Synthesis of 2-Substituted-5-methylthiazolo[3,2-*b*]-1,2,4-triazoles and Acylated 3-Amino-2-imino-4-methyl-2-thiazolines

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Received June 25, 1976

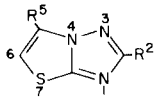
3-Amino-2-imino-4-methyl-2-thiazoline, I, underwent ring closure with ethyl formate, cyanogen bromide and carbon disulfide, giving moderate yields of 2-substituted-5-methylthiazolo[3,2-*b*]-1,2,4-triazoles, II. Reaction of I·HCl with acid anhydrides (acetic, propionic, trifluoroacetic) resulted in the formation of the corresponding II compounds, whereas other anhydrides (benzoic, perfluoropropionic, perfluorobutyric) gave high yields of 3-acylamido-2-acylimido-4-methyl-2-thiazolines. With acid chlorides and I·HCl, in the presence of triethylamine, mixtures of 2-acylimino-3-amino-4-methyl-2-thiazolines and 2-acylimino-3-(diacylamido)-4-methyl-2-thiazolines are formed. Spectral characteristics are reported.

J. Heterocyclic Chem., **13**, 1225 (1976).

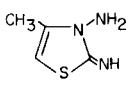
The preparation of thiazolo-*s*-triazoles of the [3,2-*b*] system, **A**, has been investigated by several research groups. One of the best routes to **A** developed previously involves the reaction of 5-substituted-*s*-triazole-3-thiols with α-haloketones (1,2,3,4,5) or propargyl bromide (4,5).

Since 3-amino-2-iminothiazolines have been less readily available than *s*-triazolethiols (2), general synthesis routes of ring system **A** involving ring closure onto a thiazolo nucleus to form the *s*-triazole ring are relatively rare and complex. There are only three reports of this type of ring closure involving a thiazole ring. In the first example (6), 3,4-dihydro-2-imino-5-(2-phthalamidoethyl)-2*H*-1,3,4-thiadiazine rearranged under the influence of concentrated hydrochloric acid to give 3-amino-2-imino-4-(2-phthalamidoethyl)-2-thiazoline hydrochloride. Reaction of the latter compound with anhydrous formic acid gave **A** (R^2 = H, R^5 = 2-phthalamidoethyl). The ring closure of 3-amino-2-imino-4-methylthiazoline to **A** (R^2 = $N(CH_3)_2$, R^5 = CH_3) has been accomplished by the use of *N*-(dichloromethylene)-*N*,*N*-dimethylammonium chloride (7) ("phosgene immonium chloride"). Dehydration of 3-amino-2-acylamidothiazolium mesitylenesulfonates leading to **A** (R^2 = H, CH_3, C_6H_5; R^5 = H, CH_3) in high yield has been reported (8,9); this route is analogous to that reported for *s*-triazolo[1,5-*a*]pyridines from 1,2-diaminopyridinium salts (10).

Since the original route (6) to **A** (R^2 = H, R^5 = 2-phthalamidoethyl) proceeded through a 3-amino-2-imino-2-thiazoline intermediate, we decided to investigate a synthetic approach to ring system **A** using the reaction of 3-amino-2-imino-4-methyl-2-thiazoline, I, and its hydrochloride (11,12), Ia, with acid anhydrides, acid chlorides, ethyl orthoformate, cyanogen bromide, and carbon disulfide.



A



I

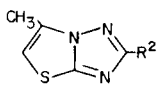
Ia: HCl-salt

Results and Discussion

Refluxing Ia with an excess of acetic or propionic anhydride for 3-4 hours led directly to IIa and IIb, respectively. When the initially exothermic reaction between Ia and trifluoroacetic anhydride subsided (evolution of hydrogen chloride) and heating in a sealed glass cylinder was maintained at 100° for 4.5 hours, the reaction mixture contained two products. Separation by silica chromatography gave IIc (20%) in addition to the di-acylated compound IIIa (18%). In anticipation that pentafluoropropionic and heptafluorobutyric anhydrides would participate in a similar condensation reaction, it was rather surprising to discover that these anhydrides, after 4 hours reflux, produced exclusively the di-acylated derivatives IIIb (94%) and IIIc (98%), respectively. When Ia was treated with 8.3 molar excess of benzoic anhydride at 160-170° (8.5 hours), the reaction product that was isolated in 65% yield was IIId.

