Synthesis of Fused Ring 1,2,4-Triazoles by Intramolecular Cycloaddition of Nitrile Imines to the Nitrile Function

Luisa Garanti, Angelo Scandroglio, and Gaetano Zecchi

Istituto di Chimica Industriale dell'Universita', Centro del C.N.R. per la Sintesi e Stereochimica di speciali sistemi organici, 20133 Milano, Italy

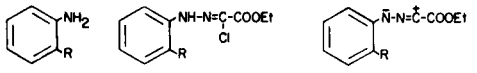
Received July 1, 1976

Treatment of 1-chlorohydrazones (IIa-c) with triethylamine gave fused ring 1,2,4-triazoles arising from an intramolecular cycloaddition of the intermediate nitrile imines (IIIa-c). This reaction was not observed in the case of one compound (IId) bearing an unactivated nitrile group.

J. Heterocyclic Chem., **13**, 1339 (1976).

Nitriles have been shown to behave as dipolarophiles towards nitrile imines to yield regiospecifically 1,2,4-triazoles (1,2). This reaction occurs in cases where the nitrile function is activated by conjugation or by an oxygen atom in the α position. Unactivated alkyl cyanides also afforded 1,2,4-triazoles by reaction with 1-chlorohydrazones (the common precursors of nitrile imines), but only in the presence of a Lewis acid catalyst. Therefore, in the latter case, the intervention of nitrile imine intermediates was reasonably discarded (3).

On continuing our studies on the intramolecular cycloadditions of 1,3-dipoles (4-8), we undertook an investigation of the behaviour of nitrile imines bearing a nitrile function, which can be seen as useful intermediates for the synthesis of fused ring triazoles. Compounds (IIIa-d) were considered.



I II III

a, R = 

b, R = $-OCH_2CN$

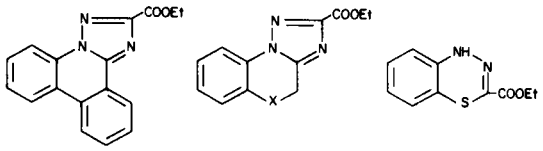
c, R = $-SCH_2CN$

d, R = $-CH_2CH_2CN$

The above nitrile imines were formed from the corresponding 1-chlorohydrazones (IIa-d), which in turn were prepared by diazotization of *ortho*-substituted anilines (Ia-c) and coupling with ethyl 2-chloroacetoacetate. Compounds (IIa-d) were treated with an excess of triethylamine in boiling benzene, with reaction times of 2, 12, 3, and 13 hours, respectively. Somewhat different results were obtained for each substrate.

A clean reaction was observed in the case of IIa, which gave triazole IV in 76% yield. A single product, *i.e.* compound Va, was also obtained from IIb, but in a lower yield due to tar formation (38%). On the other hand, in the case of IIc, the column chromatography of the reaction mixture afforded compounds VI and Vb in 35 and 10% yields, respectively (9).

Unlike the reactions of IIa-c, the treatment of IId with triethylamine led to a tarry mixture, from which products of type V could not be isolated.



IV Va, X = O; Vb, X = S VI

It is worthwhile to note that, to our knowledge, IV and Va,b are representatives of unreported ring systems.

The above results merit some comments. The lack of triazole formation by nitrile imine IIId, although not surprising due to the absence of activation of the nitrile group, is somewhat unexpected since the related 3-(2-azidophenoxy)propionitrile has been shown to undergo an intramolecular 1,3-cycloaddition to give 4,5-dihydrotetrazolo[1,5-*a*]quinoline (5).

The formation of VI, which strongly competes with the 1,3-dipolar cycloaddition in the case of IIc, may be explained by an intramolecular nucleophilic attack of the thioether function on the electron deficient carbon atom of the nitrile imine and subsequent loss of the CH_2CN grouping. The alternative mechanism involving an intramolecular displacement of the halogen by the sulphur atom in compound IIc was ruled out since IIc did not change in boiling benzene without triethylamine.

