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RETRO DIELS-ALDER REACTIONS OF HETEROCYCLIC COMPOUNDS UNDER MILD CONDITIONS

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The retro Diels-Alder reaction or $-[{}_{\pi}2_{s}+{}_{\pi}2_{s}+{}_{\pi}2_{s}]$ cycloreversion has been used in carbocyclic chemistry for the synthesis of numerous, otherwise difficultly accessible, compounds[1]. In general, this reaction is unsuitable for the preparation of heterocyclic compounds since very often rather high temperatures are required, at which most heterocycles decompose[2]. The only exception reported is the elimination of nitrogen from the adducts of 1,4-disubstituted tri- or tetrazines with ynamines[7]. We attribute the fast elimination from these adducts to the fact that both the diene and the dienophilic component are stabilized by resonance in the transition state.

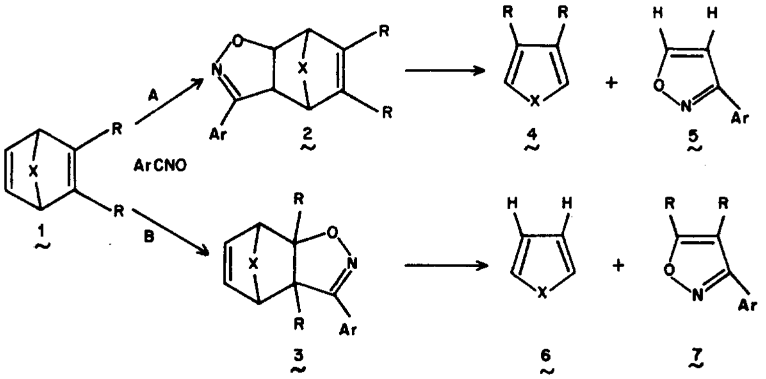
We have now investigated whether this type of reaction can be more generally applied to the synthesis of heterocyclic compounds. As starting materials we used 7-oxa-and 7-azabicyclo[2.2.1] hepta-2,5-dienes (**1** a, b), which were prepared by Diels-Alder reactions of furan and N-ethoxycarbonylpyrrole, respectively, with dimethyl acetylenedicarboxylate[8].

Reaction of **1** a with one equivalent of 2,4,6-trimethylbenzonitrile oxide in various solvents at 20 °C gave, instead of the expected 1,3-dipolar adduct (**2** or **3**), a mixture of four products. Two of these were identified as the furans **4** a and **6** a, and the others as 3-(2',4',6'-trimethylphenyl)isoxazole (**5**) and 4,5-bis(methoxycarbonyl)-3-(2',4',6'-trimethylphenyl)isoxazole (**7**).

N-ethoxycarbonylpyrrole (**1** b) reacted with 2,4,6-trimethylbenzonitrile oxide under the same conditions to yield two N-ethoxycarbonylpyrroles (**4** b and **6** b) together with **5** and **7**. Other 1,3-dipolar reagents such as diphenylnitrilimine and phenyl azide reacted similarly although in some cases only two different products were formed; the results of these reactions are summarized in the Table.

We explain these results in terms of a two-step process, namely, 1,3-dipolar addition at one of the two double bonds to give **2**, **3**, which subsequently undergo a fast retro Diels-Alder reaction. An alternative pathway to the observed products might have been a retro Diels-Alder reaction of **1** to yield either **4** and acetylene or **6** and dimethyl acetylenedicarboxylate, followed by 1,3-dipolar addition to the acetylenes, yielding e.g. **5** and **7**. Conclusive evidence against this pathway was provided by the following observations:

(i) In a separate experiment acetylene, in contrast to dimethyl acetylenedicarboxylate, did not react with the 1,3-dipolar reagents at 20 °C. This eliminates the possibility that **4** and **5** are



