v-Triazolines. Part XVI (1). Synthesis of Benzothiepino[4,5-*d*]-*v*-triazole Derivatives

*Luisa Maria Rossi and Pasqualina Trimarco**

Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy

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The cycloaddition reaction of some arylazides to enamines **4a-f** afforded *v*-triazolines **5a-i**; by subsequent acid-catalyzed hydrolysis *v*-triazoles **6a-c** were obtained. The reversibility of the cycloaddition was demonstrated on the basis of spectroscopic or chemical evidences.

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The cycloaddition reaction of arylazides to enamines derived from sulfur-containing cyclic ketones has been already investigated by our group as an entry to new heterocyclic systems (2,3).

In a previous paper (3) we reported the synthesis of some 1-aryl-9b-amino-1,3a,4,9b-tetrahydro-1-benzothiopyrano[3.4-*d*]-*v*-triazoles **2** by cycloaddition of arylazides to 4-amino-2*H*-1-benzothiopyrans **1**. In several cases only moderate yields of cycloadducts were obtained and this was rationalized as an unfavourable equilibrium between the cycloaddition and the cycloreversion reactions. In principle, this was not surprising since some examples of cycloreversion reactions of 5-amino-4,5-dihydro-*v*-triazole derivatives have been described (4).

According to the above hypothesis compounds **2** were heated in various solvents yielding a reaction mixture in which the starting enamine **1** and the arylazide could be identified (5).

However, the problem of the cycloreversion of 5-amino-4,5-dihydro-*v*-triazoles derived from arylazides and enamines of benzo-thiacycloalkanones remains still open.

With the aim to check the effect, if any, of the ring size on the thermal stability of the above mentioned dihydro-*v*-triazoles we have prepared some analogues of compounds **2** with a seven-membered ring. Moreover we were interested in the preparation of derivatives of the heretofore unknown benzothiepino[4,5-*d*]-*v*-triazole ring system.

Enamines **4a-f** were obtained by reacting the corresponding ketones **3a,b** with the appropriate secondary amine and titanium tetrachloride (6). As indicated in Table 1 analytical and spectral data are in agreement with the proposed structure. In the ^{1}H-nmr spectrum the signal associated with the enamine proton appears as a triplet at

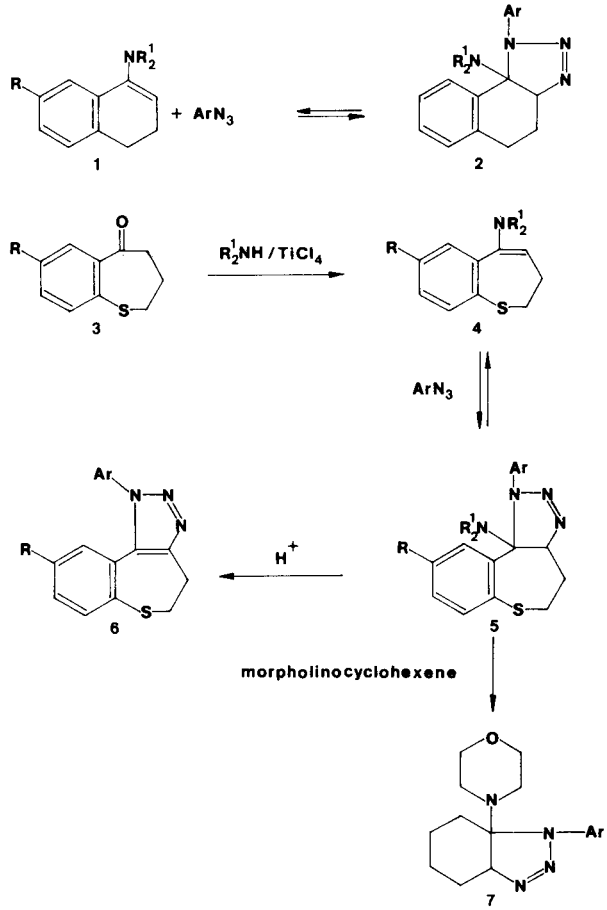

Table 1

4	R	NR_2^1	Yield %	m.p. (°C)	Found % C	H	N	Formula	Calcd. % C	H	N	Nmr ($CDCl_3$) δ CH_2S	δ CH_2	δ CH=
a	Cl	Dimethylamino	60	91	59.95	6.00	5.90	$C_{13}H_{14}ClNS$	60.10	5.90	5.85	3.35	2.13	5.25
b	CH_3	Dimethylamino	60	85	71.55	7.90	6.50	$C_{13}H_{17}NS$	71.20	7.80	6.40	3.32	2.04	5.18
c	Cl	Morpholino	50	102	59.90	5.85	4.85	$C_{14}H_{16}ClNOS$	59.65	5.70	4.95	3.32	2.06	5.32
d	CH_3	Morpholino	40	73	73.10	7.70	5.45	$C_{15}H_{19}NOS$	73.40	7.80	5.70	3.22	2.01	5.17
e	Cl	Pyrrolidino	85	59	63.50	6.10	5.05	$C_{14}H_{16}ClNS$	63.25	6.05	5.25	3.2	2.0	4.86
f	CH_3	Pyrrolidino	60	105	63.95	6.55	5.10	$C_{15}H_{19}ClNS$	64.15	6.80	5.00	3.28	~2.0	5.08

