The Addition Reaction of α-Azido Ethers and α-Azido Thioethers to Phenylacetylene

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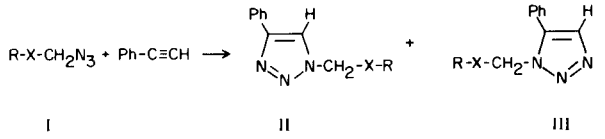
Several *v*-triazoles were synthesized by 1,3-dipolar cycloaddition of certain α-azido ethers and α-azidothioethers to phenylacetylene. In most of the cases the reaction led to the formation of the two isomeric *v*-triazoles. Structural assignments for the products obtained were made on the basis of NMR data and chemical reactions. Characteristic differences between the NMR spectra of the isomers have been noted.

As part of an investigation of the preparation of compounds bearing a methylene group linked to both a heteroatom and a heterocyclic nitrogen atom for further testing as potential anticancer agents, we directed our attention towards the 1,3-dipolar cycloaddition of several organic



I II III

a: R = CH_3; X = S
b: R = C_6H_5; X = S
c: R = $C_6H_5CH_2$; X = S
d: R = CH_3; X = SO_2
e: R = C_6H_5; X = SO_2
f: R = $C_6H_5CH_2$; X = SO_2
g: R = CH_3; X = O
h: R = C_6H_5; X = O

azides (Ia-h) to phenylacetylene. This reaction, which can result in the formation of two isomeric 1,2,3-triazoles, was reported by Böhme *et al.* (1,2) for some of the above azides but no structural details of the final products were given by these authors.

Most of the azides used in this work reacted with phenylacetylene to yield a pair of isomeric *v*-triazoles (II + III) which could be separated by fractional crystallization and column chromatography, whilst phenyl azidomethyl sulphide, methyl azidomethyl ether, and phenyl azidomethyl ether gave only one *v*-triazole derivative, the 1-substituted 4-phenyl-1,2,3-triazole. As the structure of the reaction products cannot be predicted on mechanistic grounds (3), structural assignments were made on the basis of chemical transformations and NMR evidence.

On refluxing a solution of phenylacetylene and methyl azidomethyl sulphide in toluene for twelve hours IIa (m.p. 114-115°) and IIIa (m.p. 56-57°) were obtained; likewise, the reaction of phenylacetylene with benzyl azidomethyl sulphide led to IIc (m.p. 129°) and IIIc (m.p. 51-52°).

Desulphurisation of IIa and IIc with Raney nickel gave 1-methyl-4-phenyl-1,2,3-triazole (IV) whereas IIIa and IIIc furnished upon a similar treatment 1-methyl-5-phenyl-1,2,3-triazole (V).

Structural proof for IIa was obtained through independent synthesis. Phenylacetonitrile and methyl azidomethyl sulphide gave 1-methylthiomethyl-4-phenyl-5-amino-1,2,3-triazole (VI) which on deamination afforded IIa. The

