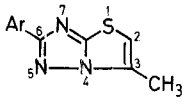
Synthesis of [1,3]Thiazolo[3,2-*b*]-*s*-triazoles and [1,3]Thiazolo[2,3-*c*]-*s*-triazoles

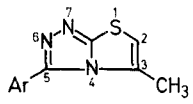
A. MIGNOT, H. MOSKOWITZ, M. MIOCQUE*

Faculty of Pharmacy, Laboratory of Organic Chemistry, Rue J. B. Clément, F-92290 Châtenay-Malabry, France

The search for anthelmintic compounds in the field of Tetramisole® (2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]-*s*-triazole) analogs has led us to study synthetic routes to the [1,3]thiazolo[1,2,4]triazole systems **1** and **2**.



1



2

[1,3]Thiazolo[3,2-*b*]-*s*-triazoles (**1**) may be synthesized from thioxodihydro-1,2,4-triazoles by reaction with α-haloketones followed by cyclization in alkaline medium[1,2]. In a recent communication[3], the synthesis of compounds **1** from 3-(2-propynylthio)-1,2,4-triazoles (**5**) by treatment with mercury(II) acetate/acetic acid was reported. Both cyclization reactions probably proceed via the same ketonic intermediate.

[1,3]Thiazolo[2,3-*c*]-*s*-triazoles (**2**) can be synthesized from 2-hydrazino-1,3-thiazoles[1,2]. Their formation from thioxodihydro-1,2,4-triazoles has been reported by Potts et al.[1] but was later doubted by Dhaka et al.[2].

We have now developed a synthesis of compounds **1** and **2** from the readily available benzaldehyde thiosemicarbazones (**3**). Compounds **3** are converted into 2-propynyl *N'*-benzylidenecarbamohydrazonothioates (**4**) by reaction with 3-bromopropyne in neutral medium [the use of a neutral medium prevents the previously reported[4] propyne-allene isomerization of products **4**]. Compounds **4** are submitted to cyclodehydrogenation by treatment with iron(III) chloride in acetic acid to give 5-aryl-3-(2-propynylthio)-1,2,4-triazoles (**5**). Heating of compounds **5** in alkaline (Method A)[5] or acidic medium (Method B) leads to intramolecular cycloaddition to give mixtures of the thiazolotriazoles **1** and **2**, the [1,3]thiazolo[3,2-*b*][1,2,4]triazoles **1** being the main products. In alkaline medium, the isomeric [1,3]thiazolo[2,3-*c*]-[1,2,4]triazoles (**2**) which are isolated by preparative T.L.C. are formed in 5–10% yield; the yield of **2** is increased in acidic medium: heating the perchlorates of **5** in 12 normal sulfuric acid affords compounds **2** in 19–28% yield.

The structures of compounds **1** and **2** were assigned on the basis of their microanalyses and ^{1}H-N.M.R. spectra.

Table 1. 5-Aryl-3-(2-propynylthio)-1,2,4-triazoles (**5**)

5	Ar	Yield [%]	m.p. Base	m.p. Perchlorate	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5a	C_6H_5	80	130° (benzene/PE)	152°	$C_{11}H_9N_3S$ (215.2)	12.2 (s, 1H, exch. D_2O); 8 (m, 2H); 7.45 (m, 3H); 3.95 (d, 2H, J = 2 Hz); 2.25 (t, 1H, J = 2 Hz)
5b	—C_6H_4—OCH_3(2)	75	120° (benzene/PE)	136°	$C_{12}H_{11}N_3OS$ (245.2)	12 (s, 1H, exch. D_2O); 8.3 (dd, 1H); 7.60–6.95 (m, 3H); 4 (s, 3H); 3.95 (d, 2H, J = 2 Hz); 2.2 (t, 1H, J = 2 Hz)
5c	—C_6H_4—OCH_3(4)	70	127° (benzene)	192°	$C_{12}H_{11}N_3OS$ (245.2)	9.7 (s, 1H, exch. D_2O); 7.9 (m, 2H); 6.90 (m, 2H); 3.95 (d, 2H, J = 2 Hz); 3.80 (s, 3H); 2.25 (t, 1H, J = 2 Hz)