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Table 2

5	R	NR^1_2	Ar	Yield %	m.p. (a) (°C)	Recrystallization Solvent	Found % C	H	N	Formula	Calcd. % C	H	N	NMR CDCl$_3$ δH_{3a}
a	Cl	Dimethylamino	C_6H_4F-4	65	141-142	Methanol	57.75	4.75	15.10	$C_{18}H_{18}ClFN_4S$	57.35	4.80	14.85	4.63
b	CH_3	Dimethylamino	$C_6H_4NO_2$-4	70	172	Chloroform/diisopropyl ether	59.85	5.35	18.40	$C_{19}H_{21}N_5O_2S$	59.50	5.50	18.25	(b)
c	Cl	Dimethylamino	$C_6H_4NO_2$-4	85	153	Chloroform/diisopropyl ether	53.40	4.29	17.19	$C_{18}H_{18}ClN_5O_2S$	53.50	4.50	17.35	4.85
d	CH_3	Pyrrolidino	C_6H_5	60	111	Ethanol	69.50	6.70	15.50	$C_{21}H_{24}N_4S$	69.20	6.65	15.35	4.68
e	CH_3	Pyrrolidino	$C_6H_4NO_2$-4	60	143	Ethanol	61.30	5.80	16.75	$C_{21}H_{23}N_5O_2S$	61.60	5.65	17.10	4.95
f	Cl	Pyrrolidino	C_6H_4-Cl	45	120	Ethanol	57.10	4.55	13.35	$C_{20}H_{20}Cl_2N_4S$	57.25	4.80	13.35	4.64
g	Cl	Pyrrolidino	$C_6H_4NO_2$-4	65	139	Diisopropyl ether (c)	55.75	4.75	16.25	$C_{20}H_{20}ClN_5O_2S$	55.85	4.70	16.30	4.53
h	Cl	Morpholino	$C_6H_4NO_2$-4	50	138	Ethanol	58.50	4.45	15.40	$C_{20}H_{20}ClN_5O_3S$	58.85	4.50	15.70	4.98
i	CH_3	Morpholino	$C_6H_4NO_2$-4	70	164-166	Diisopropyl ether	59.55	5.30	16.65	$C_{21}H_{23}N_5O_3S$	59.25	5.45	16.45	5.08

(a) With decomposition. (b) Owing to insolubility a satisfactory spectrum could not be obtained. (c) Purified by extraction with warm solvent.

Table 3

6	R	Ar	Starting compound	Yield (%)	m.p. (°C)	Recrystallization solvent	Found % C	H	N	Formula	Calcd. % C	H	N
a	CH_3	$C_6H_4NO_2$-4	5i	80 70	189	Methanol	60.00	4.25	16.30	$C_{17}H_{14}N_4O_2S$	60.35	4.15	16.55
b	Cl	$C_6H_4NO_2$-4	5c	85 75	227	Ethanol	53.50	2.95	15.40	$C_{16}H_{11}ClN_4O_2S$	53.55	3.10	15.60
c	Cl	C_6H_4Cl-4	5f	60	183	Ethanol	55.35	3.10	11.90	$C_{16}H_{11}ClN_3S$	55.20	3.20	12.05

4.86-5.32 δ.

By reacting **4a-e** with arylazides in benzene solution the aminoaryltriazoles **5a-i** were obtained in variable yield. The better results were obtained for the 4-nitrophenyl-substituted derivatives which, owing to their low solubility, precipitated largely from the reaction solution. Analytical and spectral data are in agreement with the proposed structure (Table 2).

The triazoles **6a-c** could be easily obtained from the appropriate compounds **5** by acid-catalyzed deamination.

The thermolysis of the isolated compounds **5b,c,e,f,i** was performed by refluxing in acetonitrile or ethanol solution. This reaction yielded essentially only the starting reagents (**4** and arylazide). For example compound **5i** underwent cycloreversion to the extent of 50% after 0.5 hours. After about 3 hours only about 10% of the starting triazoline was still present. The progress of the cycloreversion reaction was evidenced by one of the three following ways: (i) by ir through identification in the reaction mixture the azide bond (ν N_3 = 2120 cm^{-1} (7)); (ii) by nmr through the signals of the enamine proton and the signal associated with H_{3a} of compound **5** and (iii) by performing the cycloreversion reaction in the presence of 1-morpholinocyclohexene. The enamine added the arylazide yielding the cycloadduct **7** which could be easily identified by comparison with an authentical sample (tlc) (8-9).