Table

Compound	Yield %	M.p. °C	Ir (Nujol) cm^{-1}	Nmr (deuteriochloroform): τ	*Anal.*	Found C, H, N	Calcd. C, H, N
IIa	23	123	3320 (NH) 2220 (CN) 1725 (CO)	1.9 (1H, broad s, NH), 2.0-2.9 (8H, m, ar), 5.69 (2H, q, CH_2CH_3), 8.62 (3H, t, CH_2CH_3)	62.03	4.38	12.71
					62.27	4.31	12.82
IIb	41	108	3320 (NH) 1725 (CO)	1.3 (1H, broad s, NH), 2.2-3.1 (4H, m, ar), 5.13 (2H, s, CH_2O), 5.60 (2H, q, CH_2CH_3), 8.59 (3H, t, CH_2CH_3)	50.98	4.23	15.00
					51.11	4.29	14.91
IIc	57	96	3300 (NH) 2240 (CN) 1720 (CO)	0.9 (1H, broad s, NH), 2.2-3.1 (4H, m, ar), 5.62 (2H, q, CH_2CH_3), 6.53 (2H, s, CH_2S), 8.60 (3H, t, CH_2CH_3)	48.62	4.10	14.01
					48.39	4.06	14.11
IId	67	67	3290 (NH) 2225 (CN) 1730 (CO)	1.6 (1H, broad s, NH), 2.5-3.0 (4H, m, ar), 5.62 (2H, q, CH_2CH_3), 6.8-7.4 [4H, m, $(CH_2)_2$], 8.62 (3H, t, CH_2CH_3)	56.19	5.11	14.88
					55.80	5.05	15.02

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument with TMS as internal standard. Ir spectra were measured on a Perkin-Elmer Model 377 spectrophotometer.

Amines Ia (10), Ib (11), and Id (5) were prepared according to literature methods.

2-(2-Aminophenylthio)acetonitrile (Ic).

2-Aminothiophenol hydrochloride (12) (80 mmoles) was added to a solution of sodium ethoxide (160 mmoles) in ethanol (300 ml.) under a nitrogen atmosphere. 2-Chloroacetonitrile (90 mmoles) was then added dropwise and the mixture was stirred at room temperature for 3 hours. After removal of the solvent, the residue was taken up with water and extracted with chloroform, and the organic solution was dried and evaporated. The product was chromatographed on a silica gel column (400 g.) with ether-benzene (4:1) as eluent to give amine Ic (25%), b.p. 155-160°, 0.2 mm; ir (film): 3360, 3500 (NH_2), and 2250 cm^{-1} (CN); nmr (deuteriochloroform): τ 2.4-3.5 (4H, m, ar), 5.6 (2H, broad s, NH_2), 6.61 (2H, s, CH_2).

Anal. Calcd. for $C_8H_8N_2S$: C, 58.53; H, 4.91; N, 7.07. Found: C, 58.71; H, 5.13; N, 6.90.

General Procedure for the Preparation of 1-Chlorohydrazones (II).

A solution of sodium nitrite (10 mmoles) in water (5 ml.) was added to a solution of amine I (10 mmoles) in 0.5*N* hydrochloric acid (50 ml.) under vigorous stirring and ice-cooling. The mixture was adjusted to *p*H 4 by sodium acetate and ethyl 2-chloroacetoacetate (10 mmoles) in methanol (10 ml.) was added dropwise at 0°. The mixture was stirred for 30 minutes, then extracted with ether. The organic layer was dried and evaporated, and the residue was chromatographed on silica gel column (ether-light petroleum 9:1 as eluent) to afford compound II (see Table).

Treatment of IIa with Triethylamine.

A solution of IIa (3 mmoles) and triethylamine (12 mmoles) in dry benzene (30 ml.) was refluxed for 2 hours. The mixture was washed with aqueous hydrochloric acid, dried, and evaporated. Recrystallization of the residue from diisopropyl ether-ethanol (4:1) gave 2-carbethoxy[1,2,4]triazolo[1,5-*f*]phenanthridine (IV) (76%), m.p. 178°; ir (Nujol): 1725 cm^{-1} (CO); nmr (deuteriochloroform): τ 1.5-2.0 (4H, m, ar), 2.2-2.5 (4H, m, ar), 5.40 (2H, q, CH_2CH_3), 8.45 (3H, t, CH_2CH_3).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 69.59; H, 4.40; N, 14.15.

