SIMPLE PREPARATION OF METHYL 4-CHLOROMETHYL- AND METHYL 5-CHLOROMETHYL-2-THIOPHENECARBOXYLATE

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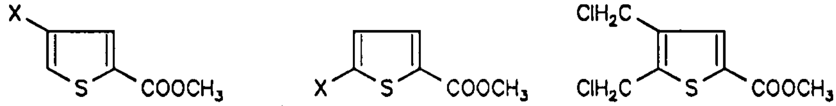
Received July 2, 1991
Accepted January 22, 1992

Selective reduction of a mixture of methyl 4-chloromethyl-2-thiophenecarboxylate (*I*) and the 5-chloromethyl isomer *II*, prepared by chloromethylation of methyl 2-thiophenecarboxylate (*III*), gave pure 4-chloromethyl derivative *I* and 5-methyl-2-thiophenecarboxylate (*V*) which on treatment with sulfuryl chloride was converted into the 5-chloromethyl isomer *II*.

For our synthetic studies in the prostaglandin chemistry[1] we needed greater amounts of methyl 4-chloromethyl-2-thiophenecarboxylate (*I*) and methyl 5-chloromethyl-2-thiophenecarboxylate (*II*). Whereas the 4-chloromethyl derivative *I* has not been described so far and syntheses of 4-(X-substituted methyl) derivatives of 2-thiophenecarboxylic acid (X = OH, CH_3COO, or Br) are rather complicated, usually giving low yields of products[2], some authors[3,4] claim to obtain the pure 5-chloromethyl derivative *II* by chloromethylation of methyl 2-thiophenecarboxylate (*III*). Such statements are at variance with investigations of the Japanese authors[5,6] who after chloromethylation of ester *III* isolated a mixture of 4-chloromethyl and 5-chloromethyl derivatives (*I* and *II*, respectively) and a small amount of methyl 4,5-bis(chloromethyl)-2-thiophenecarboxylate (*IV*) and identified the compounds by ^{1}H NMR. This finding is in accord[7] with the course of electrophilic reactions on the thiophene nucleus in derivatives substituted in position 2 by electron-accepting substituents (CN, CHO, $COCH_3$, COOH). A similar mixture of products was obtained by Gogte and collaborators[8] in chloromethylation of ethyl 2-thiophenecarboxylate: they did not succeed in isolation (by distillation, crystallization or chromatography) of the individual regioisomers even after conversion into the corresponding acetoxymethyl, hydroxymethyl, or formyl derivatives.

In the present paper we describe a simple method of separating a mixture of 4-chloromethyl and 5-chloromethyl derivatives *I* and *II*, obtained by chloromethylation of ester *III*, based on the different reactivity of their chloromethyl groups. Chloromethylation of ester *III* according to ref.[2] afforded a mixture containing compounds *I*, *II*, *III*, and *IV*. On fractionation of this mixture we obtained the starting ester *III* (28 – 30%), a 1 : 2 mixture of esters *I* and *II* (about 48%) and the bis-derivative *IV* (5%). The ratio of the isomers *I* and *II* was determined by ^1H NMR spectroscopy according to a described procedure[6]. To influence favourably the formation of the 5-chloromethyl derivative *II*, we performed a series of experiments under



I, X = CH_2Cl *II*, X = CH_2Cl *IV*
VI, X = CH_3 *III*, X = H
V, X = CH_3

various reaction conditions. We proved that with increasing amount of paraformaldehyde the amount of the bis-derivative in the reaction mixture increases. On the other hand, the ratio of *I* to *II* is not affected by a temperature change in the range –15 °C to 60 °C (see Table I). Subsequent treatment of the mixture of chloro derivatives *I* and *II* with zinc powder in acetic acid at room temperature resulted in preferential reduction of the chlorine atom in the 5-chloromethyl derivative *II* whereas the 4-chloromethyl isomer *I* did not react. Fractional distillation of the reaction mixture gave then pure methyl 5-methyl-2-thiophenecarboxylate (*V*) and the chloro derivative *I* in good yields. With increasing temperature the selectivity of the reduction decreased and performing the reduction at reflux we identified and isolated a mixture of methyl derivatives *V* and *VI*. Treatment of the ester *I* with zinc in boiling acetic acid afforded pure methyl 4-methyl-2-thiophenecarboxylate (*VI*) in almost quantitative yield. The desired methyl 5-chloromethyl-2-thiophenecarboxylate (*II*) was prepared in good yield

TABLE I
Chloromethylation of methyl 2-thiophenecarboxylate *III* (Procedure *A*)

Reaction temperature, °C	Yield		Ratio *I* : *II*
	I + *II*	*IV*	
–25 to –35	0	0	–
–15 to –10	17	~0.5	1 : 1.6
0 to 5	42	1.5	1 : 1.7
15 to 20	44	3	1 : 2.2
25 to 30	48	5	1 : 2.0
50 to 60	55	6	1 : 2.0

from the ester *V* by reaction with sulfuryl chloride in the presence of a catalytic amount of α,α′-azoisobutyronitrile.

