a]
1	**5a**	**6a**	**7a** – 68%	**8a** – 71%
2	**5b**	**6a**	**7a** - 92%	**8b** – 94%
3	**5c**	**6a**	**7b** - 47%	**8b** – 53%
4	**5b**	**6b**	**7c** - 38%	**8c** – 44%
5	**5a**	**6c**	**7d** - 39%	**9** - 42%
6	**5b**	**6c**	**7d** - 45%	**8e** – 56%
7	**5c**	**6c**	**7e** - 42%	**8e** – 37%

(a) Yield of analytically pure product based on starting dienamine

In order to establish the scope and limitations of the process, other tetrazine derivatives (**6b,c**) were also reacted with the azolyldienamines. The 3,6-bis-(trifluoromethyl)tetrazine **6b**[7] underwent prompt reaction with the tetrazolyldienamine **5b** (Table 1, entry 4) and two products were formed, which were identified as the pyridazine derivatives **7c** and **8c** (Scheme 2). The methylated azolyldienamines **5a–c** were also reacted with 3,6-di-(2-pyridyl)tetrazine **6c**[8] (Table 1, entries 5–7). Due to the decreased reactivity of this tetrazine derivative the reactions were carried out at 80°C instead of room temperature. All of the azolyldienamines reacted with two equivalents of the tetrazine, and the azolylpyridazines **7d,e** were isolated in moderate yield. Under the conditions applied we could isolate only one of the dihydropyridazine products **8e** while the morpholine derivative aromatised to the pyridazine **9** (Scheme 2).

The course of the first addition step may be influenced by steric and electronic factors, but quantum chemical calculations[9] suggest that the electronic properties along the diene chain do not differentiate the two double bonds substantially. On the other hand, introduction of the methyl group onto the diene chain makes one of the double bonds trisubstituted, a factor which has been shown[10] to be accompanied by a marked decrease in reactivity; therefore we assume that the hetaryldienamines are first transformed to intermediate **10** (Scheme 3). The addition of a second molecule of tetrazine to the enamine side-chain of **10** — which can be further activated by conjugation to the enamine subunit of the dihydropyridazine — results in the bis-adduct **11**, which on disproportionation, gives the pyridazine **7** and dihydropyridazine **8** products. The experimental evidence that the second tetrazine molecule adds faster than the first also excludes the formation of an intermediate **12** where the first tetrazine adds onto **5** next to the amine, since the remaining double bond of **12** is expected to be much less reactive than in **10**.[11]



Scheme 3.

General procedure: The reaction of 3-methyl-4-morpholino-1-[2-(4-chlorophenyl)-tetrazol-5-yl]-1,3-butadiene **5a** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **6a**: a solution of **6a** (40 mg, 0.22 mmol) in 2 ml acetonitrile was added dropwise to a solution of **5a** (33 mg, 0.1 mmol) in 2 ml acetonitrile and the reaction was stirred at 25 °C for 2 h. After evaporation of the solvent the products were separated by flash column chromatography on silica gel using hexane–ethyl acetate as eluent to yield **7a** (25 mg) and **8a** (20 mg).

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References

1. Kotschy, A.; Hajós, Gy.; Messmer, A. *J. Org. Chem.* **1995**, *60*, 4919–4921.
2. Kotschy, A.; Timári, G.; Hajós, Gy.; Messmer, A. *J. Org. Chem.* **1996**, *61*, 4423–4426.
3. Boger, D. L.; Panek, J. S.; Patel, M. *Org. Synth.* **1992**, *70*, 79–82.
4. Kotschy, A.; Smith, D. M.; Bényei, A. Cs. *Tetrahedron Lett.* **1998**, *39*, 1045–1048.
5. A similar reaction of 2,3-dimethyl-1,3-butadiene and 3,6-bis-trifluoromethyl-tetrazine has also been reported: Klindert, T.; von Hagel, P.; Baumann, L.; Seitz G. *J. prakt. Chem.* **1997**, *339*, 623.
6. A similar reaction has been published where oxidation of the intermediate was postulated. Borthakur, D. R.; Prajapati, D.; Sandhu, J. S. *Heterocycles* **1987**, *26*, 337–341.
7. Brown, H. C.; Cheng, M. T.; Parcell, L. J.; Pilipovich, D. *J. Org. Chem.* **1961**, *26*, 4407; Barlow, M. G.; Haszeldine, R. N.; Picket, J. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 363–366.
8. Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318–320.
9. Hajós, Gy.; Kotschy, A. *Acta Chim. Slov.* **1998**, *45*, 285–354.
10. Hierstetter, T.; Tischler, B.; Sauer, J. *Tetrahedron Lett.* **1992**, *33*, 8019–8022.
11. Semiempirical quantum chemical calculations on **10** and **12** (Q=CO_2Me, R=CH_3, NR_2=morpholinyl, Het=2-methyltetrazol-5-yl) show that the highest occupied molecular orbital energies with a reasonable *pi* contribution from the olefinic sidechains lie at −8.00 eV (cp_z: 0.35, 0.26) and −10.23 eV (cp_z: 0.16, 0.22), respectively.