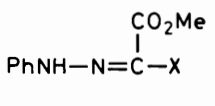
The Reaction of *C*-Azidohydrazones with Enamines

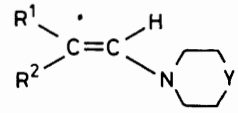
Luca Bruché, Luisa Garanti, and Gaetano Zecchi *
Istituto di Chimica Industriale dell'Università, Centro del C.N.R. per la Sintesi e Stereochimica di Speciali Sistemi Organici, 20133 Milano, Italy

Methyl azido(phenylhydrazono)acetate (**1**) reacts with variously substituted enamines (**4**)—(**7**) to give product mixtures including 1,4,5,6-tetrahydro-1,2,4-triazines (**8**)—(**13**) and 1,2,4-triazoles (**14**)—(**16**). A mechanism is proposed involving a preliminary 1,3-dipolar cycloaddition to give unstable Δ^2-1,2,3-triazolines (**17**).

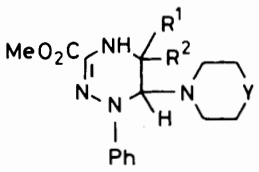
The known versatile reactivity of the azido group [1] suggests that hydrazonoyl azides (*C*-azidohydrazones) may be useful intermediates in heterocyclic syntheses. Indeed, in spite of the easy accessibility of these substrates through nucleophilic substitution of the corresponding hydrazonoyl halides, little attention has been given to them.[2,3] Apart from a recent paper describing an intramolecular cyclisation of *ortho*-substituted *N*-aryl-*C*-azidohydrazones,[4] there are no reports of the behaviour of this class of azides towards potential dipolarophiles. Therefore we synthesized the azidohydrazone (**1**) and subjected it to reaction with ethylene derivatives. While compound (**1**) was inert towards cyclohexene and styrene, so that only decomposition products were formed under prolonged heating, a greater reactivity was observed in the presence of electron-rich alkenes such as enamines. The reactions of (**1**) with the enamines (**4**)—(**7**) are reported here.



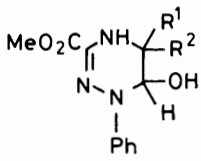
(**1**) X = N_3
(**2**) X = Cl
(**3**) X = N⟨O⟩



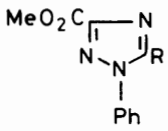
(**4**) $R^1 = R^2 = Me$, Y = O
(**5**) $R^1 = R^2 = Me$, Y = CH_2
(**6**) $R^1 = Me$, $R^2 = H$, Y = CH_2
(**7**) $R^1 = Ph$, $R^2 = H$, Y = O



(**8**) $R^1 = R^2 = Me$, Y = O
(**9**) $R^1 = R^2 = Me$, Y = CH_2
(**10**) $R^1 = Me$, $R^2 = H$, Y = CH_2
(**11**) $R^1 = Ph$, $R^2 = H$, Y = O



(**12**) $R^1 = R^2 = Me$
(**13**) $R^1 = Me$, $R^2 = H$



(**14**) R = Pr^i
(**15**) R = Et
(**16**) R = H

Results and Discussion

The previously unknown azidohydrazone (**1**) was prepared in good yield on reaction of the corresponding chlorohydrazone (**2**) with sodium azide under phase-transfer conditions. Treatment of (**1**) with an excess of the enamines (**4**)—(**7**) in boiling benzene led to mixtures of several components which were isolated by chromatographic separation. Reaction times, products, and yields are collected in Table 1. In addition, trivial side-products due to hydrolysis of the starting enamines were sometimes isolated.† Some uncharacterisable material was also formed, particularly in the reaction of (**1**) with (**7**). This reaction was then repeated at room temperature; under these conditions, compound (**1**) had partially reacted after 3 days to give (**11**) as the predominant product.

The hydroxy derivative (**13**) was shown to be absent in the crude reaction mixture from (**6**), while being formed in the course of the separation procedure. It was then ascertained that (**10**) can be converted into (**13**) under mild hydrolytic conditions. Analogously compounds (**8**) and (**9**) represent plausible precursors of the isolated product (**12**); this view is supported by the n.m.r. spectrum of the crude product mixture arising from (**4**), which shows a singlet at δ_H 4.4.

While compounds (**3**)[5] and (**16**)[6] were recognised upon comparison with authentic samples prepared by literature methods, the previously unreported triazoles (**14**) and (**15**) were synthesized independently on treating (**2**) with isobutyronitrile and propionitrile, respectively, in the presence of triethylamine. The new structures (**10**)—(**13**) were assigned on the basis of elemental analyses, molecular weights, and spectral data (see Table 2). Isomeric formulae having reversed substituents at positions 5 and 6 were discarded because compound (**10**) exhibits vicinal coupling between the NH proton and the methinic hydrogen adjacent to the methyl group (*J* 3.7 Hz).‡

† Control experiments showed that the carbonyl compounds deriving from the hydrolysis of the enamines are not responsible for the formation of the products listed in Table 1.

