THE SYNTHESIS OF 4-SUBSTITUTED 2-THIOPHENECARBOXYLIC ACIDS*

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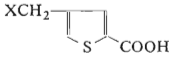
Received December 3rd, 1973

A new method of preparation of 4-methyl-2-thiophenecarboxylic acid (*Ia*) was described, starting with 3-methylthiophene, and of 4-bromomethyl-2-thiophenecarboxylic acid (*Ib*), starting with 2-thiophenealdehyde.

4-Substituted 2-thiophenecarboxylic acids of general formula *I* are relatively difficult to prepare. In connection with other physico-chemical measurements we have now elaborated an advantageous synthesis of substances of general formula *I*.



I

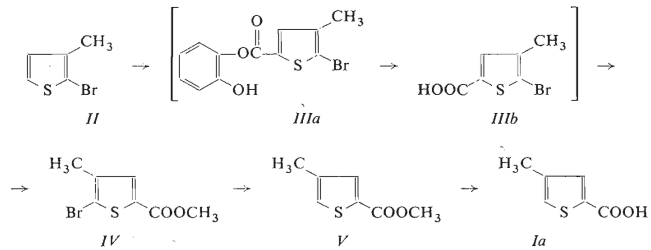
The synthesis of 4-methyl-2-thiophenecarboxylic acid (*Ia*) is described in literature several times[1-4]. The methods based on metalation of 3-methylthiophene do not afford good results. Substitution with lithium of 3-methylthiophene, using alkyllithium[1], and subsequent reaction with carbon dioxide leads to a mixture of 4-methyl-2-thiophenecarboxylic and 3-methyl-2-thiophenecarboxylic acids in a 3 : 1 ratio (see[3,5]). The use of thienylsodium[2,3] enables the preparation of pure acid *Ia* only when the operation is carried out at a low conversion, otherwise the by-product is 3-methyl-2,5-thiophenedicarboxylic acid. Recently a much more tedious synthesis of acid *Ia* has been described, but its total yield is, unfortunately, very low[4].

The synthesis of 4-bromomethyl-2-thiophenecarboxylic acid which we consider as the most suitable starting material for the preparation of other acids *I* has not yet been described in literature. The known ethyl 4-bromomethyl-2-thiophenecarboxylate[4] cannot be converted to free acid *Ib*.

In this paper we describe the preparation of acids *Ia* and *Ib*, which gives high yields. 2-Bromo-3-methylthiophene (*II*) obtained on bromination of 3-methylthiophene in dioxan was used as starting material for the synthesis of acid *Ia*. Carboxylation of compound *II* using pyrocatechol dichloromethylene acetal[6,7] gave 4-methyl-

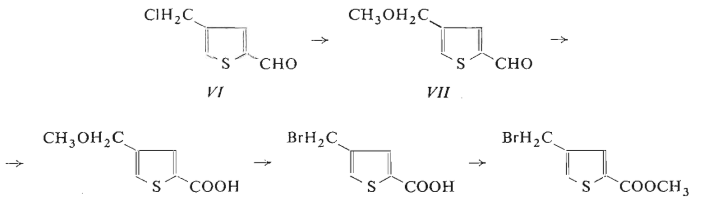
* Part VIII in the series Studies in the Thiophene Series; Part VII: This Journal *39*, 959 (1974).

-5-bromo-2-thiophenecarboxylic acid (*IIIb*) almost quantitatively (Scheme 1). For the esterification of this acid diazomethane was used because other comon esterification methods did not give satisfactory results. The reduction of bromine with zinc dust in acetic acid afforded 4-methyl-2-thiophenecarboxylate in a 90% yield. The total yield referred to 3-methylthiophene is 70% and the chromatographic purity of the product is better than 98·5%.



SCHEME 1

The synthesis of acid *Ib* starts from 2-thiophenealdehyde. 4-Chloromethyl-2-thiophenealdehyde (*VI*) was prepared on chloromethylation of the starting compound with bis(chloromethyl) ether and aluminum chloride in chloroform[8]. Chloromethyl derivative *VI* was converted to methoxy derivative *VII* using sodium methoxide in methanol. Oxidation with silver oxide in water gave acid *VIII*. This acid was submitted to the effect of boron tribromide in dichloromethane, giving rise to 4-bromomethyl-2-thiophenecarboxylic acid (*Ib*) (Scheme 2). An alternative method – radical bromination of tert-butyl 4-methyl-2-thiophenecarboxylate with N-bromosuccinimide and dibenzoyl peroxide, followed by hydrolysis in trifluoroacetic acid – did not afford the required acid *Ib* in spite of the fact that 5-bromomethyl-3-thiophenecarboxylic acid has been prepared in this manner[5].



SCHEME 2

EXPERIMENTAL

The temperature data were not corrected. The NMR spectra were measured on a Varian XL 100—15 (100 MHz) instrument in deuteriochloroform with tetramethylsilane as internal reference. The mass spectra were recorded on a LKB 9000 Gas Chromatograph-Mass Spectrometer (70 eV).

