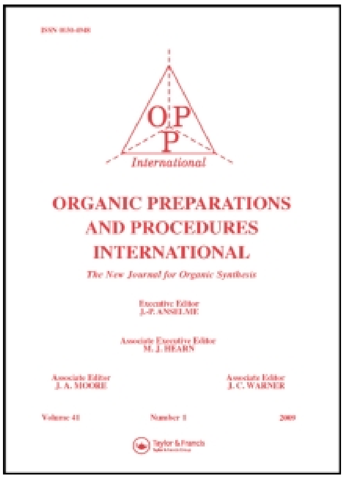

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Corral, C. , Lissavetzky, J. , Alvarez-Insúa, A. S. and Valdeolmillos, A. M.(1985) 'SYNTHESIS OF 3-MERCAPTOTHIOPHENE-2-AND 4-CARBOXYLIC ACIDS', Organic Preparations and Procedures International, 17: 3, 163 — 167

To link to this Article: DOI: 10.1080/00304948509355493

URL: http://dx.doi.org/10.1080/00304948509355493

ORGANIC PREPARATIONS AND PROCEDURES INT. 17(3), 163-167 (1985)

SYNTHESIS OF 3-MERCAPTOTHIOPHENE-2- AND 4-CARBOXYLIC ACIDS

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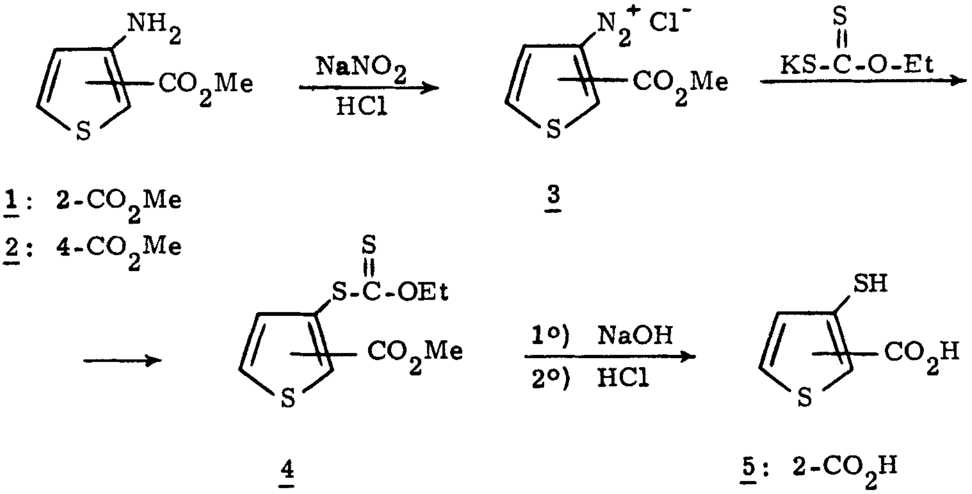
A recent paper[1] described the synthesis of 3-mercaptothiophene-2-carboxylic acid (5) by the Newman Karnes phenol-thiophenol conversion applied to 3-hydroxy-2-methoxycarbonylthiophene. However, 3-mercaptothiophene-4-carboxylic acid (6), could not be synthesized by the same procedure, because the starting material, 3-hydroxy-4-methoxycarbonylthiophene is extremely labile to bases.[2]

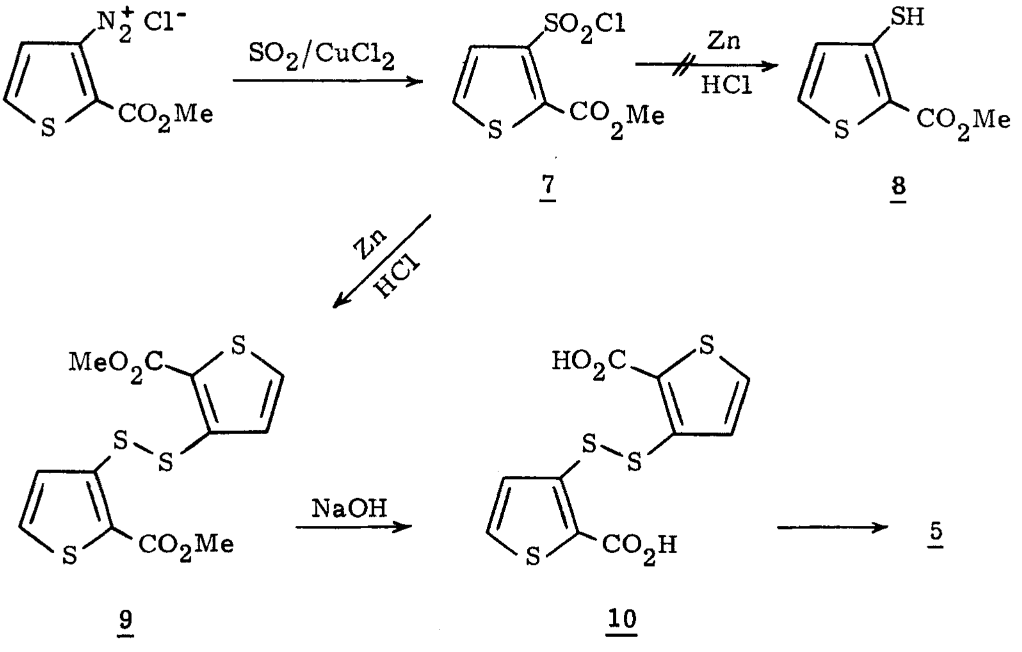
We report here the first synthesis of compound 6 and an improved preparation of compound 5 from the corresponding 3-amino-2 or 4-methoxycarbonylthiophenes (1,2). The method (Scheme 1) is based on the