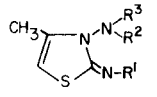
A further departure from the reactions described so far

was realized when a solution containing Ia and triethylamine in dimethylformamide was treated with acetyl chloride (molar ratio 1:2:1). Thin-layer chromatography indicated the formation of two compounds. However, only the major component could be isolated by silica chromatography and was identified as the mono-acetyl derivative IIIe (46%). When this reaction was repeated using Ia, triethylamine and acetyl chloride in the molar ratio of 1:5:3, the minor compound that had escaped attempts at isolation could now be isolated in 7% yield.

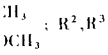


II

a. $R^2 = CH_3$
b. $R^2 = C_2H_5$
c. $R^2 = CF_3$
d. $R^2 = H$
e. $R^2 = NH_2$
f. $R^2 = NHC(=O)CH_3$
g. $R^2 = N(C(=O)CH_3)_2$
h. $R^2 = SCH_3$



III

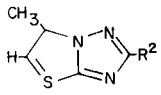
a. $R^1,R^2 = CF_3C(=O)$; $R^3 = H$
b. $R^1,R^2 = C_2F_5C(=O)$; $R^3 = H$
c. $R^1,R^2 = C_3F_7C(=O)$; $R^3 = H$
d. $R^1,R^2 = C_6H_5C(=O)$; $R^3 = H$
e. $R^1 = CH_3C(=O)$; $R^2,R^3 = H$
f. $R^1,R^2,R^3 = CH_3C(=O)$
g. $R^1 = C_2H_5C(=O)$; $R^2,R^3 = H$
h. $R^1,R^2,R^3 = C_2H_5C(=O)$
i. $R^1,R^2,R^3 =$ 
j. $R^1 =$  ; $R^2,R^3 = H$

Its analytical and spectral properties are in full agreement with the structure of IIIf. Under the same conditions, reaction of Ia in the presence of triethylamine with propionyl chloride (molar ratio 1:2.5:1) gave IIIg (46%); however, increasing the amounts of triethylamine and propionyl chloride to a molar ratio of 1:3:2 gave IIIh exclusively and in high (67.5%) yield. The dropwise addition of cyclopropylcarbonyl chloride to a stirred solution of Ia (molar ratio 3.5:1) in pyridine at ambient temperature gave exclusively IIIi in 53% yield. Addition of *N*-methoxy-*N*-methylcarbamoyl chloride to a stirred slurry of Ia in refluxing tetrahydrofuran containing an excess of triethylamine caused no reaction at all. Likewise, addition of *N*-methoxy-*N*-methylcarbamoyl chloride to a solution of Ia in pyridine at 10-25° did not lead to carbamoylation. However, addition of triethylamine to this solution caused an exothermic reaction leading to the formation of the urea IIIj in 66% yield; higher carbamoylated products were not detected.

The nmr characteristics of the mono- and di-acylated derivatives, were particularly useful for structural determinations. In the mono-acylated (IIIe, IIIg, IIIj) compounds, the chemical shift of the two NH protons is in the region 4.8-5.1 ppm. The two NH protons appear as a sharp