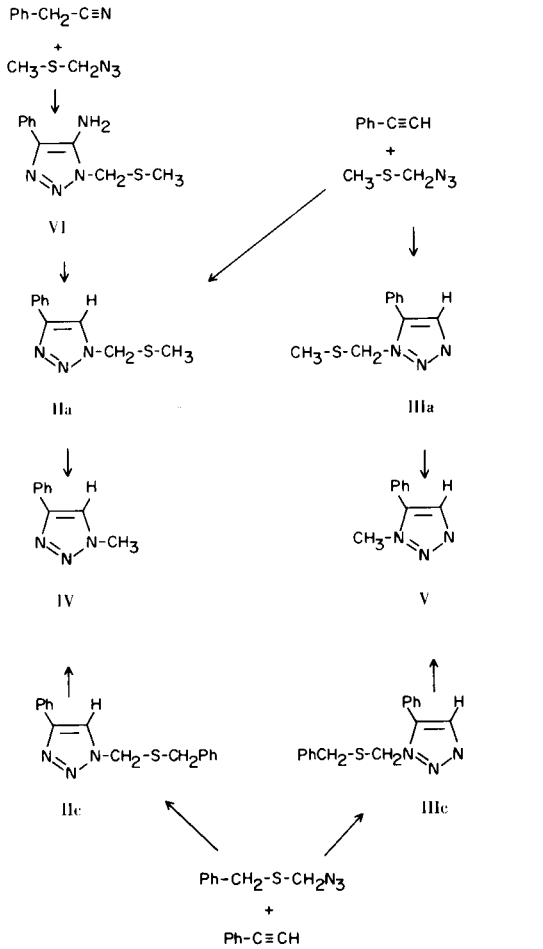


TABLE I

Chemical Shifts of 1-Substituted-5-phenyl-1,2,3-triazoles

R	Solvent	Mole, %	τ-values 4-H	Phenyl	$\tau_{m,p} - \tau_o$ (a)	Substituents
CH_3	CCl_3D	~3	2.32	2.59	0	5.95
CH_3-S-CH_2-	CCl_3D	~3	2.30	2.52	0	7.75 4.69
Ph-CH_2-S-CH_2-	CCl_3D	4.1	2.23	2.50	0	6.03 4.76 2.60
CH_3-SO_2-CH_2-	CCl_3D	2.8	2.23	2.47	0	6.83 4.53
	DMSO	2.2	2.03	2.45	0	7.00 4.08
Ph-SO_2-CH_2-	CCl_3D	3.8	2.32	2.25-2.40	0.15	4.36 2.59
	DMSO	2.4	2.08	2.40-2.55	0.15	3.80 2.53
Ph-CH_2-SO_2-CH_2-	CCl_3D	3.3	2.23	2.52	0	5.42 4.76 2.52

(a) $(\tau_{m,p} - \tau_o)$ is the difference between the τ values of the phenyl *meta* and *para* protons (assumed to be coincident) and those of the *ortho* protons.

position of each substituent in VI was known from the fact that the type of reaction involved in its preparation always results in a *v*-triazole derivative in which the amino group and the substituent from the azide are adjacent (4).

We also examined the NMR spectra of the above *v*-triazoles. The proton chemical shifts for the compounds obtained are listed in Tables I and II.

In the case of the sulfur containing *v*-triazoles it was observed that the phenyl protons resonance consists of a multiplet (1-substituted 4-phenyl-1,2,3-triazole) where the relative shift $(\tau_{m,p} - \tau_o)$ between the resonance of *meta* and *para* protons and that of the *ortho* protons is about 0.45 p.p.m. In the case of the 1-substituted 5-phenyl-1,2,3-triazoles the phenyl protons resonance becomes a singlet ($\cong$ 2.5 τ) with the only exception of the 1-phenyl-sulphonylmethyl-5-phenyl-1,2,3-triazole, where a small relative shift ($\tau_{m,p} - \tau_o$ = 0.15) was found. These facts have been already found for some phenyl pyrazoles (5-9), 5-aryltetrazoles (10) and other heterocyclic biaryls, but exceptions are known in the case of some phenyl pyrazole derivatives (11). The difference on the phenyl protons resonances as observed may be rationalized in terms of the extent of coplanarity of both the phenyl and the triazole rings, and it can be used as a criterium to distinguish between isomers. However, this point requires a more detailed study on the effect of different types of substituents on the phenyl protons resonance.

In order to further confirm the above facts 1-methylthiomethyl-4,5-diphenyl-1,2,3-triazole was obtained. Its NMR spectrum showed a singlet (2.56 τ) due to the 5-phenyl group and a multiplet ($\tau_{m,p} - \tau_o$ = 0.36 ppm) due to 4-phenyl group. Finally, it was observed that NMR spectrum of 4(5)-phenyl-1,2,3-triazole showed a splitting for the aromatic phenyl protons (0.45 ppm) similar to that of 1-substituted 4-phenyl-1,2,3-triazoles.

