v-Triazolines. Part 8.[1] 1-Aryl-4-alkyl- and -aryl-thiomethyl-5-amino-*v*-triazolines: Synthesis and Reactions with Bases

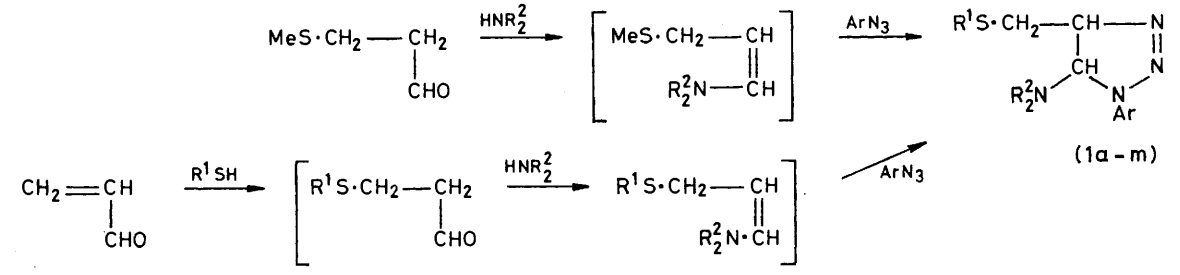
By **Goffredo Bolis, Donato Pocar,* Riccardo Stradi,** and **Pasqualina Trimarco,** Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano, 20131 Milano, Italy

A series of 1-aryl-4-alkyl- and -aryl-thiomethyl-5-amino-*v*-triazolines has been synthesized and characterized. On reaction with bases they underwent amine and/or thiol elimination yielding 1-aryl-4-alkyl- or -aryl-thiomethyl-*v*-triazoles (2) and 1-aryl-4-methyl-5-amino-*v*-triazoles (3), respectively. These latter compounds were formed through aromatization of the 4-methylene-*v*-triazolines (6) arising primarily from the adducts (1) by thiolate elimination.

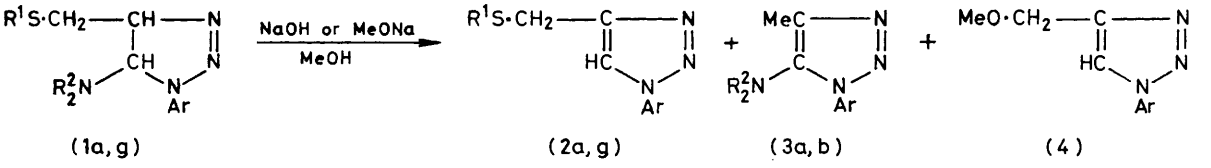
In order to try to shed more light on the reaction mechanism of the acid-catalysed rearrangement of hexahydrothiopyrano[3,4-*d*]-*v*-triazoles,[1] it seemed of interest to us to synthesize a series of open-chain 1-aryl-4-alkyl- and -aryl-thiomethyl-5-amino-*v*-triazolines (1). Moreover, this class of compounds was *a priori* interesting with regard to their behaviour with basic reagents. In fact, base-catalysed amine elimination from 1-aryl-5-amino-*v*-triazolines bearing at least one hydrogen atom in position 4 is the only known entry to 1-aryl-*v*-triazoles from the corresponding 5-amino-*v*-triazolines.† This reaction has been postulated to occur through abstraction of the hydrogen atom on C-4 and elimination of the amine residue.[3,4] Despite the great number of examples described we are not aware of cases in which the elimination of amine could be competitive with an alternative elimination process, as actually occurs in the case of the triazolines (1).

We report here the results of treating the triazolines (1) with bases.‡

Triazolines (1a—m).—The triazolines (1a—f) could be prepared easily by treating 3-(methylthio)propanal with the appropriate secondary amine and aryl azide (Scheme 1), according to a general procedure.[5] Compounds (1g—k) were obtained from the reaction of propenal with a benzenethiol, followed by treatment of the crude reaction mixture with the secondary amine and the aryl azide. Analytical and ^{1}H n.m.r. data are reported in Table 1.