Table I

2-Substituted-5-methylthiazolo[3,2-*b*]-1,2,4-triazoles, II

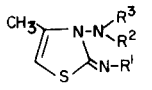


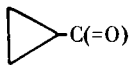
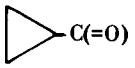
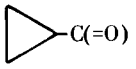
R^2	M.p., °C	% Yield	C Calcd. Found	H Calcd. Found	N Calcd. Found	δ (ppm) Nuclear 6-H	δ (ppm) Magnetic Resonance 5-CH_3	Positions R^2
CH_3	64-66 (a)	60	47.1 46.8	4.6 4.6	27.5 27.6	6.5 (q)	2.5 (d) (J = 1.0 Hz)	2.5 (s, CH_3)
C_2H_5	(b)	49	50.3 50.7	5.4 5.5	25.1 24.7	6.4 (q)	2.5 (d) (J = 0.8 Hz)	1.4 (t, CH_3), 2.9 (q, CH_2)
CF_3	105-107	20	34.8 34.6	1.9 1.8	20.3 20.4	6.8 (q)	2.6 (d) (J = 0.8 Hz)	---
H	70-71 (c)	36	43.2 43.1	3.6 3.6	30.2 30.3	6.63 (q)	2.53 (d) (J = 2 Hz)	8.12 (s, H)
NH_2	192-193	9.7	39.0 39.0	3.9 3.9	36.4 36.5	6.77 (q)	2.38 (d) (J = 1 Hz)	5.85 (s, NH_2)
$NHC(=O)CH_3$	177-179	15	42.8 42.7	4.1 4.1	28.5 28.6	7.1 (q)	2.45 (d) (J = 2 Hz)	10.63 (s, NH) 2.13 (s, CH_3CO)
$N(C(=O)CH_3)_2$	187-189	80	45.3 45.3	4.2 4.2	23.6 23.5	(d)		
SCH_3	48-49	54	38.9 38.8	3.8 3.8	22.7 22.9	6.52 (q) 6.52 (q)	2.48 (d) (J = 2 Hz) 2.48 (d) (J = 2 Hz)	2.67 (s, CH_3S)

(a) Lit. (2) m.p. 68-69°. (b) Liquid at room temperature. (c) Lit. (4) m.p. 64-66°. (d) Insoluble in DMSO.

Table II

Acylated 3-Amino-2-imino-4-methyl-2-thiazolines, III



R^1	R^2	R^3	% Yield	m.p., °C	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
$CH_3C(=O)$	H	H	46	126-128	41.9	42.1	5.2	5.3	24.4	24.6
$C_2H_5C(=O)$	H	H	47	109-113	45.4	45.6	5.9	6.0	22.7	22.3
$CH_3O\diagdown\diagup NC(=O)$	H	H	66	114-117	38.8	38.8	5.6	5.7	25.9	25.6
$CF_3C(=O)$	$CF_3C(=O)$	H	18	177-179	29.9	29.7	1.6	1.4	13.1	13.3
$C_2F_5C(=O)$	$C_2F_5C(=O)$	H	94	172-175	28.5	28.3	1.2	1.1	10.0	10.1
$C_3F_7C(=O)$	$C_3F_7C(=O)$	H	98	114-116	27.6	27.4	1.0	0.9	8.1	8.1
$C_6H_5C(=O)$	$C_6H_5C(=O)$	H	65	95-97	64.1	63.8	4.4	4.5	12.4	12.6
$CH_3C(=O)$	$CH_3C(=O)$	$CH_3C(=O)$	7	152-156 (a)	47.1	47.1	5.1	5.1	15.7	15.5
$C_2H_5C(=O)$	$C_2H_5C(=O)$	$C_2H_5C(=O)$	43	85-87	52.4	52.6	6.4	6.5	14.1	13.8
			53	141-142	57.7	57.5	5.7	5.8	12.6	12.9

(a) Lit. (11) m.p. 167°.

singlet. This agrees well with the observed chemical shift for the NH_2-protons of I (δ 4.85 ppm). By comparison, the signal for the =NH porotn of I is observed at 6.6 ppm. In the di-acylated compounds, IIIa, IIIb, IIIc, IIId, the chemical shift of the remaining NH proton is in the range δ 9.6-11.7 ppm; the actual value is difficult to determine because of the broadness of the signal.

