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DIELS-ALDER REACTIONS WITH INVERSE ELECTRON DEMAND. II. THE REACTION OF BENZAMIDINE WITH π-DEFICIENT HETEROAROMATIC COMPOUNDS(1).

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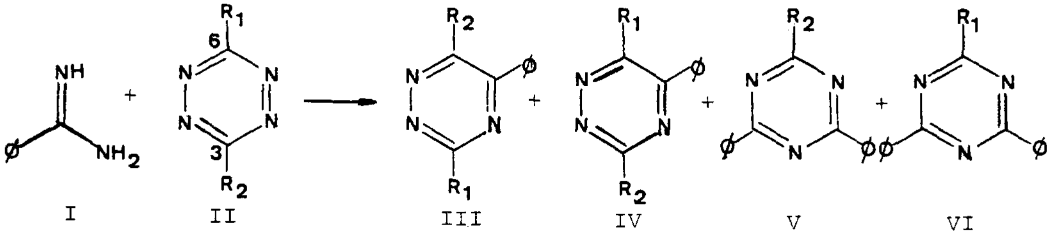
Summary : Benzamidine (I) reacts with several s-tetrazines to give as-triazines in moderate to good yield, together with some s-triazines; separate experiments have shown that these are due to the fact that (I) also undergoes Diels-Alder-reactions with as- and even with s-triazines.

Although the so-called "Diels-Alder reaction with inverse electron demand" of various π-deficient heteroaromatic compounds with electron-rich triple and double carbon-carbon bonds is a well-documented field(2), very few reactions of this type have been described where the dienophile is an open-chain C=N double bond, suitably activated by electron-donating substituents(3). Imidates react with 3,6-dimethoxycarbonyl-s-tetrazine (DMCT) at 60° (dioxane) to give the corresponding as-triazines in very poor yield (13-27%); no reaction occurs with the less activated 3,6-diphenyl-tetrazine(4). Very recently, it has been shown that aldehydic hydrazones on the other hand react with DMCT in a very satisfactory manner(5), leading to the expected cycloadducts even at room temperature (yield 60-80%).

As part of our investigations on the possibility of using amidines as dienophiles in this type of reaction, we now wish to report that benzamidine (I) not only reacts with a variety of tetrazines, but also with several as- and s-triazines.

When I is allowed to react with the tetrazines II_{a-e}(2,6) in refluxing toluene untill their characteristic carmine red color had disappeared (7) a mixture of as- and s-triazines is obtained as described in Figure 1. The as-triazines III and IV are, on the basis of previous findings(4,5), the expected reaction products resulting from the [4+2] cycloaddition of the benzamidine at the 3,6-positions of the tetrazine, with subsequent loss of nitrogen and ammonia (Figure 2); if II is asymetrically substituted, complete regioselectivity is obtained in some cases (e.g. $II_{d,e}$). This reaction obviously constitutes a new and convenient method for the preparation of as-triazines differently substituted at the 5- and 6-positions(8).

According to previous experimental observations when enamines(10) or hydrazones (5) are used as dienophiles in this type of reactions loss of N_2 from the initial cycloadduct may be supposed to lead to a dihydro-pyridazine intermediate which subsequently aromatizes.



	II		III	IV	V	VI	Reaction Time (in hours)	Ratio I/ II (moles)
	R_1	R_2						
a	2-pyridyl	2-pyridyl	33%		5%		1.5	0.5
b	ϕ	ϕ	34%		—		40	0.25
c	ϕ	2-pyridyl	7.5%	30%	28%	6%	24	0.25
d	ϕ	Me	-	70%	-	7%	7.5	0.23
e	2-pyridyl	Me	-	35%	-	-	6	0.4