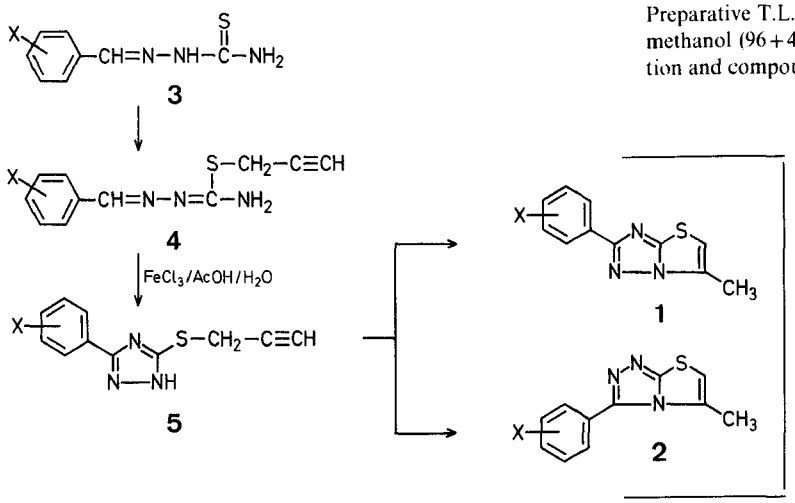
[a] All products **5** gave satisfactory microanalyses: C, ±0.30; H, ±0.25; N, ±0.30.

Table 2. [1,3]Thiazolo[3,2-*b*]-*s*-triazoles (**1**) and [1,3]Thiazolo[2,3-*c*]-*s*-triazoles (**2**)

Product	Ar	Yield [%] Method A	Yield [%] Method B	m.p.	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
1a	C_6H_5	69[b]	44[c]	124°	$C_{11}H_9N_3S$ (215.2)	8.4–8.1 (m, 2H); 7.6–7.3 (m, 3H); 6.5 (q, 1H, J = 1 Hz); 2.5 (d, 3H, J = 1 Hz)
1b	—C_6H_4—OCH_3(2)	65[b]	42[c]	90°	$C_{12}H_{11}N_3OS$ (245.2)	8.0 (dd, 1H); 7.6–6.9 (m, 3H); 6.55 (q, 1H, J = 1 Hz); 3.95 (s, 3H); 2.6 (d, 3H, J = 1 Hz)
1c	—C_6H_4—OCH_3(4)	70[b]	51[c]	122°	$C_{12}H_{11}N_3OS$ (245.2)	8.2 (m, 2H); 7.0 (m, 2H); 6.45 (q, 1H, J = 1 Hz); 3.90 (s, 3H); 2.55 (d, 3H, J = 1 Hz)
2a	C_6H_5	6[d]	21[c]	150° (benzene/PE)	$C_{11}H_9N_3S$ (215.2)	7.6 (m, 5H); 6.6 (q, 1H, J = 1 Hz); 2.2 (d, 3H, J = 1 Hz)
2b	—C_6H_4—OCH_3(2)	10[d]	28[c]	172° (benzene/PE)	$C_{12}H_{11}N_3OS$ (245.2)	7.7–6.9 (m, 4H); 6.6 (q, 1H, J = 1 Hz); 3.75 (s, 3H); 2.05 (d, 3H, J = 1 Hz)
2c	—C_6H_4—OCH_3(4)	5[d]	19[c]	128° (benzene/PE)	$C_{12}H_{11}N_3OS$ (245.2)	7.60 (m, 2H); 7.05 (m, 2H); 6.55 (q, 1H, J = 1 Hz); 3.95 (s, 3H); 2.15 (d, 3H, J = 1 Hz)

[a] All products **1** and **2** gave satisfactory microanalyses: C, ±0.30; H, ±0.25; N, ±0.30.
[b] Isolated directly from the reaction mixture and recrystallized.
[c] Isolated by preparative T.L.C.
[d] Isolated by preparative T.L.C. from mother liquor of recrystallization of **1**.

0039–7881/79/0132–0052 $ 03.00



2-Propynyl *N'*-Benzylidenecarbamohydrazonothioates Hydrobromides (4); General Procedure:

To a stirred solution of the benzaldehyde thiosemicarbazone (**3**; 0.1 mol) in ethanol (100 ml) is added a solution of propynyl bromide (12 g, 0.1 mol) in ethanol (20 ml). The mixture is refluxed for 2 h and then cooled. The solution is diluted with ether (400 ml) and the resultant solid isolated by filtration.