Orthoesters appear to be effective as cyclizations reagents (13). For example, cyclization of I with ethyl orthoformate under reflux for six hours led directly to IId in 36% yield.

Cyanogen bromide was found to react with I in refluxing methanol (4 hours), giving IIe, albeit in low (9.7%) yield. Treatment of IIe with acetic anhydride under reflux (3 hours) led to a mixture of mono-acetyl and di-acetyl derivatives, IIf and IIg, which were readily separated by crystallization and chromatography techniques. The structures of IIe, IIf and IIg are evident from analytical and spectral data (Table I and Experimental).

Reaction of I with carbon disulfide in refluxing aqueous methanol (2 hours) containing potassium hydroxide gave 5-methylthiazolo[3,2-*b*]-1,2,4-triazole-2-thiol, which was readily converted into IIh with methyl iodide.

The nmr spectra of all 2-substituted-5-methylthiazolo-[3,2-*b*]-1,2,4-triazoles, IIa-IIh, show H-6 at δ 6.4-7.1 (q) and 5-CH_3 at δ 2.38-2.60 (d) (Table I); these positions are consistent with reported values (2,8,9).

EXPERIMENTAL

2,5-Dimethylthiazolo[3,2-*b*]-1,2,4-triazole (IIa).

A suspension containing 16.5 g. (0.1 mole) of Ia in 200 ml. of acetic anhydride was refluxed for 8 hours, poured into ice water and stirred for 1 hour. The product was extracted into ether and the extract was washed with aqueous bicarbonate, dried (magnesium sulfate), and concentrated. The residual solid crystallized from ether-hexane to give 9.3 g. (60%) of IIa, a white crystalline solid, m.p. 60-63° (lit. (2) 68-69°); ir (potassium bromide): no NH or C=O absorption; mass spectrum: (70 eV) m/e 153(M^+).

5-Methyl-2-(trifluoromethyl)thiazolo[3,2-*b*]-1,2,4-triazole (IIc) and 4-Methyl-3-(trifluoroacetamido-2-(trifluoroacetimino)-2-thiazoline (IIIa).

The addition at ambient temperature of 75 g. (0.33 mole) of trifluoroacetic anhydride to 6.6 g. (0.04 mole) of Ia caused an exothermic reaction accompanied by the evolution of hydrogen chloride. The resulting clear solution was heated in a sealed glass cylinder on a steam bath for 4.5 hours. The reaction mixture was concentrated to dryness, triturated with water and filtered. Silica chromatography of the solid using a solvent mixture consisting of (by volume) hexane (80), ethyl acetate (16), tetrahydrofuran (4) gave 1.9 g. (20%) of IIc, a white crystalline solid, m.p. 105-107°; ir (potassium bromide): no apparent NH and C=O absorption, but CF_3-absorption at 1180 cm^{-1}.

The second fraction consisted of 2.3 g. (18%) of IIIa, a white crystalline solid, m.p. 177-179° (from ether-hexane); ir (potassium bromide): 3180 (NH), 1770 (C=O), 1630 and 1595 (C=) and *ca.* 1200 cm^{-1} (CF_3); nmr (DMSO-d_6): δ 2.3 (3, d, CH_3), 7.1 (1, d, CH=) and 9.6 ppm (1, s, NH_2); mass spectrum: (70 eV) m/e 321 (M^+), 274, 252 (M^+-CF_3).

3-Heptafluorobutyramido-2-(heptafluorobutyrimino)-4-methyl-2-thiazoline (IIIc).

A suspension of 6.6 g. (0.04 mole) of Ia in 75 g. (0.18 mole) of heptafluorobutyric anhydride was refluxed for 4 hours, poured into water, and stirred for 1 hour. The solid product was filtered, washed with water and dried affording 20.4 g. (98%) of IIIc, a white crystalline solid, m.p. 114-116°; ir (potassium bromide): 3190 (NH), 1765 (C=O) and 1230 cm^{-1} (CF_3); nmr (DMSO-d_6): δ 2.2 (3, d, CH_3) and 7.15 ppm (1, q, CH=).