Scheme 1



Scheme 2

All the triazolines had the *trans*-configuration, as inferred from the $J_{4,5}$ value of *ca.* 3 Hz,[4,6]

Reactions with Bases.—The triazoline (1a) reacted with sodium hydroxide in methanol yielding a mixture of triazole derivatives. Column chromatography afforded compounds (2a), (3a), and (4) (Table 2) in the ratio shown in Table 3. The products were identified by analytical

† When a 5-alkyl or 5-aryl substituent is present, acid-catalysed amine elimination may be used as well.[2]

‡ By treating the triazolines (1) with acid, only fragmentation products were isolated (secondary amine, arylamine, thiol, and 2-oxopropanal). The formation of these compounds can be explained by a mechanism similar to that already described for the acid-catalysed decomposition of 1-aryl-5-amino-4-aminomethyl-*v*-triazolines.[4]

[1] Part 7, D. Pocar, L. M. Rossi, R. Stradi, and P. Trimarco, *J.C.S. Perkin I*, 1977, 2337.
[2] R. Fusco, G. Bianchetti, and D. Pocar, *Gazzetta*, 1961, **91**, 849.
[3] N. E. Munk and Y. K. Kim, *J. Amer. Chem. Soc.*, 1964, **88**, 2213; P. Ferruti, D. Pocar and G. Bianchetti, *Gazzetta*, 1967, **97**, 109.
[4] D. Pocar, R. Stradi, and L. M. Rossi, *J.C.S. Perkin I*, 1972, 769.
[5] R. Stradi and D. Pocar, *Gazzetta*, 1969, **99**, 1131.
[6] R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, 1967, **100**, 1802; D. Pocar, R. Stradi, and L. M. Rossi, *J.C.S. Perkin I*, 1972, 619.

TABLE 1

Preparation and properties of the triazolines (1)

	R^1	R^2_2N	Ar	^{1}H N.m.r. (CDCl$_3$) δ_{H-4}	δ_{H-5}	$J_{4,5}$/Hz	Reaction time (h)	Cryst. solvent	M.p. (°C)	Yield (%)	Found (%) [Reqd. (%)] C	H	N
(1a)	Me	Morpholino	4-NO_2·C_6H_4	4.80	4.83	3	2	PhH–pentane	146	40	49.95 [49.85	5.75 5.65	20.8 20.75]
(1b)	Me	Me_2N	4-NO_2·C_6H_4	4.69	4.88	3	3	PhH–pentane	95—96	45	49.1 [48.8	6.0 5.75	23.45 23.7]
(1c)	Me	PhNMe	4-NO_2·C_6H_4	4.75	5.94	3	2	PhH–pentane	116—118	20	57.1 [57.15	5.15 5.3	19.25 19.6]
(1d)	Me	Morpholino	Ph	4.60	4.77	3.5	20		(Oil) ‡	10			
(1e)	Me	Pyrrolidino	4-NO_2·C_6H_4	4.61	5.12	3	7	EtOH	85	35	52.25 [52.35	6.0 5.9	21.55 21.8]
(1f)	Me	Morpholino	4-MeO·C_6H_4	4.50	4.70	3	8		(Oil) ‡	25			
(1g)	Ph	Morpholino	4-NO_2·C_6H_4	4.70	4.87	3.5	3	AcOEt	147	30	56.95 [57.15	5.4 5.25	17.35 17.55]
(1h)	Ph	Me_2N	4-NO_2·C_6H_4	4.62	4.82	3	3	EtOH	105	60	56.85 [57.15	5.45 5.3	19.45 19.6]
(1i)	Ph	PhNMe	4-NO_2·C_6H_4	4.60	5.87	3	2	EtOH	127	30	63.1 [63.0	5.2 5.0	16.7 16.7]
(1j)	Ph	4-MeO·C_6H_4·NMe	4-NO_2·C_6H_4	4.58	5.67	3	5	EtOH	100—101	35	61.5 [61.5	4.95 5.1	15.55 15.6]
(1k)	4-MeO·C_6H_4	PhNMe	4-NO_2·C_6H_4	4.49	5.84	3	3	EtOH	123	35	61.8 [61.5	5.4 5.1	15.7 15.6]

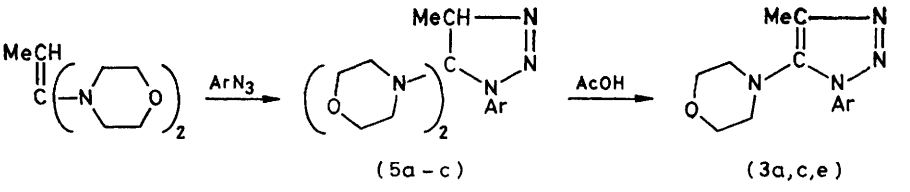
‡ Not distillable; poor analyses obtained.