EXPERIMENTAL

The temperature data are uncorrected. The melting points were determined on a Boetius block (Zeiss, Jena). ^{1}H NMR spectra were measured on a Bruker AM 400 instrument in deuteriochloroform with tetramethylsilane as internal standard, chemical shifts are given in ppm (δ-scale). IR spectra were taken on a Perkin–Elmer 325 spectrometer in chloroform (wavenumbers in cm^{-1}).

Chloromethylation of Methyl 2-Thiophenecarboxylate (*III*)

Procedure A. Dry hydrogen chloride was introduced for 5 h at room temperature into a vigorously stirred mixture of ester *III* (64 g, 0.45 mol), paraformaldehyde (13.5 g, 0.45 mol), fused zinc chloride (9.0 g, 0.066 mol) and dry 1,2-dichloroethane (270 ml). After treatment with a water–ice mixture (200 ml), the organic phase was separated and the aqueous one was extracted with dichloroethane (2 × 20 ml). The combined organic portions were successively washed with water (30 ml), saturated sodium chloride solution (30 ml), and water (30 ml). After drying over magnesium sulfate, the solvent was evaporated under diminished pressure. Fractionation of the residue (65.9 g) afforded 18.2 g (28%) of the starting ester *III*, 41.1 g (48%) of a mixture of chloromethyl derivatives *I* and *II*, b.p. 102 – 112 °C / 270 Pa (reported[5] 100 – 120 °C / 330 – 400 Pa) and 5.6 g (5%) of bis-derivative *IV*, b.p. 135 – 142 °C / 75 Pa which solidified on cooling and melted at 71 – 73 °C (reported[5] m.p. 77 – 78 °C).

Procedure B. A mixture of ester *III* (14.2 g, 0.1 mol), paraformaldehyde (6.0 g, 0.2 mol), zinc chloride (4.1 g, 0.03 mol) and 1,2-dichloroethane (60 ml) was treated as described under *A* and afforded 2.15 g (15%) of the starting ester *III*, 10.9 g (57%) of a mixture of monochloromethyl derivatives *I* and *II*, and 3.7 g (15%) of bis-derivative *IV*.

Reduction of Mixture of Chloro Derivatives *I* and *II*

Procedure A. A mixture of chloro derivatives *I* and *II* (1 : 2.4; 52.0 g, 0.27 mol), zinc powder (17.6 g, 0.24 mol) and acetic acid (190 ml) was stirred at room temperature for 24 h. The undissolved material was filtered off and washed with chloroform (100 ml). The clear filtrate was diluted with ice-cold water (500 ml) and neutralized with sodium hydrogen carbonate. After separation of the organic phase the aqueous layer was extracted with chloroform (3 × 100 ml) and the combined organic portions were successively washed with saturated sodium chloride solution (100 ml), saturated solution of sodium hydrogen carbonate (100 ml), and water (100 ml). After drying over magnesium sulfate, the solvents were evaporated under diminished pressure and the residue (40.2 g) was fractionated to give 25.9 g (61%) of methyl derivative *V* and 12.1 g (23%) of 4-chloromethyl derivative *I*.

Methyl 5-methyl-2-thiophenecarboxylate (V), b.p. 125 – 128 °C / 2.4 kPa (reported[9] b.p. 107 – 108 °C / 2.4 kPa). ^{1}H NMR spectrum: 2.53 s, 3 H (CH_3); 3.83 s, 3 H (OCH_3); 6.75 d, 1 H (H-4); 7.6 m, 1 H (H-5, J = 3.7). IR spectrum: 3 020 m, 2 960 m, 1 705 s, 1 470 s, 1 260 s.