The above results, though qualitative, confirm the general reversibility of the cycloaddition reaction of arylazides to enamines of benzotiacycloalkanones.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded with Varian A-60 and 360 spectrometers and the chemical shifts are expressed in ppm relative to TMS as internal standard. Tlc was run on silica gel (Merck) with benzene (20-60%)-ethyl acetate as eluent.

Enamines **4a-f**.

The 7-substituted-1-benzothiepan-5-one **1a,b** (25 mmoles) was dissolved in anhydrous pentane-benzene (1:1). The secondary amine (150 mmoles) was added and the solution was cooled to −10° under nitrogen. Titanium tetrachloride (13 mmoles) was dissolved in pentane (10 ml.) and dropped in under stirring. The reaction mixture was stirred at room temperature for 24 hours and the completion of the reaction controlled by glc. The reaction suspension was filtered and the solvent evaporated under diminished pressure. The crude residue was recrystallized from *n*-pentane yielding the pure product.

1-Aryl-9-substituted-10b-amino-3a,4,5,10b-tetrahydro-1*H*-1-benzothiepino-[4,5-*d*]-*v*-triazoles **5a-i**.

The enamine **4** (5 mmoles) was dissolved in benzene (10-15 ml.) and the azide (5 mmoles) added. The reaction mixture was heated on a water bath for 2-12 hours until formation of the product (tlc). The reaction mixture was evaporated and the residue was triturated with *n*-pentane, filtered with suction and recrystallized. When the product separated out directly from the reaction mixture, it was isolated by filtration and the mother liquor was elaborated as above.

1-Aryl-9-substituted-4,5-dihydro-1*H*-1-benzothiepino-[4,5-*d*]-*v*-triazoles **6a-c**.

The triazoline **5** (1 mmole) was suspended or dissolved in ethanol (30 ml.) and hydrochloric acid (37%, 0.1 ml.) was dropped in. The reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the residue was taken up in chloroform and washed until neutral with sodium bicarbonate solution and water. After evaporation the residue was recrystallized.

In some instances the product separated out directly from the reaction mixture. It was filtered and the mother liquor elaborated as described to

obtain a second crop of product.

Thermolysis of Triazoline **5i**.

(a) The triazoline **5i** was dissolved in ethanol or in acetonitrile and refluxed. Every 30 minutes a small sample was taken and evaporated at room temperature under reduced pressure. The residue was analyzed by ir and nmr. The presence of 4-nitrophenylazide was identified by the ir band at 2120 cm^{-1} (N≡N). The enamine **4d** was identified in the nmr spectrum by the signal associated with the vinyl proton (triplet, δ 5.20).

(b) The triazoline **5i** (0.5 mmole) and 1-morpholinocyclohexene (0.5 mmole) was dissolved in acetonitrile (20 ml.). The reaction mixture was refluxed for 3 hours and evaporated. Enamine **4d** and cycloadduct **7** was identified both by nmr and tlc through comparison with authentical samples.

REFERENCES AND NOTES

(1) Part XV. S. Cilloni, D. Pocar, L. M. Rossi and P. Trimarco, *J. Chem. Res.*, (S)14, (1980).

(2) D. Pocar, L. M. Rossi, R. Stradi and P. Trimarco, *J. Chem. Soc., Perkin Trans. I*, 2337 (1977).

(3) L. M. Rossi and P. Trimarco, *Synthesis*, 465 (1978).

(4) D. Pocar, M. C. Ripamonti, R. Stradi and P. Trimarco, *J. Heterocyclic Chem.*, **14**, 173 (1977); F. Texier and J. Bourgois, *ibid.*, **12**, 505 (1975); J. Bourgois, F. Tonnard and F. Texier, *Bull. Soc. Chim. France*, 2025 (1976).

(5) Unpublished.

(6) H. Weingarten and W. H. White, *J. Org. Chem.*, **32**, 213 (1967).

(7) E. Lieber, C. N. R. Rao, T. S. Chao and C. W. W. Hoffman, *Anal. Chem.*, **29**, 916 (1957).

(8) R. Fusco, G. Bianchetti and D. Pocar, *Gazz. Chim. Ital.*, **91**, 849 (1961).

(9) In principle, the formation of **7** can be a reversible reaction. However the hexahydrobenzotriazole derivatives **7** were found to be stable under the conditions employed.