A New Convenient Synthesis of 5-Amino-1,3-thiazole-4-carboxylic Acids[1]

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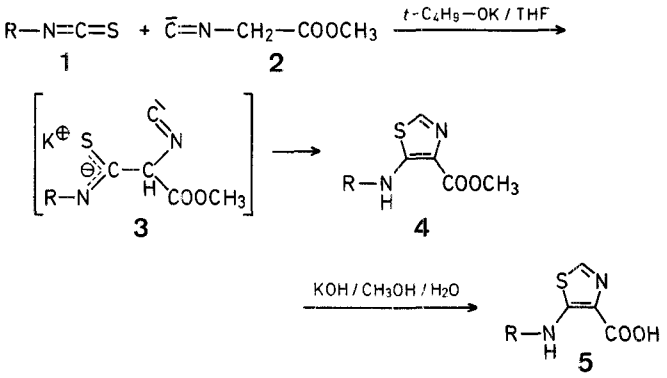
1,3-Thiazole derivatives are of considerable pharmaceutical interest and they are important intermediates for the preparation of a number of drugs. We were interested in synthesizing 5-amino-1,3-thiazole-4-carboxylic acids **(5)** which may be regarded as a structural analog of anthranilic acid. Only a few methods for the synthesis of compounds **5** have hitherto been reported, e.g., the reaction of ethyl aminocyanoacetate with sodium dithioformate[2] or with triethyl orthoformate followed by treatment with hydrogen sulfide[3,4].

In the course of our investigations on the preparative utility of α-isocyanoacetic acid derivatives, we investigated the reaction of methyl isocyanoacetate with isothiocyanates to obtain the title compounds.

The reaction of lithiated ethyl α-isocyanoacetate with isothiocyanates has been reported[5] to yield 5-methoxy-1,3-oxazole-2- or -4-thiocarboxamides, not compounds of the type **5**. Considering[6] the specific properties of isocyano compounds, we expected that the reaction of methyl α-isocyanoacetate **(2)** with isothiocyanates **(1)** would afford the desired 5-amino-1,3-thiazole-4-carboxylic acids **(5)**. In fact, we found that the reaction of methyl α-isocyanoacetate **(2)** with various isothiocyanates **(1)** in tetrahydrofuran in the presence of potassium *t*-butoxide leads to the formation of methyl 5-amino-1,3-thiazole-4-carboxylates **(4)** in good yields; alkaline hydrolysis of compounds **4** then gives the desired acids **5**.



We assume that the reaction proceeds via α-metallation of methyl α-isocyanoacetate **(2)** followed by reaction with the isothiocyanate **(1)** to give the intermediate potassio derivative **3**; the C-atom of the isocyano group of **3** then reacts with the more nucleophilic S-atom[7] in the ambident nucleophilic thiocarboxamide moiety of **3** to give the 1,3-thiazole **5**.

The I.R. and ^{1}H-N.M.R. spectra of compounds **4** and **5** are in agreement with the proposed structures.

Methyl 5-Amino-1,3-thiazole-4-carboxylates (4); General Procedure:
To a vigorously stirred solution of potassium *t*-butoxide (3.93 g, 33 mmol) in tetrahydrofuran (100 ml) is added dropwise methyl α-isocyanoacetate (**2**; 2.97 g, 30 mmol) followed by the isothiocyanate (**1**; 30 mmol). Stirring is continued for 2 h at room temperature and then acetic acid is added to neutralize the mixture. The solvent is removed in vacuo and the residue is extracted with ethyl acetate (2 × 50 ml). The extract is washed with water (20 ml), dried with anhydrous sodium sul-

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Table 1. 5-Amino-1,3-thiazole-4-carboxylic Esters (**4**)

4	R	Yield [%]	m.p. [°C]	Molecular formula[a]	
a	CH_3	65	105–107°	$C_6H_8N_2O_2S$	(172.2)
b	C_2H_5	77	syrup	$C_7H_{10}N_2O_2S$	(240.3)
c	n-C_4H_9	70	syrup	$C_9H_{13}N_2O_2S$	(213.3)
d	c-C_6H_{11}	72	syrup	$C_{11}H_{16}N_2O_2S$	(240.3)
e	C_6H_5—CH_2—	71	85–87°	$C_{12}H_{12}N_2O_2S$	(248.3)
f	C_6H_5	65	136–137°	$C_{11}H_{10}N_2O_2S$	(234.3)
g	4-Cl—C_6H_5—	53	122–123°	$C_{11}H_9N_2O_2ClS$[b]	(268.7)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.27; H, ±0.22; N, ±0.26; S, ±0.22.
[b] Cl: calc. 13.19, found 13.40.