N'-Benzylidene Derivative (**4a**); yield: 87%; m.p. 175°.

N'-(2-Methoxybenzylidene) Derivative (**4b**); yield: 90%; m.p. 160°.

N'-(4-Methoxybenzylidene) Derivative (**4c**); yield: 86%; m.p. 145°.

5-Aryl-3-(2-propynylthio)-1,2,4-triazoles (5); General Procedure[6]:

A solution of iron(III) chloride (16.22 g, 0.1 mol) in water (150 ml) is added to a solution of the hydrobromide of the compound **4** (0.1 mol) in water (150 ml) and the mixture is heated on a steam bath until decoloration occurs and then for a further 2 h. The solvent is distilled off under reduced pressure. The residue is taken up in chloroform, and the solution washed with aqueous sodium hydrogen carbonate, dried with sodium sulfate, and evaporated. The residual product is recrystallized.

5-Aryl-3-(2-propynylthio)-1,2,4-triazolium Perchlorates:

A 0.1 normal solution of perchloric acid in acetic acid (40 ml) is added to a solution of the compound **5** (4 mmol) in acetic acid (10 ml). The solvent is then evaporated, ether is added to the residue, the solid product collected by suction, and washed acid-free with ether. After drying over phosphorus pentoxide, the perchlorate can be used without further purification.

6-Aryl-3-methyl-[1,3]thiazolo[3,2-*b*]-*s*-triazoles (1) and 5-Aryl-3-methyl-[1,3]thiazolo[2,3-*c*]-*s*-triazoles (2):

Method A, in Alkaline Medium: Sodium (1.4 g, ~0.06 g-atom) is dissolved in pure ethanol (30 ml). This solution is added to a solution of the 5-aryl-3-(2-propynylthio)-1,2,4-triazole (**5**; 0.05 mol) in ethanol (50 ml) and the mixture is refluxed for 3 h. Ethanol is then distilled off under reduced pressure, the residue is taken up in ether (400 ml), the solution is washed with water (3 × 150 ml), dried with sodium sulfate, and concentrated to dryness in vacuo. The residual solid is recrystallized from ethanol/water (1:1) to give compound **1**. The mother liquor is evaporated, and the residue is submitted to preparative T.L.C. on silica gel using chloroform/methanol (96+4) as eluent to afford compound **2**.

Method B, in Acidic Medium: The 5-aryl-3-(2-propynylthio)-1,2,4-triazolium perchlorate (2 mmol) is dissolved in 12 normal sulfuric acid (40 ml), the solution heated on a steam bath for 3 h, and then allowed to cool. The mixture is neutralized by the addition of solid sodium carbonate and aqueous sodium hydroxide. It is then diluted with ethanol (100 ml), filtered, and evaporated to dryness in vacuo. The residual solid is taken up in chloroform (50 ml), the solution filtered, and concentrated in vacuo. Preparative T.L.C. of the residue on silica gel using chloroform/methanol (96+4) as eluent affords compound **1** as the first fraction and compound **2** as the second one.

Received: June 16, 1978

* Correspondence address.

1 K. T. Potts, S. Husain, *J. Org. Chem.* **36**, 10 (1971).

2 K. S. Dhaka, J. Mohan, V. K. Chadha, H. K. Pusari, *Indian J. Chem.* **12**, 485 (1974).

3 V. Pramod Upadhyaya, T. G. Surendra Nath, V. R. Srinivasan, *Synthesis* **1978**, 228.

4 V. Pramod Upadhyaya, T. G. Surendra Nath, V. R. Srinivasan, *Indian J. Chem.* [B] **15**, 220 (1977).

5 S. Kano, *Yakugaku Zasshi* **92**, 935 (1972); *C. A.* **77**, 126492 (1972).

6 E. Hoggarth, *J. Chem. Soc.* **1949**, 1160.

0039–7881/79/0132–0053 $ 03.00

Errata

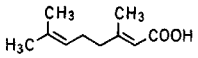
A. Mignot, H. Moskowitz, M. Miocque, *Synthesis* **1979** (1), 52–53
The momenclature for Tetramisole[66] should be 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*] thiazole.