TABLE 2

Triazoles (2)—(4)

	R^1	R^2_2N	Ar	^{1}H N.m.r.‡ (δ)	M.p. (°C)	Cryst. solvent	Found (%) [Reqd. (%)] C	H	N
(2a)	Me		4-NO_2·C_6H_4	3.88; 8.01	130	EtOH	48.0 [48.0	3.8 4.0	22.5 22.4]
(2b)	Ph		4-NO_2·C_6H_4	4.32; 7.87	150—151	EtOH	57.45 [57.1	4.20 3.85	17.60 17.95]
(2c)	4-MeO·C_6H_4		4-NO_2·C_6H_4	4.16; 7.74	128—129	EtOH	56.45 [56.15	4.2 4.1	16.15 16.35]
(3a)		Morpholino	4-NO_2·C_6H_4	2.50	154—155	EtOH	53.7 [53.95	5.2 5.2	24.1 24.2]
(3b)		Me_2N	4-NO_2·C_6H_4	2.40	125—128	PhH–n-pentane	53.6 [53.45	5.6 5.25	28.1 28.35]
(3c)		Morpholino	Ph	2.45	115—117	Cyclohexane	63.7 [63.95	6.85 6.55	22.65 22.95]
(3d)		Pyrrolidino	4-NO_2·C_6H_4	2.43	127—128	Petroleum	56.9 [57.15	5.4 5.5	25.75 25.65]
(3e)		Morpholino	4-MeO·C_6H_4	2.43	102—103	H_2O	61.0 [61.3	6.55 6.55	20.3 20.45]
(3f)		PhNMe	4-NO_2·C_6H_4	2.17	140—141	EtOH	61.9 [62.15	5.15 4.85	22.40 22.65]
(3g)		4-MeO·C_6H_4·NMe	4-NO_2·C_6H_4	2.14	126—127	EtOH	60.4 [60.15	4.85 5.0	20.5 20.65]
(4)	(MeO·CH_2)		4-NO_2·C_6H_4	4.65; 8.06	169	EtOH	51.15 [51.3	4.05 4.25	23.6 23.95]

‡ CH_2 and H-5 signals for (2) and (4); CH_3 signals for (3).



SCHEME 3

TABLE 3

Yields of triazoles (2) and/or (3) and/or (4)

Starting compound	Base/Solvent	Overall yield [(2) + (3) + (4)]	Ratio (2) : (3) or (2) : (3) : (4)
(1a)	NaOH/MeOH	85	50 : 30 : 10
(1a)	MeONa/MeOH	90	90 : 9 : 1
(1g)	NaOH/MeOH	80	40 : 40 : 30
(1a)	Bu^{t}OK/Bu^{t}OH	30	0 : 100
(1b)	Bu^{t}OK/Bu^{t}OH	60	5 : 95
(1c)	Bu^{t}OK/Bu^{t}OH	70	100 : 0
(1d)	Bu^{t}OK/Bu^{t}OH	30	0 : 100
(1e)	Bu^{t}OK/Bu^{t}OH	85	5 : 95
(1f)	Bu^{t}OK/Bu^{t}OH	60	0 : 100
(1g)	Bu^{t}OK/Bu^{t}OH	70	0 : 100
(1h)	Bu^{t}OK/Bu^{t}OH	70	5 : 95
(1i)	Bu^{t}OK/Bu^{t}OH	65	40 : 60
(1j)	Bu^{t}OK/Bu^{t}OH	75	45 : 55
(1k)	Bu^{t}OK/Bu^{t}OH	65	60 : 40

