

Ketone Enamines as Dipolarophiles towards C-Azidohydrazones

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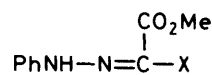
The reaction of methyl azido(phenylhydrazono)acetate (1) with the enamines (4)—(7) leads to different kinds of ring-closed products, namely 1,2,4-triazines (8)—(10), 1,2,3-triazoles (12)—(15), and 1,2,4-triazoles (16)—(19). An open-chain azo compound (20) is also formed. In one case, an intermediate 4,5-dihydro-1*H*-1,2,3-triazole (11) has been isolated. A mechanistic picture is proposed involving preliminary cycloaddition of the azido group to the enamine and subsequent reaction of the 4,5-dihydro-1*H*-1,2,3-triazoles according to various concurrent pathways.

Along a line of research dealing with the synthetic potential of C-azidohydrazones, we have reported that the reaction of compound (1) with aldehyde enamines gives 1,4,5,6-tetrahydro-1,2,4-triazines and 1,2,4-triazoles, the formation of which has been tentatively ascribed to different modes of evolution of 4,5-dihydro-1*H*-1,2,3-triazole intermediates.¹ On studying the reaction of the same azidohydrazone (1) with ketone enamines, new results have been obtained which support the above mechanistic hypothesis and bring to light an intriguing variety of behaviour patterns by the primary cycloaddition products.

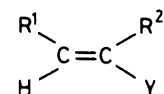
Results and Discussion

Compound (1) was treated with an excess of the enamines (4)—(7) in benzene solution under reflux as well as at room temperature. Apart from some uncharacterised material and trivial side-products such as the corresponding ketones and the hydrazones (2) and (3),² particularly in the case of (7) at 80 °C, the reaction led to the products listed in Table 1. Analytical and spectral data of the new compounds are presented in Table 2. For the 1,2,4-triazines (8) and (9), clear cut diagnostic evidence is given by the coupling (*J* 3.7 Hz) between the methine hydrogen and the NH group, which excludes regioisomeric structures having the carbocyclic double bond at position 5. The same is true for the exocyclic double bond in (10). In the case of the stereoisomeric pairs of the 1,2,3-triazoles (12)—(15), the distinction between *Z* and *E* structures was based on the frequency of the carbonyl i.r. absorption, which is lower in (12) and (14) since the *E* configuration permits an intramolecular hydrogen bond between the NH and CO groups. The structure (20), suggested by analytical and spectral properties, was confirmed by an X-ray diffraction study.³ A control experiment showed that compound (11) is unstable, decomposing upon heat treatment to give the triazine (8) in fair yield.

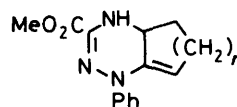
The most striking aspect of the above results is the apparent variety of products, the relative proportion of which is strongly dependent on the substituents at the ethylenic bond. However, the experimental findings can be reconciled within the frame of the mechanistic picture given in the Scheme, which involves the 1,3-dipolar cycloadducts (21) as the common first-formed products. The intermediacy of 4,5-dihydro-1*H*-1,2,3-triazoles previously proposed for the reaction of (1) with aldehyde enamines,¹ is now demonstrated by the isolation of (11) and its conversion into (8). In most cases, however, the initial cycloadducts (21) behave as transient intermediates in line with the known thermal lability of 4,5-dihydro-1*H*-1,2,3-triazoles.⁴ While morpholine elimination providing 1,2,3-triazoles (12)—(15) constitutes a minor pathway, the main mode of evolution of (21) implies fission of the endocyclic N—N bond and loss either of nitrogen to give aziridines (23) or of a diazoalkane to give amidines (25). Owing to the intramolecular, nucleophilic



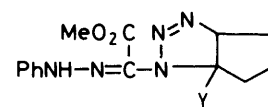
- (1) X = N₃
 (2) X = morpholino
 (3) X = NH₂



- (4) R¹, R² = (CH₂)₃
 (5) R¹, R² = (CH₂)₄
 (6) R¹ = Me, R² = Et
 (7) R¹ = H, R² = Ph



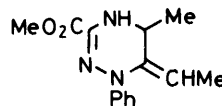
- (8) n = 1
 (9) n = 2



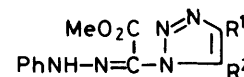
(11)

