A New Synthesis of 6-Acetylimidazo[2,1-*b*]thiazole Derivatives

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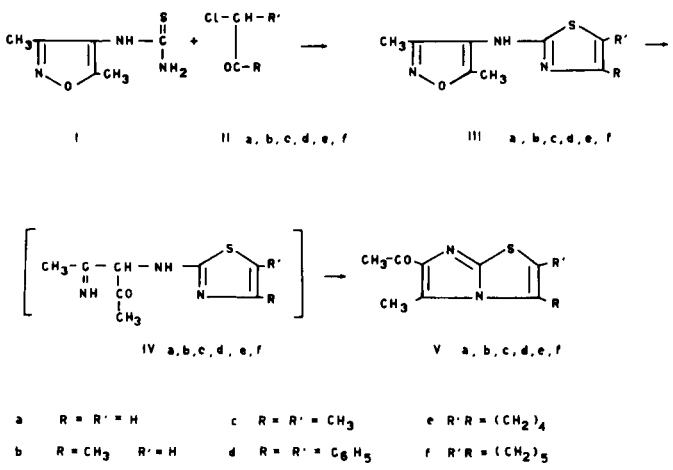
No general route has been reported thus far for the preparation of 6-acetylimidazo[2,1-*b*]thiazoles (V). One route which appeared feasible was a sequence involving the synthesis of the substituted 4-(2-thiazolyl)amino-isoxazoles (III) followed by cyclization of intermediates resulting from isoxazole ring opening by hydrogenolysis.

SCHEME I



The compounds IIIa, b, c, d, e, f were obtained in good yield by the action of α-haloketones on *N*-(3,5-dimethylisoxazol-4-yl)thiourea (I). The intermediates IVa, b, c, d, e, f which were not isolated, readily underwent cyclization by refluxing in acetic acid or ethanol with hydrochloric acid to Va, b, c, d, e, f.

Analytical and spectroscopic data were in agreement with the assigned structures.

Several of the compounds listed in the Tables I and II were tested by Bristol Laboratories, Syracuse, New York. However, none of the compounds showed any biological activity.

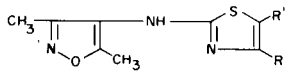
EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected; ultraviolet absorption spectra were measured on a Beckmann DB recording spectrophotometer and ir absorption spectra using nujol mulls with Perkin-Elmer infracord 137; nmr spectra (pyridine-d_5) were determined using TMS as an internal standard with a Jeolco/C-60 H spectrometer.

General Procedure for the Synthesis of Thiazolylaminoisoxazole Derivatives (III).

TABLE I

4-(2-Thiazolylamino)-3,5-dimethylisoxazoles

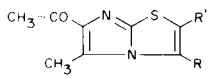


	R	R′	M.p., °C	Recryst. from	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	H	H	204-205	(a)	$C_8H_9N_3OS$ (a)	49.23	4.65	21.53	49.06	4.66	21.40
IIIb	CH_3	H	160-161	(b)	$C_9H_{11}N_3OS$ (b)	51.67	5.30	20.09	51.62	5.26	19.72
IIIc	CH_3	CH_3	171-172	(c)	$C_{10}H_{13}N_3OS$ (c)	53.80	5.87	18.83	53.81	5.78	18.57
IIId	C_6H_5	C_6H_5	254-255	(d)	$C_{20}H_{17}N_3OS$ (d)	69.15	4.93	12.10	69.12	4.94	11.94
IIIe	$(CH_2)_4$		172-173	(e)	$C_{12}H_{15}N_3OS$ (e)	57.82	6.07	16.86	57.52	5.99	16.70
IIIf	$(CH_2)_5$		186-187	(f)	$C_{13}H_{17}N_3OS$ (f)	59.30	6.51	15.96	59.24	6.41	16.24

(a) Ethanol; ir 3160 (NH), 1650 cm^{-1} (C=N). (b) 70% Aqueous ethanol; ir 3160 (NH), 1650 cm^{-1} (C=N). (c) 70% Aqueous ethanol; ir 3170 (NH), 1650 cm^{-1} (C=N). (d) Butanol; ir 3160 (NH), 1650 cm^{-1} (C=N). (e) Dioxane; ir 3160 (NH), 1650 cm^{-1} (C=N). (f) Ethanol; ir 3130 (NH), 1620 cm^{-1} (C=N).

