Preparation of 2-Thiazolecarboxylic Acids

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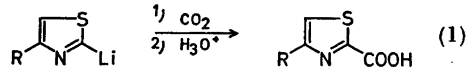
In order to develop earlier work [1] on electrolytic reduction of 2-thiazolecarboxylic acid derivatives into a preparative procedure, an efficient synthesis of the parent acids was needed. Optimum conditions for the synthesis of these compounds in high yields by carbonation of the corresponding lithium derivatives [1,2] are reported here. The reaction is shown in eqn. (1), and as the parent bases or their



(1)

2-bromo derivatives are readily available,[3,4] this seems to be the method of choice, at least with the two examples tried. Experiments have been made with both direct and reverse addition in the carbonation step, and the results are given in Table 1.

Table 1. Yields (%) in carbonation of 2-thiazole lithium on a 0.2 mole scale.

R	Direct addition	Reverse addition
H	94	90
CH_3	79	86

These results indicate that direct addition of solid carbon dioxide into the reaction flask is preferable with the unsubstituted acid, while reverse addition gives a slightly higher yield of the 4-methyl compound. The formation of ketones in the direct carbonation of organolithiums as reported by Gilman and Van Ess [5] has not been observed by the present method.

The essential features of the procedure are: a) short reaction time, b) cold hydrolysis with a minimum volume of water, and c) precipitation of the amino acid with an equivalent amount of conc. hydrochloric acid. The necessary data are known from the usual double titration [6] of the butyllithium solution. Much heat is evolved in the carbonation step and it is not convenient to run the reaction with direct carbonation on more than a 0.2 mole scale; also, more concentrated solutions of the 2-thiazolyllithium compounds usually will give less pure products, but the yield of crude product is about the same. The 2-thiazolecarboxylic acids cannot be stored at room temperature because of the easy decarboxylation.

Experimental. All melting points are uncorrected.

2-Carboxythiazole. 0.21 mole of butyllithium [6] in 350 ml of ether is cooled below −75°, and 32.8 g (0.20 mole) of redistilled 2-bromothiazole [3] in 50 ml of ether are added as quickly as possible keeping the temperature below −70° (approximately 20 min); the red-brown reaction mixture is stirred for a further 15 min in the bath, and a little finely crushed dry-ice is cautiously added with vigorous stirring. A white precipitate is formed at once, the temperature rises rapidly to about −40° (good cooling capacity is indispensable) for a moment, decreases again, and then excess carbon dioxide is rapidly added. The bath is removed and the stirring continued for 1 h; 75 ml of water and 5 ml of conc. hydrochloric acid are cautiously added, the layers separated (filtration unnecessary), and the ether washed with 25 ml of water. The combined aqueous extracts are cooled and the rest of the total base contents of the butyllithium solution is neutralized by the calculated amount of conc. hydrochloric acid with shaking. A thick cream-coloured precipitate of the amino acid is formed and the mixture is left in the refrigerator for some hours. Yield 23.7−24.3 g (92−94%) of dry material; m.p. 100−101° (decomp.); (97−98°),[2] (102).[7] A practically colourless acid is obtained when the 2-thiazolyllithium (light-yellow solution) is made by metalation of thiazole itself or when the halogen-metal exchange is done in very dilute solution. The 2-carboxythiazole may be purified by dissolution in aqueous potassium carbonate, cooling, and reprecipitation with conc. hydrochloric acid to pH 1−2; cool storage is necessary.

4-Methyl-2-carboxythiazole. Starting with 4-methylthiazole,[4] the procedure parallels the above mentioned for the unsubstituted compound except that the solution of 4-methyl-2-thiazolyllithium is carbonated by pouring it

into a slurry of 200–300 g of finely crushed dry-ice in 200–300 ml of ether with vigorous shaking. Yield 24.6 g (86 %) of dry substance, m.p. 110–111° (95–97°) [8] (decomp.), which should be kept in a cool place.

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Small Scale Preparation of ^{131}I Labelled 3,5,3′-Tri-iodo-L-thyronine and L-Thyroxine

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Labelling of 3,5,3′-triiodo-L-thyronine (T_3) with iodine-131 has been described by Gleason,[1] who found that iodine exchanges rapidly with thyroxine as well as with triiodothyronine when the pH conditions are favourable. He also claimed that the exchange reaction is reversible, and that only the prime position, *i.e.* the *ortho* to the hydroxy group, are concerned in the exchange mechanism.

Many investigators have reported methods for the separation of T_3 in the nanogram range from other iodoamino acids and inorganic iodide. Several of these methods have been tried in this laboratory, but they were found less suitable for preparative purposes in a microgram scale.

A simple procedure has now been developed, which is useful for the preparation of 1–2 mCi ^{131}I labelled T_3 with a radiochemical purity of 96–98 % at the time of preparation. The separation is performed on a Sephadex gel column with distilled water as elution medium. Iodide and iodate ions are removed in advance by washing of the dry reaction mixture with water. The eluate from the column containing the purified T_3 is free from chemical impurities excepting traces of ammonia and ethyl alcohol. These two components may easily be removed by gentle evaporation.

The same preparation and purification procedure may be used for the production of around 2 mCi ^{131}I labelled L-thyroxine (T_4), as it is seen from Table 1. Still more

Table 1. Separation pattern from a column of Sephadex gel G-50.

Fraction	T_3 in %	T_4 in %	I^- in %	Activity in mCi
18.5–19.0 ml	82		18	0.20
19.0–19.5 »	97.6		2.4	0.73
19.5–20.0 »	98.0		2.0	0.58
20.0–20.5 »	98.4		1.6	0.64
20.5–21.0 »	99.0		1.0	0.50
21.0–21.5 »	95.0	5.0		0.46
21.5–22.5 »	35.0	65.0		0.14
22.5–23.0 »	6.0	94.0		0.50
23.0–24.0 »	2.6	97.0	0.4	0.84
24.0–25.0 »	1.0	98.0	1.0	0.56

T_4 may be obtained if an excess of I_2 is added to the reaction mixture before purification. In that case the yield of T_3 is of course accordingly less. No further studies of this effect has been performed, however, since the direct labelling of T_4, as pointed out by Gleason,[1] is considered to be more efficient.

The appearance of radioactive contaminants in stored solutions of ^{131}I labelled T_3 and T_4 has been investigated previously,[2-4] and it has been claimed that this phenomenon is mainly due to radiation decomposition.[5] It has further been suggested that the rate of decomposition is dependent on the specific activity and the radioactive concentration of the solution. On the basis of this information a series of