EXPERIMENTAL

All melting points are uncorrected. NMR spectra were recorded on a Perkin-Elmer R-10 spectrometer at room temperature with TMS as an internal standard; τ values given are accurate within 0.02 ppm. Thin layer plates were made of silica gel Merck GF_{254}; cyclohexane-ethyl acetate (1:1) was used as the developing system; spots were made visible with UV light (254 mμ).

Preparation of Azides.

Azidomethyl methyl sulphide and the sulphones derived thereof were synthesized by standard procedures (2). Preparation of azidomethyl methyl ether (lg) was carried out according to a

TABLE II

Chemical Shifts of 1-Substituted-4-phenyl-1,2,3-triazoles

R	Solvent	Mole, %	τ-values 5-H	Phenyl	$\tau_{m,p} - \tau_o$ (a)	Substituents
H-	DMSO	2.0	1.68	2.12-2.57	0.45	-
CH_3-	CCl_3D	4.4	2.32	2.24-2.68	0.44	5.98
CH_3-S-CH_2-	CCl_3D	4.1	2.06	2.19-2.65	0.46	7.90 4.70
Ph-S-CH_2-	CCl_3D	4.1	2.03	2.27-2.72	0.45	4.75 2.43
Ph-CH_2-S-CH_2-	CCl_3D	4.1	2.22	2.21-2.67	0.46	6.31 4.80 2.74
CH_3-SO_2-CH_2-	DMSO	2.2	1.34	2.09-2.57	0.48	6.86 3.86
Ph-SO_2-CH_2-	CCl_3D	4.0	1.89	2.17-2.59	0.48	4.36 2.41
	DMSO	2.3	1.46	2.12-2.58	0.46	3.63 2.27
Ph-CH_2-SO_2-CH_2-	CCl_3D	1.8	1.93	2.16-2.54	0.42	5.77 4.59 2.54
CH_3-O-CH_2-	CCl_3D	4.2	2.10	2.17-2.64	0.47	6.66 4.39
Ph-O-CH_2-	CCl_3D	3.2	2.09	2.20-2.67	0.47	3.81 2.93

(a) ($\tau_{m,p} - \tau_o$) is the difference between the τ values of the phenyl *meta* and *para* protons (assumed to be coincident) and those of the *ortho* protons.

modified Böhme's procedure (1) as follows:

A solution of chloromethyl methyl ether (59.6 g., 0.74 mole) in DMF (850 ml.) was slowly added to a stirred suspension of sodium azide (61.1 g., 0.94 mole) in DMF (100 ml.). The addition being completed, stirring was continued for one hour at room temperature and then for three hours in a boiling water bath. The reaction mixture was poured into water and extracted with ether several times. The combined ether extracts were washed with water and dried over sodium sulphate. After removal of the solvent through a Vigreux column, the azide came over at 78-80°; yield, 31.2 g. (48.5%).

Azidomethyl phenyl ether (Ih) was prepared in 75% yield from chloromethyl phenyl ether in a similar manner, b.p. 107-109°/2 mm.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.38; H, 4.69; N, 28.18. Found: C, 56.48; H, 4.86; N, 28.35.

1-Methylthiomethyl-5-phenyl-1,2,3-triazole (IIIa) and 1-Methylthiomethyl-4-phenyl-1,2,3-triazole (IIa).

A solution of azidomethyl methyl sulphide (5.35 g., 0.052 mole) and phenylacetylene (5.10 g., 0.05 mole) in anhydrous toluene (40 ml.) was heated under reflux for twelve hours. Evaporation of the solvent furnished a residue which after several recrystallizations from ethanol gave IIIa, m.p. 114-115°; yield, 2.2 g.

Anal. Calcd. for $C_{10}H_{11}N_3S$: C, 58.53; H, 5.36; N, 20.48. Found: C, 58.71; H, 5.23; N, 20.77.

The combined mother liquors from the preceding recrystallizations were evaporated to dryness and the residue chromatographed on alumina, first with petroleum ether until the elution of a yellow oil was complete, and then with ether-ethyl acetate (2:1) which eluted a solid. The latter was recrystallized from cyclohexane to give 2.7 g. of pure 1-methylthiomethyl-4-phenyl-1,2,3-triazole, m.p. 56-57°.