Treatment of IIb with Triethylamine.

A solution of IIb (2.8 mmoles) and triethylamine (11.2 mmoles) in dry benzene (30 ml.) was refluxed for 12 hours. The mixture was worked up as described in the above preparation and the residue was crystallized from *n*-hexane-ether (3:2) to give 2-carbethoxy-4*H*-[1,2,4]triazolo[5,1-*c*][1,4]benzoxazine (Va) (38%), m.p. 165°; ir (Nujol): 1735 cm^{-1} (CO); nmr (deuteriochloroform): τ 2.0-2.2 (1H, m, ar), 2.6-3.1 (3H, m, ar), 4.51 (2H, s, CH_2O), 5.47 (2H, q, CH_2CH_3), 8.52 (3H, t, CH_2CH_3).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 59.06; H, 4.58; N, 17.34.

Treatment of IIc with Triethylamine.

A solution of IIc (10 mmoles) and triethylamine (40 mmoles) in dry benzene (100 ml.) was refluxed for 3 hours. After the usual workup, the product was chromatographed on silica gel column (300 g.) with diisopropyl ether as eluent. The first fractions gave 2-carbethoxy-4*H*-1,3,4-benzothiadiazine (VI) as red crystals, m.p. 119° (from diisopropyl ether) (35%); ir (Nujol): 3300 (NH) and 1725 (CO) cm^{-1}; nmr (deuteriochloroform): τ 1.7 (1H, broad s, NH), 2.9-3.5 (4H, m, ar), 5.66 (2H, q, CH_2CH_3), 8.67 (3H, t, CH_2CH_3); Mass spectrum: m/e 222 (M^+), 194, 177, 150, 123, 96.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.25; H, 4.60; N, 12.70.

Further elution afforded 2-carbethoxy-4*H*-[1,2,4]triazolo[5,1-*c*][1,4]benzothiazine (Vb) (10%), m.p. 101° (from diisopropyl ether); ir (Nujol): 1715 cm^{-1} (CO); nmr (deuteriochloroform): τ 2.7-3.3 (4H, m, ar), 5.39 (2H, s, CH_2S), 5.67 (2H, q, CH_2CH_3), 8.64 (3H, t, CH_2CH_3).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.40; H, 4.50; N, 15.91.

REFERENCES AND NOTES

(1) R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland and G. Wallbillich, *J. Org. Chem.*, 24, 892 (1959).

(2) R. Huisgen, R. Grashey, M. Seidel, G. Wallbillich, H. Knupfer and R. Schmidt, *Ann. Chem.*, 653, 105 (1962).

(3) S. Conde, C. Corral and R. Madronero, *Synthesis*, 28 (1974).

(4) R. Fusco, L. Garanti and G. Zecchi, *Tetrahedron Letters*, 269 (1974).

(5) R. Fusco, L. Garanti and G. Zecchi, *J. Org. Chem.*, **40**, 1906 (1975).

(6) L. Garanti, A. Sala and G. Zecchi, *ibid.*, **40**, 2403 (1975).

(7) L. Garanti, A. Sala and G. Zecchi, *Synthesis*, 666 (1975).

(8) L. Garanti, A. Sala and G. Zecchi, *Synth. Commun.*, in press.

(9) The nmr analysis of the crude product, before the chromatographic separation, showed that compounds VI and Vb were present in the approximate ratio of 3:1.

(10) P. A. S. Smith, J. M. Clegg and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958).

(11) M. Mazharuddin and G. Thyagarajan, *Chem. Ind. (London)*, 178 (1971).

(12) L. Horwitz and C. A. Clark, U.S. Patent 3,102,142 (1963); *Chem. Abstr.*, **60**, 1760 (1964).