(a) X = O
(b) X = $NCOOC_2H_5$
R = $COOCH_3$
Ar = 2,4,6-TRIMETHYLPHENYL

SCHEME

TABLE

Substrate[a]	1,3-Dipolar[a] reagent	Ratio A/B[b] (See scheme)	Products (yields)[c]	
1a	2,4,6-$(CH_3)_3C_6H_2CNO$	1.17	4 a, 5 (54 %)	6 a, 7 (46 %)
1b	ditto	1.20	4 b, 5 (55 %)	6 b, 7 (45 %)
1a	$C_6H_5C\equiv\overset{\oplus}{N}-\overset{\ominus}{N}-C_6H_5$	0		6 a, 8 (100 %)
1b	ditto	0		6 b, 8 (100 %)
1a	$C_6H_5N_3$	0		6 a, 9 (100 %)
1b	ditto	0.51	4 b, 10 (36 %)	6 b, 9 (64 %)

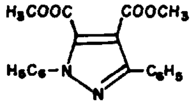
a. Molar ratio substrate/1,3-dipolar reagent = 1/1.05.

b. The conversion of substrate was quantitative (TLC) after 16h at 25 °C in diethyl ether.

c. Yields were determined by PMR spectroscopy ($CDCl_3$).

formed by a retro Diels-Alder reaction of 1.

(ii) Reaction of 1a, b with one equivalent of N-methyl-p-chlorophenylnitrone gave 1:1 cycloadducts 11 in quantitative yields[9], although in a competitive experiment the nitrone was



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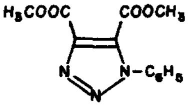

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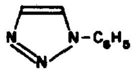
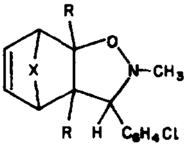


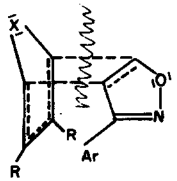
10

found to react much faster with dimethyl acetylenedicarboxylate than with 1a, b. Therefore we are tempted to conclude that compounds 1a and b, at 20 °C, are not in equilibrium with their Diels-Alder components and this leaves the formation of the reaction products via reverse Diels-Alder reaction of 2 and 3 as the only pathway.



11

X = O, $NCOOC_2H_5$
R = $COOCH_3$



12

The reason why 2 and 3 (or the adducts with the other 1,3-dipolar reagents given in the Table) undergo retro Diels-Alder cleavage under such mild conditions might be due to the stabilization of the transition state (e.g. 12)[10,12]. This also explains the relatively high thermal stability of the nitrone adduct (11), which eliminates furan only upon heating at 150 °C.

REFERENCES AND FOOTNOTES

1. For reviews on the retro Diels-Alder reaction, see e.g., H. Kwart and K. King, Chem. Rev., **68**, 415 (1968), and H. Wollweber, "Diels-Alder-Reaktion", Georg Thieme Verlag, Stuttgart 1972, p.152.
2. Recently, however, vapour-phase flash pyrolysis[3] (400-500 °C) has been applied to prevent this decomposition, e.g. in the syntheses of isobenzofuran[4], isoindole[5] and benzazete[6] via retro Diels-Alder reactions.
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9. Compounds **11** consisted of mixtures of two isomers (endo and exo) which were separated by chromatography; all novel compounds afforded satisfactory analytical and spectroscopical data.
10. In contrast to the fast Diels-Alder reaction of **2** and **3** Huisgen and Christl[11] found that the 1,3-dipolar adducts of nitrile oxides or diphenylnitrilimine with cyclopentadiene decomposed only upon heating at 140-160 °C.
11. R. Huisgen and M. Christl, Angew. Chem. Intern. Ed. Engl. **5**, 456 (1967).
12. It is well known that acetylene does not enter into cycloaddition reactions with 1,3-dipolar reagents under mild conditions. However, using **1** as "activated" acetylene, in some cases 1,3-dipolar adducts of acetylene can be obtained (e.g. **5** and **10**).