‡ The NH proton of (**10**) is also coupled with the methinic hydrogen adjacent to the piperidinyl substituent, but the small value of the observed coupling constant (~1.5 Hz) is consistent with a long-range interaction (L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon Press, Oxford, 2nd edn., 1969, p. 312).

Table 1. Reaction of compound (**1**) with enamines (**4**)—(**7**)

Compound	Temp. (°C)	Time (h)	Product[a]	Yield (%)	Eluant
(**4**)	80	5	(**12**)	13	Benzene–ethyl acetate (3:1)
			(**14**)	35	
			(**16**)	15	
(**5**)	80	4	(**12**)	17	Benzene–ethyl acetate (3:1)
			(**14**)	49	
			(**16**)	8	
(**6**)	80	1	(**10**)	43	Diethyl ether–ethyl acetate (2:1)
			(**13**)	8	
			(**15**)	19	
			(**16**)	4	
(**7**)	80	3	(**3**)	13	Diethyl ether–light petroleum (b.p. 40—60 °C) (1:1)
			(**16**)	9	
	25	70	(**11**)	39[b]	Benzene–ethyl acetate (2:1)

[a] In order of elution. [b] A quantity of (**1**) was recovered (~30%).

Table 2. Physical, spectral, and analytical data of 1,4,5,6-tetrahydro-1,2,4-triazines (**10**)—(**13**)[a]

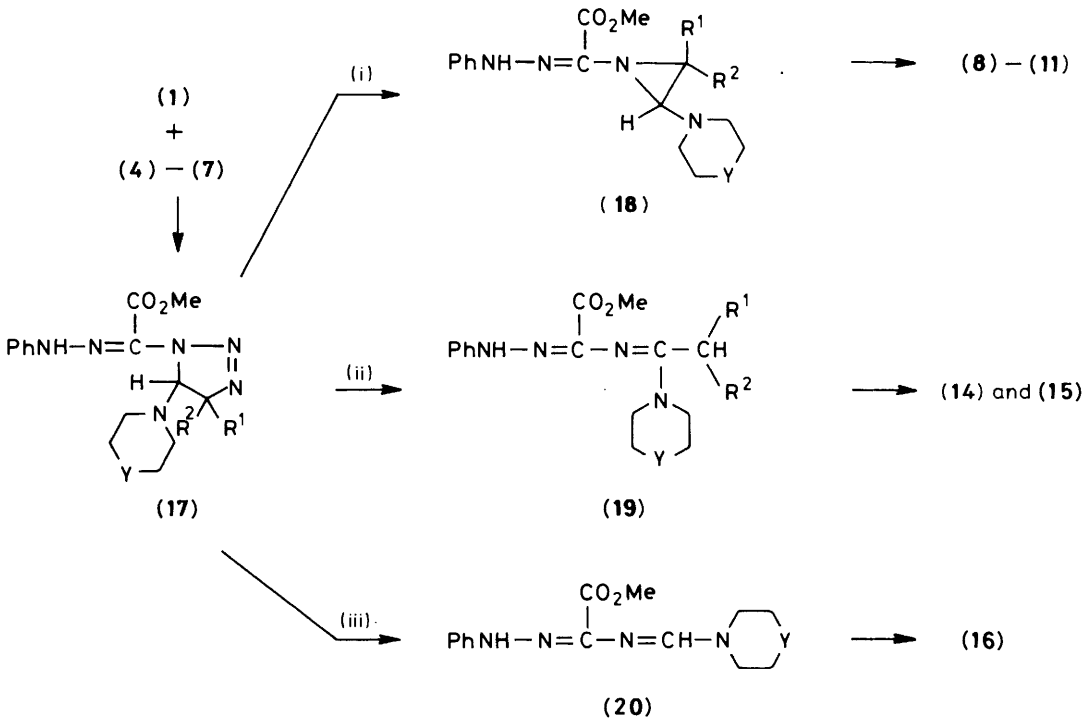
Compound	M.p.[b] (°C)	$\nu_{max.}$(Nujol)/ cm^{-1}	δ_H[c,d]	$\delta_C(CDCl_3)$[e]	Elemental analysis (%) Found (required) C	H	N
(**10**)	147	3 340, 1 710	0.70 (3 H, d, *J* 6.3), 1.1—1.5 (6 H, m), 2.50 (4 H, t), 3.28 (1 H, ddq, *J* 6.3, 3.7, and 1.5),[f] 3.51 (3 H, s), 4.22 (1 H, dd, both *J* ~1.5),[g] 5.1 (1 H, br s), 6.8—7.0 (1 H, m), 7.1—7.8 (4 H, m)	21.7 (t), 24.7 (t), 26.4 (q), 43.6 (d), 49.2 (t), 52.7 (q), 75.1 (d)	64.7 (64.5	7.7 7.6	17.6 17.7)
(**11**)	145	3 400, 1 710	2.75 (4 H, t), 3.65 (4 H, t), 3.90 (3 H, s), 4.60 (1 H, d, *J* 1.5), 4.9 (1 H, m),[g] 5.8 (1 H, br s), 6.8—7.0 (1 H, m), 7.1—7.5 (9 H, m)	48.8 (t), 52.1 (d), 52.9 (q), 67.2 (t), 74.2 (d)	66.2 (66.3	6.6 6.4	14.7 14.7)
(**12**)	155	3 500, 3 390, 1 720	1.08 (3 H, s), 1.39 (3 H, s), 2.3 (1 H, br s), 3.90 (3 H, s), 5.10 (1 H, s), 5.3 (1 H, br s), 6.8—7.0 (1 H, m), 7.2—7.5 (4 H, m)	25.1 (q), 26.4 (q), 51.0 (s), 53.0 (q), 79.5 (d)	59.4 (59.3	6.4 6.5	15.8 16.0)
(**13**)	160—161	3 500, 3 380, 1 715	1.08 (3 H, d), 2.9 (1 H, br s), 3.4—3.7 (1 H, m), 3.90 (3 H, s), 5.3 (1 H, m), 5.6 (1 H, br s), 6.8—7.1 (1 H, m), 7.2—7.5 (4 H, m)		56.1 (57.8	6.1 6.1	16.6 16.9)