Y = morpholino

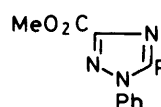
participation of the hydrazone moiety, both (23) and (25) are further transformed, thus giving rise to the final ring-closed products (8)—(10) and (16)—(17), respectively (see Scheme). It is noteworthy that tetrahydro-1,2,4-triazines of type (24; R² = H) have been found among the products of the reaction of (1) with aldehyde enamines;¹ that (8)—(10) were obtained in the



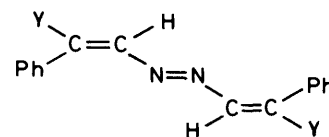
(10)



- (12) R¹ = Me, R² = Et; (*E*)-isomer
 (13) R¹ = Me, R² = Et; (*Z*)-isomer
 (14) R¹ = H, R² = Ph; (*E*)-isomer
 (15) R¹ = H, R² = Ph; (*Z*)-isomer

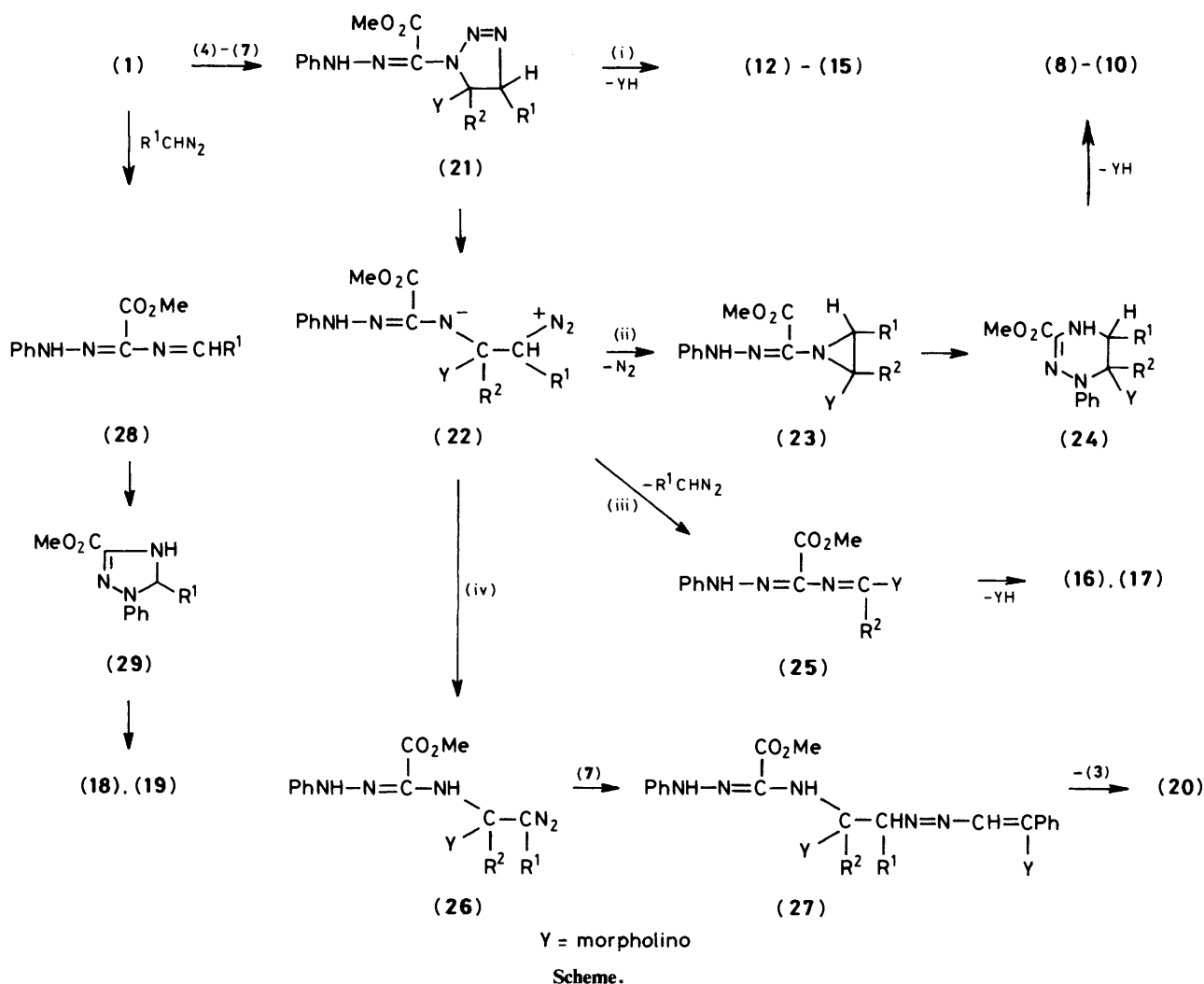


- (16) R = Et
 (17) R = Ph
 (18) R = Me
 (19) R = H



(20)

Y = morpholino



present case indicates that amine elimination from (24) occurs easily provided that an exocyclic double bond can be formed.

The formation of the 1,2,4-triazoles (18) and (19) from (6) and (7) is rather surprising and cannot be accounted for by pathway (iii). A suggested hypothesis is that these products may be due to a side-reaction between the starting azido-hydrazone and the diazoalkane formed along pathway (iii). This view was proved to be correct by the independent synthesis of (18) and (19) upon treatment of (1) with diazoethane and diazo-methane, respectively, in ethereal solution at room temperature. Although the intimate mechanism of