Anal. Calcd. for $C_{10}H_{11}N_3S$: C, 58.53; H, 5.36; N, 20.48. Found: C, 58.96; H, 5.55; N, 20.21.

1-Phenylthiomethyl-4-phenyl-1,2,3-triazole (IIb).

Equimolecular amounts of phenylacetylene and azidomethyl phenyl sulphide gave under the conditions described above IIb as a solid which recrystallized from ethanol had m.p. 96°, yield, 31%.

Anal. Calcd. for $C_{15}H_{13}N_3S$: C, 67.41; H, 4.86; N, 15.73. Found: C, 67.32; H, 4.91; N, 15.51.

The mother liquors were taken to dryness, the residue was dissolved in benzene and chromatographed on an alumina column. Elution with petroleum ether gave a white solid, m.p. 60-61° (ethanol). This compound was identified as diphenyl disulphide by comparison with an authentic sample (12).

1-Benzylthiomethyl-4-phenyl-1,2,3-triazole (IIc) and 1-Benzylthiomethyl-5-phenyl-1,2,3-triazole (IIIc).

Equimolecular amounts of phenylacetylene and azidomethyl benzyl sulphide were reacted as above. Removal of the solvent left a residue which was crystallized repeatedly from ethanol to yield 1-benzylthiomethyl-4-phenyl-1,2,3-triazole, m.p. 128-129°, yield, 25%.

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.32; H, 5.33; N, 14.94. Found: C, 68.04; H, 5.61; N, 14.65.

The combined mother liquors were chromatographed on neutral alumina as before and supplied crude 1-benzylthiomethyl-5-phenyl-1,2,3-triazole which was recrystallized from petroleum ether, m.p. 51-52°, yield 11%.

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.32; H, 5.33; N, 14.94. Found: C, 68.21; H, 5.46; N, 14.61.

1-Methylsulphonylmethyl-4-phenyl-1,2,3-triazole (IId) and 1-Methylsulphonylmethyl-5-phenyl-1,2,3-triazole (IIId).

Phenylacetylene (0.53 g., 0.0052 mole) and azidomethyl methyl sulphone (0.7 g., 0.0051 mole) in toluene solution were held under reflux for twelve hours. On cooling the reaction mixture a solid separated; it was filtered off and recrystallized from ethyl acetate to give 0.36 g. of 1-methylsulphonylmethyl-4-phenyl-1,2,3-triazole, m.p. 210-211°.

Anal. Calcd. for $C_{10}H_{11}N_3SO_2$: C, 50.63; H, 4.68; N, 17.72. Found: C, 50.33; H, 4.36; N, 17.47.

Concentration of the filtrate yielded a solid which recrystallized from ethanol gave 0.25 g. of pure 1-methylsulphonylphenyl-5-phenyl-1,2,3-triazole, m.p. 116-117°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.63; H, 4.68; N, 17.72. Found: C, 50.60; H, 4.70; N, 17.52.

1-Phenylsulphonylmethyl-4-phenyl-1,2,3-triazole (IIe) and 1-Phenylsulphonylmethyl-5-phenyl-1,2,3-triazole (IIIe).

1-Phenylsulphonylmethyl-5-phenyl-1,2,3-triazole had m.p. 102-103°, lit. (2) m.p. 96-97°. and was obtained in 28% yield; 1-phenylsulphonylmethyl-4-phenyl-1,2,3-triazole melted at 175-176°, lit. (2) 175-176° and was obtained in 15% yield. Both isomers gave correct analytical figures.

1-Benzylsulphonylmethyl-4-phenyl-1,2,3-triazole (IIf) and 1-Benzylsulphonylmethyl-5-phenyl-1,2,3-triazole (IIIf).