Scheme 1

facile conversion of the 3-aminothiophene derivatives 1 and 2 into stable diazonium salts 3 which upon treatment with potassium ethyl xanthate gave 4. These compounds were not isolated but were hydrolyzed with alkali, to 5 (96% yield) and 6 (65% yield) respectively.

Another method attempted (Scheme 2) for the synthesis of 5 gave poorer yields of this compound. The diazonium salt of 3-amino-2-methoxycarbonylthiophene was converted to the chlorosulfonyl derivative 7 by the Meerwein reaction. Compound 7 however, upon reduction gave the



Scheme 2

disulfide 9 instead of the mercaptan 8. The structural assignment for 9 was based on the IR (absence of SH group) and mass spectrum which showed a molecular ion at 346 m/e. This behaviour parallels that observed by Paulmier[3] in the synthesis of 3-mercapto-2-acetylthiophene. Compound 9 could be hydrolyzed to the diacid 10 which was reduced to 5 with zinc and hydrochloric acid, in a low overall yield.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-GMG mass spectrometer. IR spectra were recorded on a Perkin-Elmer 257 spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM 390 90 MHz spectrometer, with TMS as internal standard.

3-Mercaptothiophene-2-carboxylic acid (5).- 3-Amino-2-methoxycarbonylthiophene[4] (2.5 g, 16 mmol) was added gradually to a vigorously stirred 6M hydrochloric acid solution (12 ml). The reaction mixture was stirred at room temperature for 30 min. It was then cooled below 0° (ice-salt bath), it was diazotised with $NaNO_2$ (1.1 g, 16 mmol) in H_2O (8 ml) and the resulting diazonium salt was stirred another hour at this temperature and then added slowly onto a well-stirred solution of Na_2CO_3 (2.2 g, 19 mmol) and potassium ethyl xanthate (2.55 g, 16 mmol) in H_2O (25 ml) and heated at 60°. The temperature of the mixture was maintained at 60-70° until the evolution of nitrogen has ceased (about 1 hr.). After cooling, the mixture was extracted with ether (4x30 ml). The ethereal extract was washed with 10% NaOH solution (20 ml) and H_2O (2x20 ml), dried over $MgSO_4$ and evaporated to dryness.

To a solution of the resulting reddish oil in EtOH (15 ml) was added a solution of 4H NaOH (125 ml) and the mixture was refluxed for 4 hrs. After cooling, the solvent was removed, H_2O (25 ml) was added and this solution was extracted with ether (2x10 ml). The aqueous layer was acidified with 15% HCl to yield 2.4 g (96%) of a colourless solid, mp. 152-153° (dec.) (water).

Mass spectrum: m/e = 160 (M^+). IR (nujol): 3200-2500 (OH); 2550 (SH); 1650 cm^{-1} (C=O). ^{1}H-NMR (DMSO-d_6): δ 1.15 (s, 1H, SH); 6.27 (s, 1H, COOH); 7.20 (d, 1H, J ≃ 5 Hz, thiophene 4-H); 7.95 ppm (d, 1H, J ≃ 5 Hz, thiophene 5-H).

Anal. Calcd. for $C_5H_4O_2S_2$: C, 37.50; H, 2.50; S, 40.00
Found: C, 37.71; H, 2.43; S, 39.87

3-Mercaptothiophene-4-carboxylic acid (6). - This compound, mp. 215-216° (dec.) (acetic acid), was obtained in a similar way as described for compound 5 starting from 3-amino-4-methoxycarbonylthiophene,[5] in a 65% yield.