this novel reaction is still to be elucidated, the intermediacy of the aldehyde imine-like intermediate (28) represents a plausible mechanism. In fact, it is known that compounds of type (28), arising from the condensation of C-amino-hydrazone with aldehydes, cyclise to 4,5-dihydro-1,2,4-triazoles which are easily converted into the corresponding 1,2,4-triazoles by exposure in air.⁵

Finally, as a tentative explanation of the isolation of (20), the following sequence is conceivable: (a) prototropic isomerisation of the dipolar intermediate (22) to the diazo compound (26), (b) electrophilic attack of the latter on the electron-rich carbon of the enamine (7), and (c) elimination of a molecule of (3) from the resulting azo derivative (27). This pathway would seem acceptable bearing in mind that 4,5-dihydro-1*H*-1,2,3-triazoles are known to equilibrate with amino substituted diazoalkanes⁴ and enamines have been shown to react with diazoalkanes to give open-chain azo derivatives.⁶

Table 1. Reaction of the azido-hydrazone (1) with the enamines (4)-(7)

Enamine	Temp. (°C)	Time (h)	Product(s)	Yield (%)
(4)	80	3	(8)	16
			(11)	19
	25	96	(8)	7
			(11)	58
(5)	80	3	(9)	69
	25	140	(9)	60
(6)	80	10	(10)	13
			(12)	4
			(13)	10
			(18)	7
			(16)	6
			(10)	18
	25	240	(12)	10
			(13)	26
			(18)	9
			(16)	7
			(17)	6
			(14)	3
(7)	80	3	(15)	3
			(17)	10
			(19)	11
			(20)	39
	25	96	(14)	3
			(15)	4