Methyl 4-chloromethyl-2-thiophenecarboxylate (I), b.p. 98 – 101 °C / 270 Pa. For $C_7H_7ClO_2S$ (190.5) calculated: 44.09% C, 3.67% H, 18.64% Cl, 16.80% S; found: 44.25% C, 3.98% H, 18.90% Cl, 16.82% S. ^{1}H NMR spectrum: 3.86 s, 3 H (OCH_3); 4.55 s, 2 H (CH_2Cl); 7.49 m, 1 H (H-3); 7.76 d, 1 H (H-5, J = 1.5). IR spectrum: 3 020 m, 2 970 m, 1 715 s, 1 450 s, 1 265 s, 730 s.

Procedure B. A mixture of chloromethyl derivatives *I* and *II* (2.6 g, 13.6 mmol; ratio 1 : 1.4), zinc powder (0.89 g, 13.6 mmol) and acetic acid (10 ml) was refluxed under vigorous stirring. The reaction mixture was worked up as described under *A*, yielding 1.6 g (75%) of a 1.2 : 1 mixture of methyl derivatives *V* and *VI*, m.p. 105 – 112 °C / 2.2 kPa.

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

A stirred mixture of chloro derivative *I* (0.4 g, 2.1 mmol), zinc powder (0.17 g, 2.1 mmol) and acetic acid (3 ml) was boiled for 4 h. The usual work-up procedure gave 245 mg (82%) of ester *VI* boiling at bath temperature 102 – 105 °C and 2 kPa (reported[2] b.p. 100 – 103 °C / 2 kPa). ^{1}H NMR spectrum: 2.25 s, 3 H (CH_3); 3.86 s, 3 H (OCH_3); 7.23 m, 1 H (H-3); 7.60 d, 1 H (H-5, J = 1.5).

Methyl 5-Chloromethyl-2-thiophenecarboxylate (*II*)

A solution of ester *V* (35.5 g, 0.23 mmol), sulfuryl chloride (25.6 g, 0.19 mol), α,α'-azoisobutyronitrile (63 mg, 0.38 mmol) in benzene (430 ml) was heated under nitrogen for 1 h. Another portion of α,α'-azoisobutyronitrile (60 mg) was then added and the heating was continued. Further two 60 mg portions of the mentioned catalyst were added at 1.5 h intervals. The reaction mixture was cooled, washed with water (2 × 100 ml), saturated sodium hydrogen carbonate solution (100 ml) and water (50 ml) and dried over magnesium sulfate. After evaporation of the solvents under diminished pressure the residue (39.4 g) was distilled to give 22.2 g (62%) of the starting ester *V* and 14.9 g (34%) of the 5-chloromethyl ester *II*, b.p. 94 – 96 °C / 65 Pa (reported[3,4] b.p. 93 °C / 27 Pa and 103 °C / 66 Pa, respectively). ^{1}H NMR spectrum: 3.89 s, 3 H (OCH_3); 4.76 s, 2 H (CH_2Cl); 7.06 m, 1 H (H-4); 7.64 d, 1 H (H-3, J = 3.8). IR spectrum: 3 010 m, 2 960 m, 1 720 s, 1 470 s, 1 260 s, 760 s.

The authors are indebted to the Analytical Department of the Central Laboratories of the Institute (Dr L. Helešic, Head) for performing the elemental analyses and to the NMR Department of the same Institute (Dr R. Hrabal, Head) for measurements of the NMR spectra.

REFERENCES

1. Kozmík V., Dědek V., Paleček J., Kubelka V., Mostecký J., Veselý I., Žák B.: Czech. 253 326 (1989).
2. Němec M., Janda M., Šrogl J., Stibor I.: Collect. Czech. Chem. Commun. *39*, 3527 (1974) and references therein.
3. Lukeš R., Janda M., Kefurt K.: Collect. Czech. Chem. Commun. *25*, 1058 (1960).
4. Dvořák F.: Tech. Publ. Stredisko, Tech. Inform. Potravinar. Prumyslu No 161, 56 (1959 – 61) (Publ. 1962); Chem. Abstr. *60*, 5434a (1964).
5. Sone Ch.: Nippon Kagaku Zasshi *86*, 1331 (1965); Chem. Abstr. *65*, 13637d (1966).
6. Sone T., Takahashi K.: Org. Magn. Reson. *3*, 527 (1971).
7. Gronowitz S.: *Advances in Heterocyclic Chemistry* (A. R. Katritzky, Ed.), Vol. 1, p. 52. Academic Press, New York 1963.
8. Gogte V. N., Tilak B. D., Gadekar K. N., Sahasrabudhe M. B.: Tetrahedron *23*, 2443 (1967).
9. Janda M.: Collect. Czech. Chem. Commun. *26*, 1889 (1961)

Translated by M. Tichý.