[a] All compounds listed gave correct molecular peaks in the mass spectra. [b] From di-isopropyl ether. [c] Solvent: C_6D_6 for (**10**) and $CDCl_3$ for (**11**)—(**13**). [d] *J* in Hz. [e] Only the signals of the sp^3-hybridised carbons are described. [f] Double quartet after deuteriation of the NH group (*J* 6.3 and 1.5 Hz). [g] Doublet after deuteriation of the NH group (*J* 1.5 Hz).

Interestingly, compounds (**10**), (**11**), and (**13**) were each obtained as one stereoisomer; the observed values of the vicinal coupling constants, compared with literature data[7] for 5,6-disubstituted 1,4,5,6-tetrahydro-1,2,4-triazines, suggest a *cis* relationship.

A plausible rationale of the above results is depicted in the Scheme. It involves, as the first stage, a 1,3-dipolar cycloaddition of the azido group to the ethylenic double bond of (**4**)—(**7**) according to the typical orientation observed in the reaction of azides with enamines.[8] The thus-formed Δ^2-1,2,3-triazolines* (**17**) are not stable and can react in three different ways: (i) loss of nitrogen with concomitant ring contraction to give aziridines (**18**); (ii) loss of nitrogen followed by (or concerted with) hydride shift to give amidines (**19**); and (iii) loss of a diazoalkane to give formamidines (**20**). These decomposition pathways find precedent in the chemistry of Δ^2-1,2,3-triazolines.[9] However, in the present case, the species (**18**), (**19**), and (**20**) are further transformed owing to the participation of the hydrazone moiety. The nucleophilic nitrogen of the latter function can attack intramolecularly an electrophilic carbon bearing a potential leaving group, thus producing the ring-closed products (**8**)—(**11**), (**14**)—(**15**), and (**16**), respectively. Evidence in favour of the intermediacy of (**17**) was achieved on treating (**1**) with (**6**) at room temperature. T.l.c. analysis of the reaction mixture revealed a product whose isolation in the pure state was precluded by its lability. However, a fraction from the chromatographic separation contained it as the main component so that the following diagnostic signals (*inter alia*) become evident in the n.m.r. spectrum of mixture: δ_H 1.20 (3 H, d), 1.4—1.6 (6 H, m), 2.36 (4 H, t), 4.42 (1 H, m), 4.83 (1 H, d, *J* 2.5 Hz), and 10.4 (1 H, br s). These signals are consistent with the structure (**17**; R^1 = Me, R^2 = H, Y = CH_2). Moreover, in the light of the literature n.m.r. data for 4,5-disubstituted Δ^2-1,2,3-triazolines,[10] the observed coupling constant of the ring protons indicates a *trans* configuration, which corresponds to retention of stereochemistry in the formation of (**17**), a general feature of 1,3-dipolar cycloadditions.[11] Such a configuration can account for the lack of amine elimination from (**17**) to form 5-unsubstituted 1,2,3-triazoles.