Methyl 5-Bromo-4-methyl-2-thiophenecarboxylate (*IV*)

Anhydrous stannic chloride (44·6 g, 20 ml, 0·17 mol) was added dropwise over 30 minutes to a solution of pyrocatechol dichloromethylene acetal[6] (15 g, 11 ml, 0·076 mol) and 2-bromo-3--methylthiophene[9] (*II*) (13 g, 0·073 mol) in dichloromethane. The mixture was stirred at room temperature for 5 minutes and then refluxed on a water bath for 5 minutes. After pouring on ice and water the crude, precipitated, pyrocatechol monoester *IIIa* was filtered off and the aqueous layer extracted with dichloromethane (2 × 50 ml) and the combined organic extracts were concentrated in a vacuum, obtaining thus a second fraction of *IIIa*. The monoester *IIIa* was hydrolysed by one hour's refluxing with 10% aqueous potassium hydroxide in the presence of a trace of sodium thiosulfate. After filtration with charcoal and acidification with hydrochloric acid 17 g of crude acid *IIIb* were obtained. After esterification with ethereal diazomethane (0·2 mol) the ethereal solution was dried over magnesium sulfate and evaporated to yield 16 g (93%) of ester *IV*. NMR spectrum (δ): 2·20 (s, 3, CH_3), 3·84 (s, 3, OCH_3), 7·44 (s, 1, H-3). For $C_7H_7BrO_2S$ (235·1) calculated: 35·75% C, 3·00% H, 33·98% Br, 13·64% S; found: 35·61% C, 2·84% H, 34·50% Br, 13·76% S.

Methyl 4-Methyl-2-thiophenecarboxylate (*V*)

A solution of ester *IV* (15 g, 0·064 mol) in acetic acid (65 ml) was added dropwise to a well stirred suspension of zinc dust (10 g, 0·15 gat) in water (45 ml) and the mixture was refluxed for 3 hours. A second portion of zinc (3 g) and acetic acid (10 ml) was added and the mixture refluxed for 5 hours and stirred at room temperature overnight and poured into 65 ml of conc. ammonia with ice. After extraction with ether (5 × 50 ml) the organic phases were washed with water and dried over magnesium sulfate. Ether was evaporated and the residue distilled to give 8·9 (90%) of ester *V*, b.p. 100—103°C/15 Torr. NMR spectrum (δ) 2·25 (d, 3, CH_3), 3·86 (s, 3, OCH_3), 7·10 (m, 1, H-3), 7·57 (d, 1, H-5), $J_{3,5} = 1{\cdot}6$ Hz, $J_{3,CH_3} = 1{\cdot}0$ Hz. For $C_7H_8O_2S$ (156·2) calculated: 53·81% C, 5·16% H, 20·52% S; found: 54·00% C, 5·25% H, 20·20% S.

4-Methyl-2-thiophenecarboxylic Acid (*Ia*)

Ester *V* (7·8 g, 0·05 mol) and 100 ml of a 5% potassium hydroxide solution were refluxed for 8 hours, cooled and acidified with hydrochloric acid. Yield 6·7 g (94%) of crystals of acid *Ia*, m.p. 119—121°C (lit.[2] gives 120—121°C). NMR spectrum (δ): 2·30 (s, 3, CH_3), 7·26 (d, 1, H-3), 7·70 (d, 1, H-5), $J_{3,5} = 1{\cdot}5$ Hz. Mass spectrum, *m/e* (% rel. int.): 142 (100), 141 (33), 125 (65), 97 (80), 53 (24), 45 (37).

4-Chloromethyl-2-thiophenealdehyde (*VI*)

2-Thiophenealdehyde[11] (56 g; 0·5 mol) was added dropwise to a stirred suspension of bis(chloromethyl) ether[10] (115 g, 1·0 mol) and aluminum chloride (120 g, 0·9 mol) in chloroform (160 ml) and the mixture refluxed for 5 hours. After pouring on a mixture of ice and water the organic layer was separated and the aqueous layer extracted with chloroform (3 × 50 ml). The combined organic extracts were washed with water and saturated sodium bicarbonate solution, dried over magne-

sium sulfate, and evaporated *in vacuo*. The residue was rectified through a Vigreux column to afford 50·5 g (63%) of aldehyde *VI*, b.p. 85–90°C/0·03 Torr (lit.[8] 90–94°C/0·5 Torr. NMR spectrum (δ): 4·63 (s, 2, CH_2), 7·70 (m, 1, H-3), 7·79 (d, 1, H-5), 9·90 (d, 1, CHO), $J_{3,5}$ = 1·6 Hz.