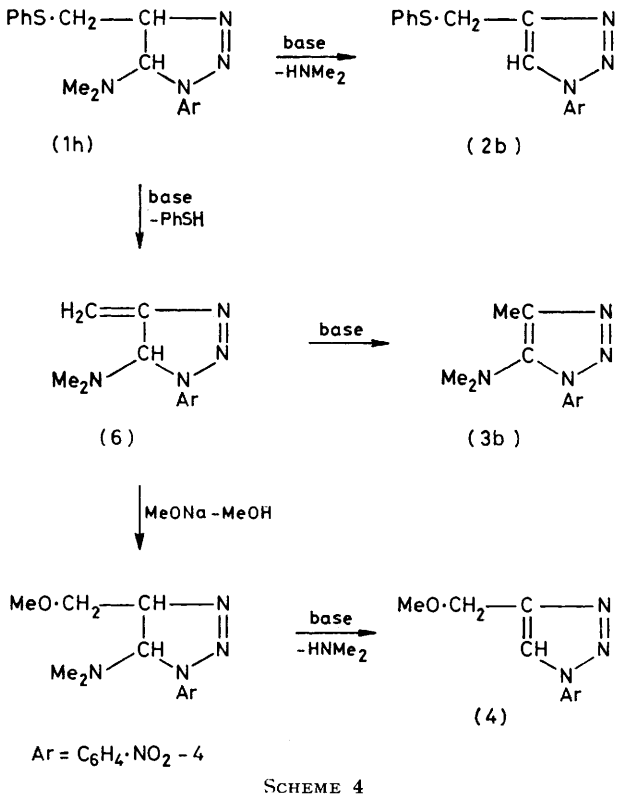
and spectroscopic methods; compound (3a) was identical with an authentic sample independently prepared (Scheme 3) by treating 1,1-dimorpholinopropene [7] with 4-nitrophenyl azide and deaminating the adduct (5a) primarily formed with acetic acid. Similarly were prepared authentic samples of the triazoles (5c and e).

TABLE 4

1-Aryl-4-methyl-5,5-dimorpholino-*v*-triazolines (5)

	Ar	^{1}H N.m.r. (CDCl$_3$) δ_{Me}	^{1}H N.m.r. (CDCl$_3$) δ_H	Cryst. solvent	M.p. (°C)	Yield (%)	Yield of triazole (3) (%)	Required (%) C	Required (%) H	Required (%) N	Found (%) C	Found (%) H	Found (%) N
(5a)	C_6H_4·NO_2-4	1.58	*ca.* 4.35 ‡	MeOH	170	90	98	54.25	6.4	22.35	54.15	6.2	22.2
(5b)	Ph	1.56	4.24	EtOH	149—150	25	95	61.65	7.55	21.15	61.55	7.75	20.9
(5c)	C_6H_4·OMe-4	1.55	4.21	EtOH	139	15	95	51.85	7.45	19.4	59.75	7.4	19.4

‡ Owing to insolubility only a poor spectrum was obtained.



SCHEME 4

(The relevant data are collected in Table 4.) Similar behaviour was observed with the triazoline (1g). By using sodium methoxide instead of sodium hydroxide, the triazoline (1a) afforded a mixture of the same triazoles, though in a different ratio.

The above results may be rationalized in terms of the reaction course showed in Scheme 4 for the triazoline (1g). The usual deamination of 5-amino-*v*-triazolines in the presence of bases leads to the triazole (2b).[3,4] The alternative elimination of PhSH affords 5-dimethylamino-4-methylene-1-(4-nitrophenyl)-*v*-triazoline (6), which aromatizes under basic catalysis to the triazole (3b). The formation of the product (4) can be explained through addition of methanol and deamination of the resulting 4-methoxymethyl-substituted triazoline.*

In agreement with the above reaction path the reaction of the triazoline (1g) with a base of low nucleophilicity (potassium t-butoxide in t-butyl alcohol) afforded only the triazole (3b). Moreover, by treating the triazoline (1h) with potassium t-butoxide at room temperature and carefully working up the reaction mixture, the intermediate (6) was isolated in good yield and identified from analytical and spectroscopic data. Compound (6) was stable in benzene solution for 24 h at 65 °C, but aromatized to 4-methyl-1-(4-nitrophenyl)-5-dimethylamino-*v*-triazole (3b) in the presence of t-butoxide. Reaction with 1% sodium hydroxide in methanol afforded the triazole (4), whereas sodium benzenethiolate in ethanol gave the corresponding 4-phenylthiomethyltriazole (2b).