* 4,5-Dihydro-1*H*-1,2,3-triazoles.



Scheme.

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 (^{1}H) and XL-100 (^{13}C) instruments; chemical shifts are given in p.p.m. from internal $SiMe_4$. H.p.l.c. analyses were performed on a Millipore Waters 'Mod. 244 with gradient' Liquid Chromatograph.

Compounds (2),[5] (4),[12] (5),[13] (6),[13] (7)[14] were prepared as previously reported.

Methyl Azido(phenylhydrazono)acetate (1).—A solution of compound (2) (4 mmol) in benzene (60 ml) was treated with a solution of sodium azide (20 mmol) and hexadecyltributylphosphonium bromide (0.4 mmol) in water (60 ml). The mixture was heated at 40 °C and vigorously stirred for 5 h. The aqueous layer was removed and the organic solution was washed with water and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was taken up with a little diisopropyl ether and filtered to give compound (1) (59%), m.p. 89—90 °C (from pentane); $\nu_{max.}$(Nujol) 3 300, 2 150, and 1 720 cm^{-1}; δ_H($CDCl_3$) 3.90 (3 H, s), 6.9—7.4 (5 H, m), and 8.1 (1 H, br s).

Reaction of Azidohydrazone (1) *with Enamines* (4)—(7).—A solution of compound (1) (10 mmol) and an enamine (25 mmol) in benzene (40 ml) was refluxed for the time given in Table 1. The solvent was removed under reduced pressure and the residue was left *in vacuo* to eliminate volatile side-products. The remaining mixture was chromatographed on a silica gel column. Eluants, products, and yields are reported in Table 1.

Independent Synthesis of 1,2,4-*Triazoles* (14) *and* (15).—A solution of compound (2) (3 mmol) and triethylamine (15 mmol) in isobutyronitrile (50 ml) was refluxed for 3 h. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with benzene–ethyl acetate (1:1) as eluant to give the 1,2,4-*triazole* (14) (36%), m.p. 126 °C (Found: C, 63.6; H, 6.4; N, 16.9. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%); $\nu_{max.}$(Nujol) 1 750 cm^{-1}; δ_H($CHCl_3$) 1.38 (6 H, d), 3.0—3.4 (1 H, m), 4.04 (3 H, s), and 7.3—7.6 (5 H, m); *m/z* 245 (M^+).

Treatment of compound (2) with triethylamine in propionitrile under similar conditions yielded the 1,2,4-*triazole* (15) (43%), m.p. 37—39 °C (Found: C, 62.3; H, 5.5; N, 18.1. $C_{12}H_{13}N_3O_2$ requires C, 62.3; H, 5.7; N, 18.2%); $\nu_{max.}$(Nujol) 1 740 cm^{-1}; δ_H($CDCl_3$) 1.37 (3 H, t), 2.90 (2 H, q), 4.03 (3 H, s), and 7.3—7.6 (5 H, m); *m/z* 231 (M^+).

References

1 'The Chemistry of the Azido Group,' ed. S. Patai, Interscience, London, 1971.
2 See ref. 1, pp. 90, 93, and 517.
3 A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1972, 44.
4 L. Bruché, L. Garanti, and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 1982, 755.
5 R. Fusco and R. Romani, *Gazz. Chim. Ital.*, 1946, **76**, 419.
6 K. Matsumoto, M. Suzuki, M. Tomie, N. Yoneda, and M. Miyoshi, *Synthesis*, 1975, 609.
7 D. L. Trepanier, E. R. Wagner, G. Harris, and A. D. Rudzik, *J. Med. Chem.*, 1966, **9**, 881.
8 A. G. Cook, in 'Enamines: Synthesis, Structure, and Reactions,' ed. A. G. Cook, Marcel Dekker, New York, 1969, p. 244.
9 See ref. 1, pp. 256, 260, 347, 353, and 359.
10 T. J. Batterham, 'NMR Spectra of Simple Heterocycles,' Wiley-Interscience, New York, 1973, p. 222.
11 R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291.
12 G. Opitz and F. Zimmermann, *Justus Liebigs Am. Chem.*, 1963, **663**, 178.
13 C. Mannich and H. Davidsen, *Chem. Ber.*, 1936, **69**, 2106.
14 G. Bianchetti, D. Pocar, and P. Dalla Croce, *Gazz. Chim. Ital.*, 1963, **93**, 1714.

Received 20*th October* 1983; *Paper* 3/1859