4-Methoxymethyl-2-thiophenealdehyde (*VII*)

A mixture of aldehyde *VI* (21 g, 0·13 mol) and sodium methoxide (7·1 g, 0·13 mol) in methanol (200 ml) was refluxed for 6 hours, then concentrated under reduced pressure to half its volume, poured into water (400 ml) and extracted with ether (5 × 100 ml). The combined ethereal extracts were dried over magnesium sulfate and evaporated. Distillation of the residue gave 10·1 g (49%), of aldehyde *VII*, b.p. 83–88°C/0·1 Torr. NMR spectrum (δ): 3·40 (s, 3, OCH_3), 4·48 (s, 2, CH_2), 7·65 (m, 1, H-3), 7·75 (d, 1, H-5), 9·90 (s, 1, CHO), $J_{3,5}$ = 1·6 Hz). For $C_7H_8O_2S$ (156·2) calculated: 53·81% C, 5·16% H, 20·52% S; found: 53·48% C, 5·28% H, 20·88% S.

4-Methoxymethyl-2-thiophenecarboxylic Acid (*VIII*)

To a solution of silver nitrate (22 g, 0·13 mol) in 45 ml of water a solution of sodium hydroxide (10·5 g, 0·26 mol) in 45 ml of water was added under occasional stirring. The suspension of silver oxide, cooled to 0°C, was shaken with aldehyde *VII* for 5 minutes. The undissolved material was filtered off and the filtrate acidified with conc. nitric acid. Yield 10·5 g (90.5%) of acid *VIII*, m.p. 90–92°C. NMR spectrum (δ): 3·42 (s, 3, OCH_3), 4·47 (s, 2, CH_2), 7·51 (d, 1, H-3), 7·82 (d, 1, H-5), $J_{3,5}$ = 1·5 Hz. Mass spectrum *m/e* (% rel. int.): 172 (35), 142 (86), 141 (100), 111 (54), 97 (55), 45 (85). For $C_7H_8O_3S$ (172·2) calculated: 48·83% C, 4·68% H, 18·62% S; found: 48·82% C, 4·69% H, 19·07% S.

4-Bromomethyl-2-thiophenecarboxylic Acid (*Ib*)

A solution of boron tribromide (48·6 g, 18 ml, 0·193 mol) in dichloromethane (130 ml) was added to a stirred solution of acid *VIII* (10·0 g, 0·058 mol) in dichloromethane (250 ml) at 0°C. The mixture was allowed to stand at room temperature overnight, poured on ice and water and extracted with ether (2 × 150 ml). The combined extracts were dried over magnesium sulfate and evaporated. Yield 12·0 g (92·5%) of acid *Ib* which was sufficiently pure for further esterification. After sublimation at 130°C and 0·1 Torr, m.p. 172–175°C. NMR spectrum (δ): 4·50 (s, 2, CH_2), 7·58 (d, 1, H-3), 7·89 (d, 1, H-5), $J_{3,5}$ = 1·6 Hz. Mass spectrum, *m/e* (% rel. int.): 222 (4), 220 (4), 141 (100), 97 (10), 45 (25). For $C_6H_5BrO_2S$ (221·1) calculated: 32·60% C, 2·28% H, 14·50% S, 36·14% Br; found: 32·63% C, 2·50% H, 15·31% S, 36·58% Br.

Methyl 4-Bromomethyl-2-thiophenecarboxylate (*IX*)

Crude acid *Ib* (10·0 g, 0·045 mol) was treated with ethereal diazomethane solution (0·1 mol) dried over potassium hydroxide. The ethereal solution was filtered, the filtrate evaporated and the residue weighed. Yield 8·0 g (75%) of ester *IX* (m.p. 65–67°C). NMR spectrum (δ): 3·89 (s, 3, OCH_3), 4·46 (s, 2, CH_2), 7·48 (d, 1, H-3), 7·79 (d, 1, H-5), $J_{3,5}$ = 1·6 Hz. Mass spectrum, *m/e* (% rel. int.): 236 (4), 234 (4), 155 (100), 96 (19), 45 (12).

REFERENCES

1. Gronowitz S.: Arkiv Kemi *7*, 364 (1954).
2. Schick J. W., Hartough H. D.: J. Am. Chem. Soc. *70*, 1645 (1948).

3. Ramanathan V., Levine R.: J. Org. Chem. *27*, 1667 (1962).
4. Gogte V. N., Tilak B. D., Gadekar K. N., Sahasrabudhe M. B.: Tetrahedron *23*, 2443 (1967).
5. Stibor I., Němec M.: Unpublished results.
6. Gross H., Rusche J., Mirsch M.: Chem. Ber. *96*, 1382 (1963).
7. Janda M., Šrogl J., Němec M., Stibor I.: Org. Prep. Proc. Int. *3*, 295 (1971).
8. Belenkij L. I., Karmanova I. B., Goldfarb J. L.: Ž. Org. Chim. *7*, 1743 (1971).
9. Reinecke M. G., Adickes H. W., Pyun C.: J. Org. Chem. *36*, 2690 (1971).
10. Buc S. R.: Org. Syn. Coll. Vol. *4*, 101 (1967).
11. Campaigne E., Archer W. L.: J. Am. Chem. Soc. *75*, 989 (1953).

Translated by Ž. Procházka.