Figure 1

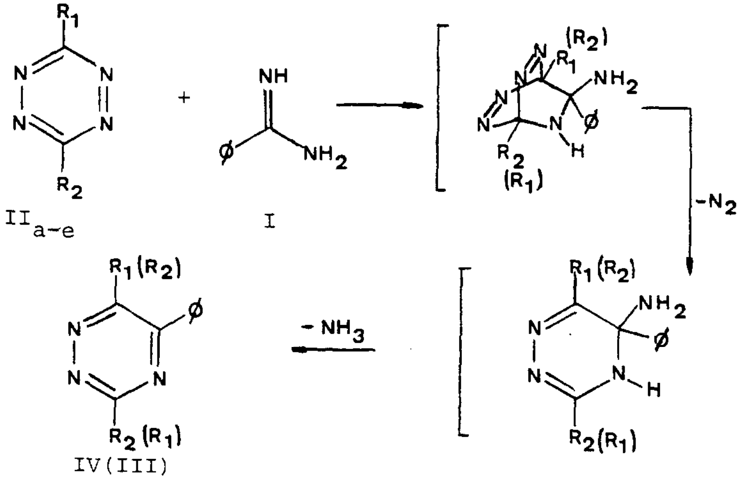
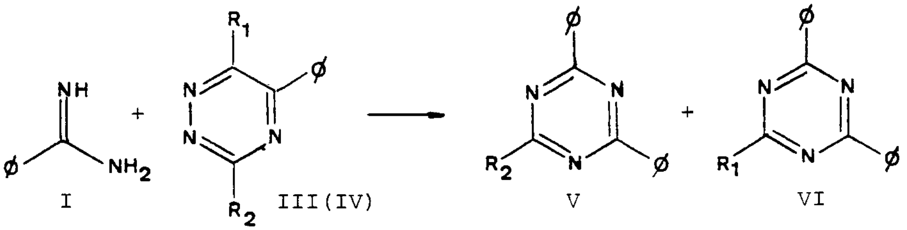


Figure 2

Separate experiments showed that the s-triazines V and VI resulted from the subsequent reaction of I with the corresponding as-triazines (see Figure 3); this is easily rationalized by the mechanism shown in Figure 4, implying the addition of I at the 2,5-positions of III (IV); similar reactions at the same positions of the as-triazines have indeed been shown to occur with ynamines$^{(9)}$.



	R_1	R_2	V	VI	Reaction time (in hours) and conversion ratio	Ratio I/ III(IV) (moles)
III_c	2-pyridyl	ϕ	66%	-	90h - 75%	0.29
IV_c	ϕ	2-pyridyl	37%	26%	72h - 64%	0.50
IV_d	ϕ	Me	-	66%	90h - 60%	0.25

Figure 3

In order to obtain s-triazines however, the amidinic nitrogen atom have to react with the carbon atom C_5 of the heterocycle; the preferred loss of R_1CN from the bicyclic reaction intermediate, implying a N-N single bond breaking, can easily been understood on the basis of thermochemical arguments. No isomeric as-triazines could be detected during these reactions, showing the regiospecific character of both addition- and elimination-steps.

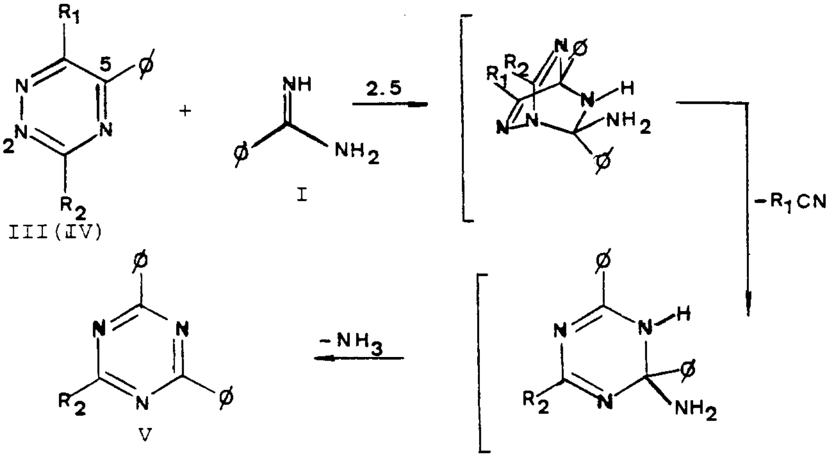


Figure 4

This scheme however does not explain the formation of VI_c and VI_d from respectively IV_c and IV_d (Figure 3). If V_c however is allowed to react with I in refluxing toluene for 90h., a 63% yield of VI_c is obtained; this can well be interpreted by the addition of I at the 1,4-positions of the s-triazine as shown in Figure 5 :