Table 2. 5-Amino-1,3-thiazole-4-carboxylic Acids (**5**)

5	R	Yield [%]	m.p. [°C]	Molecular formula[a]	
c	n-C_4H_9	88	135–136° (dec)	$C_8H_{12}N_2O_2S$	(200.3)
d	c-C_6H_{11}	78	135–136° (dec)	$C_{10}H_{14}N_2O_2S$	(226.3)
e	C_6H_5—CH_2—	86	146–147° (dec)	$C_{11}H_{10}N_2O_2S$	(234.3)
f	C_6H_5	62	164–167° (dec)	$C_{10}H_8N_2O_2S$	(220.3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.08; H, ±0.08; N, ±0.08; S, ±0.26. Exception: **5e**; C, −0.43.

Table 3. Spectral Data of Compounds **4** and **5**

Compound	I.R.[a] ν [cm^{-1}]	^{1}H-N.M.R. (solvent/TMS_{int})[b] δ [ppm]		
		N=CH	NH	OCH_3
4a	3360, 3100, 1665[c]	7.80	7.25	3.90[e]
4b	3320, 3090, 1662[d]	7.82	7.25	3.92[e]
4c	3320, 3090, 1662[d]	7.80	7.30	3.92[e]
4d	3300, 3090, 1660[d]	7.80	7.30	3.92[e]
4e	3350, 3050, 1660[c]	7.80	7.75	3.91[e]
4f	3270, 3100, 1660[c]	7.91	9.70	3.98[e]
4g	3250, 3090, 1662[c]	7.98	9.75	4.03[e]
5c	3320, 3100, 1670[c]	7.98	7.50[f]	
5d	3300, 3100, 1662[c]	8.00	7.42[f]	
5e	3400, 3100, 1700[c]	7.95	8.05[f]	
5f	3120, 3080, 1670[c]	8.25	7.10[f]	

[a] I.R. spectra measured on a Shimadzu IR-27 G infrared spectrometer.
[b] ^{1}H-N.M.R. spectra measured on a Hitachi Perkin-Elmer R-20 A high resolution N.M.R. spectrometer.
[c] In nujol.
[d] Film.
[e] In $CDCl_3$.
[f] In DMSO-d_6.

fate, and concentrated in vacuo. The resultant residue is column-chromatographed on silica gel (120 g) using chloroform as eluent to give the product **4** which is recrystallized from ethyl acetate/diisopropyl ether.

5-Amino-1,3-thiazole-4-carboxylic Acids (5c, d, e); General Procedure:

A mixture of ester **4c, d, e** (8 mmol), 85% potassium hydroxide (1.6 g, 24.2 mmol), methanol (10 ml), and water (5 ml) is stirred for 2 h at 50–60 °C. Then, water (10 ml) is added to the mixture and methanol is removed in vacuo. The residue is acidified with concentrated hydrochloric acid with cooling. The resultant crystals are collected by suction and recrystallized from aqueous ethanol.

5-Anilino-1,3-thiazole-4-carboxylic Acid (5f):

Potassium Salt of **5f**: A mixture of ester **4f** (550 mg, 2.3 mmol), 85% potassium hydroxide (1.0 g, 15.2 mmol), methanol (7 ml), and water (3 ml) is stirred for 3 h at 60 °C. The precipitate is then collected by suction with cooling to give the potassium salt of **5f**; yield: 400 mg; m.p. 250–252 °C (dec).

I.R. (Nujol): ν = 3300, 3070, 1710 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 11.71 (s, 1H, NH); 8.13 (s, 1H, CH); 6.7–7.0 ppm (m, 5H_{arom}).

Free Acid **5f**: The potassium salt (400 mg) is dissolved in acetic acid (10 ml) at 80 °C and water (5 ml) is added to the solution to precipitate colorless prisms of **5f**; yield: 320 mg (62%); m.p. 164–167 °C. M.S.: m/e = 220 (M^+).

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