The triazolines (1a—k) were all treated with t-butoxide in t-butyl alcohol. In each case the same concentrations of reactants were employed, and heating was continued until disappearance (t.l.c.) of the starting compound. The products [triazole (2) and/or (3)] were isolated by column chromatography.† The ratios of compounds (2) and (3) are reported in Table 3.‡

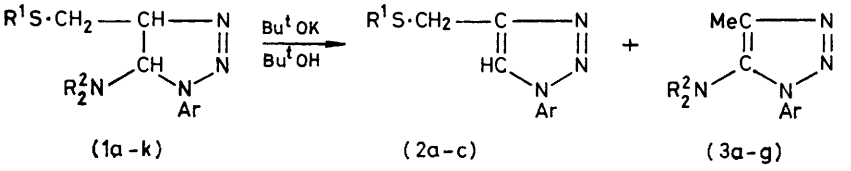
* A direct nucleophilic substitution of the phenylthio-group of (2b) can be ruled out, since (2b) under the same conditions afforded only traces of (4b) after a longer reaction time. For the conversion of (6) into (4) an S_N2' mechanism can also be envisaged (we thank a referee for this suggestion).

† Owing to the thermal lability of 5-amino-*v*-triazolines small amounts of decomposition products were often formed. For example in the base-catalysed reactions of (1a) a small amount of *N*-(1-morpholino-3-methylthiopropylidene)-4-nitroaniline was always detected, this being the main product of the thermal decomposition of (1a) in boiling xylene.[8]

‡ Overall yields are for isolated compounds, but the (2) : (3) ratios were determined from the crude reaction mixture by ^{1}H n.m.r.

[7] H. Baganz and L. Domaschke, *Chem. Ber.*, 1962, **95**, 2095.
[8] R. Fusco, G. Bianchetti, and D. Pocar, *Gazzetta*, 1961, **91**, 933.

Some conclusions can be drawn about the effect of the substituents on the triazoline ring on the (2) : (3) ratio. The similarity in the behaviour of (1a), (1d), and (1f) towards t-butoxide shows that the substituents on the benzene ring have only minor importance. The reactivity of the groups directly involved in the elimination reaction is in good qualitative agreement with their predictable leaving ability. The results obtained from (1a, b, and e) and (1c), respectively, show that the elimination of the MeS^- group is strongly preferred to that of an aliphatic amine and the formation of triazoles (3) predominates. In the case of (1c) the aromatic amino-group is preferentially eliminated, and essentially only the triazole (2) was obtained. Triazolines having an arylthio-substituent behave analogously. In the case of the triazolines (1i—k) similar amounts of the two elimination products were obtained (see Table 3), in accord with the predictable increased leaving ability of the arylthio-group, making the two elimination pathways competitive.



SCHEME 5

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a Varian A-60 spectrometer operating at 60 MHz (Me_4Si as internal standard).

Preparation of the Triazolines (1a—f).—The secondary amine (20 mmol) was dropped into a solution of 3-(methylthio)propanal (20 mmol) and an aryl azide [9] (20 mmol) in benzene (25 ml). The mixture was stirred for 2—12 h at room temperature until reaction was complete (t.l.c.). The water formed was removed with anhydrous sodium sulphate and the product was precipitated from the filtered solution by adding n-pentane. For the more soluble compounds the benzene solution was evaporated and the residue taken up in n-pentane. The *triazolines* (1a—f) were purified by recrystallization (Table 1).

Preparation of the Triazolines (1g—k).—Propenal (15 mmol) and the benzenethiol (15 mmol) with a drop of morpholine were stirred for 2—3 h at 5—15 °C. To the crude mixture a solution of the aryl azide (15 mmol) in benzene (20 ml) was added followed by the secondary amine (15 mmol). Separation of the water formed usually began within a few minutes. After 2—5 h at room temperature the solution was worked up as described for (1a—f) yielding the *triazolines* (1g—k).

Preparation of the Triazolines (5a—c).—1,1-Dimorpholinopropene (10 mmol) was treated with the aryl azide (10 mmol) in benzene solution (15 ml). 4-Nitrophenyl azide reacted immediately, yielding a precipitate of the *triazoline* (5a), which was filtered off and recrystallized. In the other cases the reaction mixture was stirred at room temperature for 1 h and diluted with n-pentane, yielding a crystalline precipitate which on recrystallization afforded the pure *triazolines* (5b and c).