2-(Acetylimino)-3-amino-4-methyl-2-thiazoline (IIIe) and 2-Acetylimino-3-(diacetamido)-4-methyl-2-thiazoline (IIIf).

A mixture containing Ia, 6.6 g. (0.04 mole), triethylamine, 8.1 g. (0.08 mole), and acetyl chloride, 3.2 g. (0.041 mole), in 100 ml. of DMF was stirred at ambient temperature. After 2 hours, the reaction mixture was poured into ice water and extracted with ether. Evaporation of the ether and silica chromatography of the residue gave 3.2 g. (46%) of IIIe, m.p. 126-128° (from ether-hexane); ir (potassium bromide): 3340 (NH) and 1610 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.25 (3, s, CH_3C=O), 2.3 (3, d, CH_3C=), 5.1 (2, s, NH_2) and 6.1 ppm (1, q, CH=).

When the above procedure was repeated employing Ia, triethylamine and acetyl chloride in a molar ratio of 1:5:3, work-up as above and final recrystallization from ether-hexane afforded IIIf as a colorless crystalline solid, m.p. 152-156° (lit. (11) 167°); ir (potassium bromide): no apparent NH, but C=O absorption at 1750 cm^{-1}; nmr (DMSO-d_6): δ 2.1 (6, d, $(CH_3)_2$), 2.3 (6, s, $(CH_3)_2$) and 6.7 ppm (1, q, CH=).

3-Amino-2-(*N*-methoxy-*N*-methylcarbamoylimino)-4-methyl-2-thiazoline (IIIj).

To a chilled (5-10°) solution of 6.6 g. (0.04 mole) of Ia in 100 ml. of pyridine containing 10.1 g. (0.1 mole) of triethylamine was added dropwise with stirring 6.0 g. (0.485 mole) of *N*-methoxy-*N*-methylcarbamoyl chloride (14). After 1 hour, the mixture was poured into ice water and extracted with ether. The combined ether extracts were washed with water, dried and concentrated. Recrystallization from ether-hexane gave 5.7 g. (66%) of IIIj, a colorless crystalline solid, m.p. 114-117°; ir (potassium bromide): 3320 (NH) and 1600 cm^{-1} (C=); nmr (deuteriochloroform): δ 2.3 (3, d, 4-CH_3), 3.3 (3, s, N-CH_3), 3.8 (3, s, O-CH_3), 4.8 (2, s, NH_2) and 6.0 ppm (1, q, 5-CH=).

5-Methylthiazolo[3,2-*b*]-1,2,4-triazole (IId).

Triethyl orthoformate, 75 ml. and I, 15.0 g. (0.116 mole), were heated under reflux for 8 hours forming a black tar. The excess of orthoformate was removed under reduced pressure and the residue was extracted with warm THF. The combined extracts were concentrated and purified by silica chromatography. Sublimation of a yellow product at 80° (0.01 mm) gave 6.5 g. (35.9%) of IId, a light yellow crystalline solid, m.p. 70-71°; mass spectrum: (70 eV) m/e 139 (M^+), 112 (M^+-HCN), 85, 72 (CH_3CHS), 67, 58, 45 (HCS), 32, 28, 15.

2-Amino-5-methylthiazolo[3,2-*b*]-1,2,4-triazole (IIe).

Cyanogen bromide, 39.8 g. (0.375 mole), and I, 47.2 g. (0.366 mole), in 1500 ml. of methanol were refluxed for 4 hours, and concentrated to dryness. The residue crystallized from methanol (charcoal) affording colorless crystals of IIe, 6.1 g. (9.7%), m.p. 192-193°; ir (potassium bromide): 3320, 3210 and 3100 (NH), and 1650 cm^{-1} (NH_2).