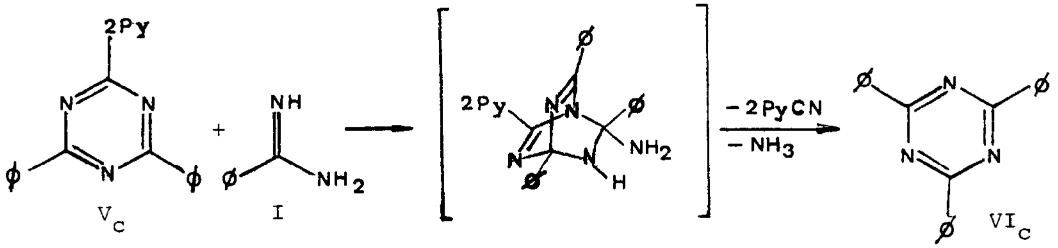


Figure 5

The reactions depicted in Fig.3 to 5 constitute the first examples of Diels-Alder reactions with inverse electron demand of an activated open-chain C=N double bond with as- respectively s-triazines . They generally necessitate longer reaction times than for the addition of I to tetrazines. However, as shown in e.g. Figure 1, the final product distribution found in these reactions should clearly depend on the relative reactivity of the various heterocycles involved.

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3. a) Several reactions involving the CN double bond of azirines however have been described : C.C. Johnson and R.H. Levin, Tetrahedron Letters 26, 2303 (1974); D.J. Anderson and A. Hassner, J.Chem.Soc.Chem.Comm., 45 (1974); D.J. Anderson and A. Hassner, Synthesis, 483 (1975); V. Nair, J. Heterocyclic Chem. 12, 183 (1975); M. Takahashi, M. Suzuki and Y. Igari, Bull.Chem. Soc.Japan 48, 2605 (1975).
   b) Very recently, the reaction between 3,6-dimethoxycarbonyl-s-tetrazine and several cyanamides have been reported : G. Seitz and W. Overheu, Chem. Zeitung 103, 230 (1979).
   c) It has been shown that aliphatic imidates react with 3,6-dimethoxycarbonyl-tetrazine in their tautemeric ketene-O,N-acetal form : G. Seitz and W. Overheu, Arch.Pharm. 310, 936 (1977).
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6. All the starting tetrazines have been previously described in the litterature(2), except II_c which was prepared by the reaction of a 0.7/1 mixture of benzamidine hydrochloride dihydrate and 2-cyano-pyridine hydrochloride with about a ten-fold excess of hydrazine hydrate for 48h. at room temperature and the crude dihydro-tetrazine so obtained oxidized by sodium nitrite in acetic acid at 0°C; yield 23% (together with 35% of 3,6-diphenyl-s-tetrazine and 1% of 3,6-di(2'-pyridyl)-s-tetrazine separated by column chromatography (SiO_2, CH_2Cl_2 and ethylacetate)); mp : 175-177°C, ^1H-NMR (100MHz, $CDCl_3$, δ in ppm) : 8.96 (1H,dq), 8.6-8.8(m,3H), 7.97(1H, td), 7.5-7.7 (4H,m).
7. Except for II_b where a conversion of 18% is observed after 40 hours.
8. Characteristics of the relevant new compounds are :
   III_c: m.p. 168°C, ^1H NMR (100MHz, $CDCl_3$, δapp. in ppm) : 8.74-8.61 (2H), 8.60(1H), 8.67(1H), 7.85(1H), 7.66-7.24(9H); IV_e : m.p. 114°C, ^1H NMR (idem) : 8.48(1H), 8.0-7.72(2H), 7.54-7.22(6H), 2.97(3H,s).
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