Deamination of the Triazolines (5a—c) *by Acid.*—The triazoline (5 mmol) was dissolved in acetic acid (5 ml) and heated at 60 °C for 30 min. The solution was diluted with water and the precipitate filtered off, washed with water, and recrystallized yielding the *triazoles* (3a, c, and e).

Reactions with Bases.—(a) *Sodium hydroxide in methanol.* The triazoline (5 mmol) was dissolved in methanol (150 ml) containing 1% sodium hydroxide (w/v). The mixture was refluxed (0.5—3 h) until disappearance of the starting compound (t.l.c.). The solution was neutralized with hydrochloric acid and evaporated, and the residue was extracted with water. The solid residue was filtered off and dissolved in chloroform, and the solution was dried (Na_2SO_4), and evaporated. The crude mixture was separated by column chromatography (silica gel; AcOEt–PhH), affording the *triazoles* (2)—(4).

(b) *Sodium methoxide in methanol.* The triazoline (1a) (1.2 mmol) was treated with sodium methoxide (1.2 mmol) in absolute methanol (80 ml). The solution was refluxed for 8 h and worked up as described above yielding the *triazoles* (2a), (3a,) and (4).

(c) *Potassium t-butoxide in t-butyl alcohol.* The triazoline (1a—k) (1.2 mmol) was dissolved in warm t-butyl alcohol (80 ml). Potassium t-butoxide (1.2 mmol) was then added and the mixture refluxed for 1—10 h until disappearance of the starting compound (t.l.c.). The solution was neutralized with hydrochloric acid and evaporated. The residue was extracted with water; the residue was filtered off and dissolved in chloroform and the solution dried (Na_2SO_4) and evaporated. The crude mixture was chromatographed on a silica gel column affording the *triazole* (2) and/or (3).

5-Dimethylamino-4-methylene-1-(4-nitrophenyl)-v-triazoline (6.)—The triazoline (1h) (0.6 g, 1.68 mmol) was dissolved in warm t-butyl alcohol (110 ml). After cooling a solution of potassium t-butoxide (0.2 g, 1.68 mmol) in t-butyl alcohol (30 ml) was added. The mixture was stirred at room temperature for 30 min, diluted with water (300 ml), and extracted with ether (5 × 100 ml). The ethereal layers were combined, dried (Na_2SO_4), and evaporated. The residue was chromatographed (silica gel 30 g; AcOEt–PhH, 60 : 40) yielding the *triazoline* (6) (0.06 g, 15%) as pale yellow crystals, m.p. 78 °C (Found: C, 53.15; H, 4.95; N, 28.1. $C_{11}H_{13}N_5O_2$ requires C, 53.45; H, 5.25; N, 28.35); δ (C_6D_6) 4.48 (1 H, H-5), 4.82 [1 H, :CH*H*(*cisoid*), and 5.72 [1 H, :CH*H*(*transoid*)]; * J_{gem} 1.1, J_{cisoid} 2.3, $J_{transoid}$ 2.8 Hz.

* The signal at 4.48 was assigned to H-5 since it shows in acidic medium a greater downfield shift. The chemical shifts of the methylene protons were assigned by assuming $J_{cisoid} < J_{transoid}$.[10]

[9] Prepared as described in Houben–Weyl, 'Methoden der Organischen Chemie,' Thieme–Verlag, Stuttgart, 1965, **10/3**, 807.

[10] M. Barfield, R. J. Spear, and S. Sternhell, *Chem. Rev.*, 1976, **76**, 593.

Reactions of the Triazoline (6).—(a) *With sodium methoxide in methanol.* Compound (6) was dissolved in methanol and a trace of sodium methoxide was added. After 2 h at 40 °C the triazoles (3b) and (4) were identified in the reaction mixture by t.l.c.

(b) *With benzenethiol.* Compound (6) was dissolved in ethanol and equimolecular amounts of benzenethiol and triethylamine were added. After 2 h at room temperature the triazole (2b) was identified by t.l.c.

[7/692 *Received*, 25*th April*, 1977]