TABLE II

6-Acetylimidazo[2,1-*b*]thiazoles



	R	R'	M.p., °C	Recryst. from	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	H	H	179-180	(a)	$C_8H_8N_2OS$ (a)	53.33	4.48	15.55	53.67	4.49	15.20
Vb	CH_3	H	153-155	(b)	$C_9H_{10}N_2OS$ (b)	55.66	5.19	14.43	55.99	5.27	14.34
Vc	CH_3	CH_3	134-135	(c)	$C_{10}H_{12}N_2OS$ (c)	57.68	5.81	13.46	57.36	6.02	13.45
Vd	C_6H_5	C_6H_5	169-170	(d)	$C_{20}H_{16}N_2OS$ (d)	72.28	4.85	8.43	72.22	4.84	8.41
Ve	$(CH_2)_4$		176-177	(e)	$C_{12}H_{14}N_2OS$ (e)	61.52	6.02	11.96	61.96	5.92	12.08
Vf	$(CH_2)_5$		141-142	(f)	$C_{13}H_{16}N_2OS$ (f)	62.89	6.50	11.28	63.07	6.64	11.18

(a) Ethanol; ir 1680 cm^{-1} (CO); uv λ max nm log ε 245 (4.63); nmr 2.63 δ (3H, s) and 2.73 δ (3H, s) (CH_3 and CH_3-CO), 7.15 δ (1H, d, H at C_2, J = 3.0 Hz), 7.60 δ (1H, d, H at C_3, J = 3.0 Hz). (b) 70% Aqueous ethanol; ir 1680 cm^{-1} (CO); uv λ max nm log ε 245 (4.99); nmr 2.25 δ (3H, d, CH_3 at C_3, J = 1.8 Hz), 2.71 δ (3H, s) and 2.77 δ (3H, s) (CH_3 and CH_3-CO), 6.50 δ (1H, q, H at C_2, J = 1.8 Hz). (c) Methanol; ir 1670 cm^{-1} (CO); uv λ max nm log ε 246 (4.03) 268 sh (3.99); nmr 2.09 δ (3H, s) and 2.13 δ (3H, s) (CH_3 at C_2 and C_3), 2.77 δ (3H, s) and 2.82 δ (3H, s) (CH_3 at C_5 and CH_3-CO). (d) In the first crystallization from ethanol an insoluble product melting at 218-220° was separated in such a low yield that is was neglected; ir 1670 cm^{-1} (CO); uv λ max nm log ε 288 (4.37); nmr 2.20 δ (3H, s) and 2.80 δ (3H, s) (CH_3 and CH_3-CO), 7.00-7.50 δ (10H, a set of signals 2 x C_6H_5). (e) Ethanol; ir 1680 cm^{-1} (CO) uv λ max nm log ε 248 (4.00) 272 sh (3.92); the nmr spectrum in DMSO-d_6 indicated that the two methyl groups are equivalent since there was only a signal at 2.73 (6H); however, addition of a few drops of deuteriochloroform to the solution resulted in two signals separated by 1 cycle, 1.40-2.60 δ (8H, m, $(CH_2)_4$). (f) Methanol; ir 1680 cm^{-1} (CO); uv λ max nm log ε 246 (4.07) 262 sh (3.85); nmr 1.50-2.60 δ (10H, m, $(CH_2)_5$), 2.76 δ (3H, s) and 2.80 δ (3H, s) (CH_3 and CH_3-CO).

To a stirred solution of I (1) (0.02 mole) in water (20 ml.) were added in small portions compounds IIa, b, c, d (2), e (3), f (4), (0.02 mole). The resulting mixture was refluxed for 2 hours. The cold solution was made basic with ammonia and the insoluble material was collected by filtration.

Pure products were obtained after two crystallizations from an appropriate solvent (yields 70-75%). The thiazolylaminoisoxazoles obtained by this procedure are listed in Table I.

General Procedure for Preparation of Imidazothiazole Derivatives (V).

A mixture of 0.02 mole of IIIa, b, c, d, e, f, 170 ml. of ethanol and 4 g. of W_2 Raney-Nickel (5) was hydrogenated in a Parr apparatus at 45-50 psi for 24 hours at room temperature. Removal of the catalyst and evaporation of ethanol left a residue which was refluxed for 2 hours in acetic acid (20 ml.) in the case of IIIa, b, c, e and ethanol (20 ml.) and 12% aqueous hydrochloric acid (3 ml.) in the case of IIId, f. After evaporation under vacuum, the residue was mixed with water (50 ml.) and made basic with ammonia to give the title compounds, yields 60-70% after recrystallization. The imidazothiazole derivatives prepared by this procedure are listed in Table II

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