Mass spectrum: m/e = 160 (M^+). IR (nujol): 3300-2500 (OH); 2600 (SH); 1675 cm^{-1} (C=O). ^1H-NMR (DMSO-d_6): δ 2.10 (s, 1H, SH); 3.90 (s, 1H, COOH); 7.40 (d, 1H, J ≃ 3 Hz, thiophene 5-H); 8.40 ppm (d, 1H, J ≃ 3 Hz, thiophene 2-H).

Anal. Calcd. for $C_5H_4O_2S_2$: C, 37.50; H, 2.50; S, 40.00
Found: C, 37.43; H, 2.48; S, 40.21

3-Chlorosulfonyl-2-methoxycarbonylthiophene (7). - The diazonium salt of 3-amino-2-methoxycarbonylthiophene (16 mmol) obtained as described previously was added to a freshly prepared solution obtained by addition of $CuCl_2$ (0.95 g) in H_2O (0.95 ml) to SO_2 (34.19 g) in AcOH. The resulting reaction mixture was poured onto ice-water (65-80 ml) and the solid so formed was collected washed with H_2O, dried and crystallized from n-hexane to yield 1.58 g (41%) of a colourless solid, mp. 63-64°.

IR (nujol): 1730 (C=O); 1375, 1200 cm^{-1} (SO_2). ^1H-NMR (DMSO-d_6): δ 4.10 (s, 3H, CH_3); 7.35 (d, 1H, J ≃ 5 Hz, thiophene 4-H); 7.75 (d, 1H, J ≃ 5 Hz, thiophene-5H).

Anal. Calcd. for $C_6H_5ClO_4S_2$: C, 29.94; H, 2.09; S, 13.32
Found: C, 29.83; H, 2.03; S, 12.89

Bis-[2-methoxycarbonyl-3-thienyl]-disulfide (9). - Compound 7 (4.0 g, 17 mmol) was added to a vigorously stirred solution of concentrated HCl (5.1 ml) in ice. Zinc dust (5.2 g, 80 mmol) was then added in portions; the temperature was maintained between 10-15°. The reaction mixture was stirred at room temperature for 4 hrs. and then extracted with ether (2x20 ml) to yield 3.23 g (56%) of a colourless solid, mp. 169-171° (ethanol), by evaporation of the ethereal extracts.

Mass spectrum: m/e = 346 (M^+). IR (nujol): 1700 cm^{-1} (C=O). ^1H-NMR (DMSO-d_6): δ 3.95 (s, 3H, CH_3); 7.40 (d, 1H, J ≃ 5 Hz, thiophene

4-H); 7.55 (d, 1H, J≃ 5Hz, thiophene 5-H).

Anal. Calcd. for $C_{12}H_{10}O_4S_4$: C, 41.60; H, 2.91; S, 37.01
Found: C, 41.62; H, 2.89; S, 37.04

Bis-[2-carboxy-3-thienyl]-disulfide (10). - A suspension of compound 9 (0.56 g, 1.6 mmol) in 2N NaOH (4.85 ml) was heated at reflux for 1 hr. After cooling, the reaction mixture was acidified (to pH 1) with 15% HCl to yield 0.46 g (90%) of a colourless solid, mp. 240-241° (ether-n-hexane).

Mass spectrum: m/e = 318 (M^+). IR (nujol): 3100-2500 (OH); 1655 cm^{-1} (C=O). ^{1}H-NMR (DMSO-d_6): 3.60 (s, 1H, COOH), 7.20 (d, 1H, J≃ 5Hz, thiophene 4-H); 7.80 (d, 1H, J≃ 5Hz, thiophene 5-H).

Anal. Calcd. for $C_{10}H_6O_4S_4$: C, 37.72; H, 1.90; S, 40.28
Found: C, 37.47; H, 2.15; S, 39.99

3-Mercaptothiophene-2-carboxylic acid (5) from Compound 10. - Zinc dust (1.8 g, 28 mmol) was added gradually to a well-stirred mixture of diacid 10 (1.5 g, 4.7 mmol), concentrated HCl (1.6 ml) and H_2O (1.6 ml). The reaction mixture was refluxed for 4 hrs., the hot solution was filtered rapidly and compound 5 (0.9 g, 60%) crystallized from the filtrate.

Acknowledgment. - We are indebted to our Department of Analysis and Instrumental Techniques for all the analytical and spectroscopic data.

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(Received November 26, 1984; in revised form February 12, 1985)