K. Herrmann, G. Simchen, *Synthesis* **1979** (3), 204–205
The lines 10 to 17 of the text (p. 204) should read as follows:

sche Acrylcyanide zugänglich[1,5,6]. Aliphatische Carbonsäure-halogenide hingegen setzten sich mit Tetraethylammoniumcyanid zu Acyloxymalodinitrilen („dimere Acrylcyanide") um, wofür auch die hohe Cyanidionen-Konzentration verantwortlich ist[1]. Die Reaktion aliphatischer Säurechloride **(2)** mit Cyanotrimethylsilan **(1)**[7-10] sollte deshalb eine geeignete Synthesenmethode für 2-Oxoalkannitrile (aliphatische Acrylcyanide, **3)** darstellen. Bisher konnte allerdings nur

Errata and Addenda 1979

M. Contento, D. Savoia, C. Trombini, A. Umani-Ronchi, *Synthesis* **1979** (1), 30–32;
The structure for compound **3c** (p. 31, Table 1) should be:

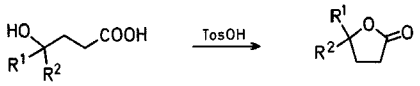


A. Mignot, H. Moskowitz, M. Miocque, *Synthesis* **1979** (1), 52–53;
The correct name for Tetramisole® should be 6-phenyl-2,3,5,6-tetrahydroimidazolo[2,1-*b*]thiazole.

A. N. Pudovik, I. N. Konovalova, *Synthesis* **1979** (2), 81–96;
The first sentence of the experimental procedure on p. 96 should read as follows:
Dialkyl phosphite or phosphorothioate (0.01 mol) is added to the azo compound (0.01 mol) in ether (10 ml).

In Table 13 (p. 96) the entries R^2 for compounds **63b** and **63c** should be 4-H_3C—C_6H_4 and 4-O_2N—C_6H_4, respectively.

Abstract 5422, *Synthesis* **1979** (2), 160;
The formula scheme for the conversion **3**→**4** should be:



3 **4**

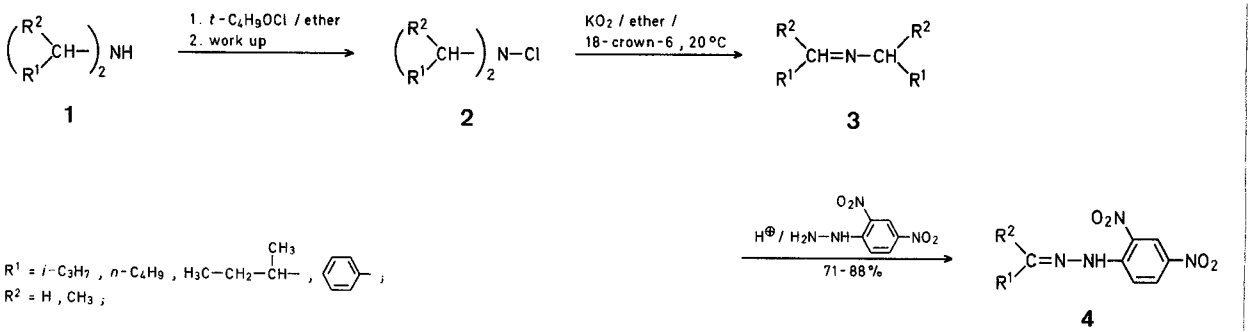
N. Blažević, D. Kolbah, B. Belin, V. Šunjić, F. Kajfež, *Synthesis* **1979** (3), 161–176;
Compounds **78a–e** (p. 173) should be named:
9-chloro-10b-phenyl-2,3,5,6-tetrahydro-10b*H*-[1,3]oxazolo[3,2-*c*]-quinazolines.