1-Benzylsulphonylmethyl-4-phenyl-1,2,3-triazole had m.p. 177-178°, lit. (2) m.p. 177-178°; and 1-benzylsulphonylmethyl-5-phenyl-1,2,3-triazole had m.p. 134-135°, lit. (2) m.p. 135-136°, yields were 26% and 2.6%, respectively.

1-Methoxymethyl-4-phenyl-1,2,3-triazole (IIg).

This compound was prepared according to Böhme *et al.* (1). It could be obtained in crystalline form, m.p. 70-71° (from cyclohexane).

1-Phenoxymethyl-4-phenyl-1,2,3-triazole (IIh).

Equimolecular amounts of phenylacetylene and phenyl azidomethyl ether were reacted in toluene under the conditions used in previous preparations. After removal of the solvent a product was left which recrystallized from cyclohexane to give a white solid, m.p. 87-88°, yield 70%.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.71; H, 5.17; N, 16.73. Found: C, 72.06; H, 5.54; N, 17.05.

Desulphurisation of 1-Methylthiomethyl-4-phenyl-1,2,3-triazole.

Raney-nickel (7 g.) was added to a solution of IIa (1.5 g.) in absolute alcohol (50 ml.) and the suspension was heated under reflux for eight hours. All the solid material was filtered off, the filtrate evaporated to dryness and the residue recrystallized from benzene-cyclohexane (2:1) to give IV (0.7 g.), m.p. 125-126°.

Anal. Calcd. for $C_9H_9N_3$: C, 67.92; H, 5.66; N, 26.40. Found: C, 68.22; H, 5.85; N, 26.82.

This substance was shown to be identical with the desulphurisation product of IIc.

Desulphurisation of 1-Methylthiomethyl-5-phenyl-1,2,3-triazole.

Upon desulphurisation of IIIa under similar conditions to those described above an oil was obtained (V). Its solution in ethanol was treated with picric acid (Congo red end-point) yielding a picrate, m.p. 147-148° (ethanol).

Anal. Calcd. for $C_{15}H_{12}N_6O_7$: C, 46.39; H, 3.09; N, 21.60. Found: C, 46.23; H, 3.22; N, 21.74.

Desulphurisation of 1-benzylthiomethyl-5-phenyl-1,2,3-triazole (IIIc) and subsequent treatment of the resulting material with picric acid gave an identical product.

1-Methylthiomethyl-4-phenyl-5-amino-1,2,3-triazole (VI).

Sodium (1.15 g., 0.05 g-atom) was dissolved in anhydrous ethanol (100 ml.) and to this solution a mixture of phenylacetonitrile (5.85 g., 0.05 mole) and azidomethyl methyl sulphide (5.15 g., 0.05 mole) were added. After refluxing for eight hours, the reaction mixture was poured into water and extracted repeatedly with chloroform. The combined chloroform extracts were washed with water and dried over sodium sulphate. Removal of the solvent gave a residue which on recrystallization from ethyl acetate gave 1.5 g. of pure VI, m.p. 134-135°.

Anal. Calcd. for $C_{10}H_{12}N_4S$: C, 54.54; H, 5.45; N, 25.45. Found: C, 54.48; H, 5.64; N, 25.26.

1-Methylthiomethyl-4-phenyl-1,2,3-triazole (IIa).

Deamination of the above compound under similar conditions to those used by Henry and Finnegan (13) for 3-amino-1,2,4-triazole furnished IIa. This latter was shown to be identical with the adduct IIa from phenylacetylene and azidomethyl methyl sulphide.

1-Methylthiomethyl-4,5-diphenyl-1,2,3-triazole.

A mixture of tolane (0.89 g., 0.005 mole) and azidomethyl methyl sulphide (1.03 g., 0.01 mole) was heated at 100-110° for four hours. A solid crystallized on cooling and was further recrystallized from cyclohexane, m.p. 106-107°, yield 0.79 g.

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.32; H, 5.53; N, 14.94. Found: C, 68.10; H, 5.52; N, 15.02.

4(5)-Phenyl-1,2,3-triazole.

This compound was prepared from trimethylsilyl azide and phenylacetylene (14).

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