2-Acetamido-5-methylthiazolo[3,2-*b*]-1,2,4-triazole (IIf) and 2-Bis-(acetamido)-5-methylthiazolo[3,2-*b*]-1,2,4-triazole (IIg).

Acetic anhydride, 100 ml. and IIe, 3.2 g. (20.8 mmoles), were heated under reflux for 3 hours, the excess of acetic anhydride was removed under reduced pressure, and the residue was triturated with water. Separation of the reaction mixture by silica chromatography gave 3.9 g. (80%) of IIg, a colorless crystalline solid, m.p. 187-189°; ir (potassium bromide): no amide II, 1725 and 1710 (C=O), and 3100 cm^{-1} (CH=).

The second fraction consisted of tan crystals of IIf, 0.6 g. (15%), m.p. 177-179°; ir (potassium bromide): 3100 (NH), 1715 (C=O), and 1515 cm^{-1} (amide II).

5-Methyl-2-(methylthio)thiazolo[3,2-*b*]-1,2,4-triazole (IIh).

A mixture containing 15 g. (0.13 mole) of I, 9.0 g. of potassium hydroxide and 10 ml. of water in 80 ml. of methanol and 85 ml. of carbon disulfide was refluxed (2 hours), cooled and filtered. The resulting yellow solid (12.5 g.) was dissolved in 300 ml. of DMF containing a solution of 2.9 g. (72.5 mmoles) of sodium hydroxide in 10 ml. of water. To this solution was added, at 50°, methyl iodide (35 ml.). After 2 hours at 60°, the reaction mixture was poured in 1000 ml. of water and extracted with ether. The combined ether extracts were concentrated to a yellowish oil that was purified by silica chromatography to give 7.3 g. (54%) of IIh, a colorless crystalline solid, m.p. 48-49°.

REFERENCES AND NOTES

(1) V. W. Dymek, B. Janick, A. Cygankiewicz and H. Gawron, *Acta Pol. Pharm.*, **24**, 97 (1967); *Chem. Abstr.*, **68**, 78208x (1968).

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

(3) R. S. Shadbolt, *J. Chem. Soc. (C)*, 1667 (1971).

(4) S. Kano and T. Noguchi, *Japanese Patent* 71-26,500; *Chem. Abstr.*, **75**, 140863g (1971).

(5) S. Kano, *Yakugaku Zasshi*, **92**, 935 (1972); *Chem. Abstr.*, **77**, 126492v (1972).

(6) J. Hadacek and J. Slotova-Trukova, ex *Chem. Abstr.*, **55**, 25926g (1961).

(7) F. Hervens and H. G. Viehe, *Angew. Chem.*, **85**, 446 (1973); *Angew. Chem Int. Ed. Engl.*, **12**, 405 (1973).

(8) Y. Tamura, H. Hayashi, J. H. Kim and M. Ikeda, *J. Heterocyclic Chem.*, **10**, 947 (1973).

(9) Y. Tamura, H. Hayashi, E. Saeki, J. H. Kim and M. Ikeda, *ibid.*, **11**, 459 (1974).

(10) K. T. Potts, H. R. Burton and J. Bhattacharyya, *J. Org. Chem.*, **31**, 260 (1960).

(11) J. McLean and F. J. Wilson, *J. Chem. Soc.*, 556 (1937); *Chem. Abstr.*, **31**, 4316 (1937).

(12) H. Beyer, W. Lässig and E. Bulka, *Chem. Ber.*, **87**, 1385 (1954).

(13) Cyclization of 2-hydrazinothiazoles with orthoesters is documented for the preparation of thiazolo[2,3-*c*]-*s*-triazoles (see Reference 2).

(14) D. Bertin, J. Perronnet, *French Patent* 1,584,840; *Chem. Abstr.*, **74**, 42183v (1971).