K. Herrmann, G. Simchen, *Synthesis* **1979** (3), 204–205
The lines 10 to 17 of the text (p. 204) should read as follows:

sche Acrylcyanide zugänglich[1,5,6]. Aliphatische Carbonsäure-halogenide hingegen setzen sich mit Tetraethylammoniumcyanid zu Acyloxymalodinitrilen („dimere Acrylcyanide") um, wofür auch die hohe Cyanidionen-Konzentration verantwortlich ist[1]. Die Reaktion aliphatischer Säurechloride **(2)** mit Cyanotrimethylsilan **(1)**[7–10] sollte deshalb eine geeignete Synthesenmethode für 2-Oxo-alkannitrile (aliphatische Acrylcyanide, **3**) darstellen. Bisher konnte allerdings nur

L. Caglioti, F. Gasparrini, D. Misiti, G. Palmieri, *Synthesis* **1979** (3), 207–208;
The italic sub-headings in the Table (p. 208) should be *From tosylhydrazones, From* N-*methyl*-N-*tosylhydrazones,* and *From 2,4-dinitrophenylhydrazones.*

Abstract 5440, *Synthesis* **1979** (3), 238;
The formula scheme for the conversion **1**→**4** should be as follows:

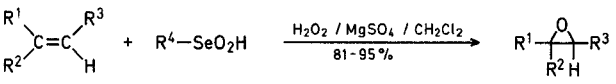


R^1 = *i*-C_3H_7, *n*-C_4H_9, H_3C—CH_2—$CH(CH_3)$—, C_6H_5—; R^2 = H, CH_3;

C. Venturello, R. D'Aloisio, *Synthesis* **1979** (4), 283–287;
Entries 3 and 4 of the Mass spectrum column of Table 1 (p. 284) should be 284 (^{35}Cl) and 318 (^{35}Cl), respectively.

J. S. Davidson, *Synthesis* **1979** (5); 359–361;
Compounds **6** (p. 360) should be named:
3,4-diaryl-5-oxo-3,4-dihydro-1*H*-1,2,4-triazoles.

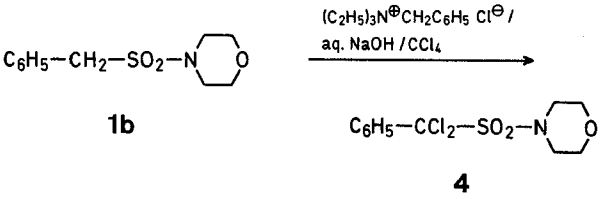
Abstracts 5494, *Synthesis* **1979** (5), 399;
The formula scheme for the conversion **1**→**3** should be as follows:



1 **2** **3**

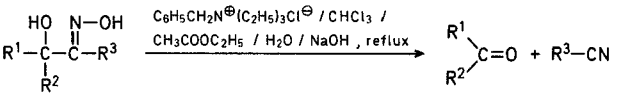
C. Skötsch, I. Kohlmeyer, E. Breitmaier, *Synthesis* **1979** (6), 449–452;
The name for compound **10a** should be:
3-Methyl-5,6,7,8-tetrahydroisoxazolo[5,4-*b*]chinolin.

J. Goliński, A. Jończyk, M. Mąkosza, *Synthesis* **1979** (6), 461–463;
The formula scheme for the conversion **1b**→**4** (p. 462) should be as follows:



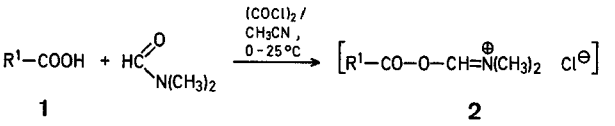
1b **4**

Abstract 5520, *Synthesis* **1979** (6), 479;
The formula scheme should be as follows:



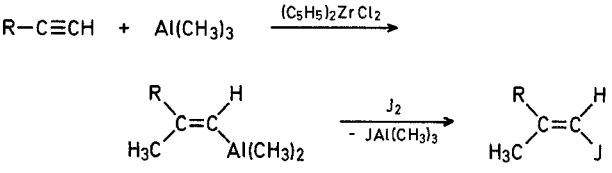
1 **2** **3**

Abstract 5521, *Synthesis* **1979** (6), 479;
The formula scheme for the conversion **1**→**2** should be as follows:



1 **2**

E. Negishi, D. E. Van Horn, A. O. King, N. Okukado, *Synthesis* **1979** (7), 501–502;
For clarity, the following formula scheme should be added:



A. McKillop, D. W. Young, *Synthesis* **1979** (7), 481–500;
The heading for Table 24 (p. 496) should be:

Table 24. Oxidation of Alcohols to Aldehydes and Ketones using Potassium Permanganate/Molecular Sieves[172].