Table 2. Physical, spectral, and analytical data of new compounds^a

Compd.	M.p. ^b (°C)	ν _{max} (Nujol) cm ⁻¹	δ ^{c,d}	Elemental analysis (%) Found (required)		
				C	H	N
(8)	129	3 350 1 700	2.2—2.7 (4 H, m), 3.90 (3 H, s), 4.2—4.5 (1 H, m), 5.17 (1 H, m), 5.6 (1 H, br s), 7.0—7.6 (5 H, m)	65.5 (65.3)	5.8 (5.9)	16.2 (16.3)
(9)	132	3 350 1 700	1.3—2.3 (6 H, m), 3.8—4.1 (4 H, overlapping signals), 5.20 (1 H, t, J 4), 5.4 (1 H, br s), 7.0—7.6 (5 H, m)	66.4 (66.4)	6.1 (6.3)	15.6 (15.5)
(10)	121	3 410 1 700	1.30, 1.35 (6 H, two d), 3.85 (3 H, s), 4.15 (1 H, dq, J 6.5 and 3.7), ^e 5.10 (1 H, q), 6.4 (1 H, br s), 6.7—7.0 (1 H, m), 7.2—7.4 (4 H, m)	64.9 (64.8)	6.5 (6.6)	16.2 (16.2)
(11) ^f	130 (decomp.)	3 340 1 710	1.5—2.3 (6 H, m), 2.5—2.8 (4 H, m), 3.8—4.0 (7 H, overlapping signals), 4.93 (1 H, dd, J 7 and 4), 6.9—7.5 (5 H, m), 11.8 (1 H, br s)	57.9 (58.0)	6.6 (6.5)	22.4 (22.6)
(12)	151	3 210 1 695	1.14 (3 H, t), 2.40 (3 H, s), 2.68 (2 H, q), 3.85 (3 H, s), 7.0—7.5 (5 H, m), 12.4 (1 H, br s)	58.8 (58.5)	5.9 (6.0)	24.2 (24.4)
(13)	146	3 190 1 710	1.13 (3 H, t), 2.30 (3 H, s), 2.61 (2 H, q), 3.93 (3 H, s), 7.0—7.5 (5 H, m), 9.8 (1 H, br s)	58.6 (58.5)	6.1 (6.0)	24.3 (24.4)
(14)	139	3 200 1 690	3.68 (3 H, s), 6.9—7.7 (10 H, m), 7.85 (1 H, s), 12.3 (1 H, br s)	63.3 (63.5)	4.5 (4.7)	21.8 (21.8)
(15)	161	3 180 1 705	3.63 (3 H, s), 6.9—7.6 (10 H, m), 7.80 (1 H, s), 9.8 (1 H, br s)	63.6 (63.5)	4.4 (4.7)	21.6 (21.8)
(20)	194		3.02 (8 H, t), 3.75 (8 H, t), 6.84 (2 H, s), 7.2—7.6 (10 H, m)	71.6 (71.3)	7.0 (7.0)	14.0 (13.8)

^a Correct molecular peaks were observed in the mass spectra. ^b From di-isopropyl ether–benzene. ^c Solvent: CD₂COCD₂ for (10), CDCl₃ for the other compounds. ^d J in Hz. ^e Quartet (J 6.5 Hz) after decoupling from the NH proton. ^f ¹³C N.m.r. (CDCl₃): δ 23.2 (t) 31.2 (t), 32.3 (t), 46.2 (t), 52.7 (q), 66.5 (t), 78.6 (d), 88.9 (s), 113.8 (d), 121.7 (d), 123.1 (s), 129.4 (d), 144.0 (s), and 162.9 (s).

Experimental

M.p.s were determined with a Büchi apparatus and are uncorrected. I.r. spectra were taken with a Perkin-Elmer 377 spectrophotometer. N.m.r. spectra were recorded with Varian EM-390 (¹H) and Bruker WP80SY (¹³C) instruments; chemical shifts are given in p.p.m. from internal SiMe₄.

Compounds (1),¹ (6),⁷ and (7)⁸ were prepared as described in the literature. Compounds (4) and (5) are commercially available products.

Reaction of the Azidohydrazone (1) with the Enamines (4)–(7).—Solutions of (1) (10 mmol) and the enamine (22 mmol) in dry benzene (150 ml) were subjected to the temperatures and reaction times given in Table 1. The solvent was evaporated under reduced pressure and the remaining mixture was left *in vacuo* to remove volatile side-products. The residue was chromatographed on a silica gel column with benzene–ethyl acetate (1:1) as eluant. Products (in order of elution) and yields are reported in Table 1.

Melting points, spectral data, and elemental analyses of the new compounds are presented in Table 2. Compounds (16),¹ (17),⁹ (18),¹⁰ and (19)¹¹ are known in the literature.

Thermolysis of the Dihydrotriazole (11).—A solution of (11) (0.15 g) in dry benzene (20 ml) was refluxed for 24 h. After removal of the solvent, the residue was chromatographed on a silica gel column with benzene–ethyl acetate (1:1) as eluant to afford compound (8) in 67% yield.

Reaction of the Azidohydrazone (1) with Diazomethane and Diazoethane.—A 0.4M ethereal solution of diazomethane (10 ml) was added slowly to a solution of (1) (3.2 mmol) in anhydrous ether (60 ml). The mixture was left at room temperature for 6 h. The solvent was evaporated and the residue chromatographed on a silica gel column with dichloromethane as eluant to give (19) in 37% yield.

Treatment of (1) with diazoethane according to the same procedure gave (18) in 41% yield.

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