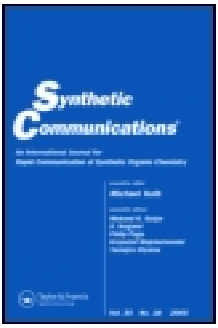

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An Easy Synthesis of 3-Amino- and 3-Nitrothiophene

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AN EASY SYNTHESIS OF 3-AMINO- AND 3-NITROTHIOPHENE

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3-Amino- and 3-nitrothiophene are readily made by the decarboxylation of the corresponding thiophene-2-carboxylic acids which are easily prepared from the commercially available methyl 3-aminothiophene-2-carboxylate.

3-Nitrothiophene is usually made by the nitration and desulfonation of 2-thiophenesulfonyl chloride[1] although other procedures have been developed[2]. We have found that methyl 3-nitrothiophene-2-carboxylate can be made from the commercially available methyl 3-aminothiophene-2-carboxylate by diazotisation and treatment with nitrite in the usual way. Previous preparations of this ester have either produced it as a minor byproduct or in very poor yield[3]. The ester cannot be

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*To whom correspondence should be addressed hydrolysed in the normal manner by heating with aqueous sodium hydroxide since this treatment totally destroys it. It is, however, possible to carry out hydrolysis using either the acid hydrolysis procedure of Loev[4] (82% crude yield) or, preferably, aqueous methanolic potassium hydrogen carbonate. Decarboxylation of the resulting acid gives 3-nitrothiophene in good yield. This procedure has the advantage that no separation of isomers is necessary at any stage.

3-Aminothiophene has been made by reduction of 3-nitrothiophene[5] and by the reaction of 3-bromothiophene with potassamide in liquid ammonia[6] as well as by the Hofmann reaction[7]. We have applied the elegant decarboxylation method used by Gewald[8] (for the decarboxylation of 2-aminothiophenecarboxylic acids) to 3-aminothiophene-2-carboxylic acid. This procedure leads to a crystalline oxalate of 3-aminothiophene which appears to be indefinitely stable, unlike the free base which gradually undergoes oligomerisation on storage[7].

Experimental

Methyl 3-nitrothiophene-2-carboxylate. Methyl 3-aminothiophene-2-carboxylate (15.7g) was suspended in concentrated hydrochloric acid (26 ml) and the suspension was diluted with water (24 ml) and warmed until most of the solid had dissolved. The liquid was then cooled to 0 - 5°C whilst a solution of sodium nitrite (7.2g) in water (16 ml) was added during *ca* 20 min with magnetic stirring. The mixture was stirred for a further 10 min at *ca* 4°C before the addition of a solution of sodium fluoborate (16 g) in water (32 ml). The thick precipitate was filtered off after standing for a further 10 min in the cold. The solid was washed with 5% aqueous sodium fluoborate solution (10 ml), ethanol (2 x 10 ml) and ether (3 x 20 ml). The beige solid was dried in a vacuum desiccator; it weighed 20.86 g (82%) and had mp 156 -157°C (if the material is to be used at once the drying stage is not necessary). The diazonium fluoborate was suspended in water (80 ml) and added portionwise during *ca* 30 min (too rapid an addition rate results in significant reduction to methyl thiophene-2-carboxylate) to a vigorously mechanically stirred mixture of copper bronze (16 g), sodium nitrite (80 g) and water (160 ml). The mixture was stirred for a further 15 min before the addition of dichloromethane and filtration through kieselguhr. The filter pad was washed with dichloromethane and the lower layer of the filtrate was separated. The aqueous layer was extracted with the same solvent (3 x) and the organic layers were combined, dried ($MgSO_4$), stirred with charcoal for 15min, filtered and evaporated to give a dark brown solid (13.49 g, 72%) mp 51.5-52.5°C (lit.[3a], 50-51°C). If required this solid may be purified by bulb distillation, bp 150°C/ 0.5 mm.

3-Nitrothiophene-2-carboxylic acid. The nitro ester (2 g), potassium hydrogen carbonate (1.4 g), methanol (20 ml) and water (4 ml) were stirred and heated under reflux and the reaction was followed by tlc ($SiO_2/CHCl_3$). After 1 hour all the ester had gone and the solvents were removed on the rotary evaporator. The residue was dissolved in the minimum amount of water and acidified with concentrated hydrochloric acid. The precipitated solid was extracted with ether (3x) and the combined ether layers were washed with water (2x), saturated brine (1x), dried ($MgSO_4$), filtered and evaporated to give a pale yellow solid (1.55g, 84%) mp 133-135°C (lit.[8] mp 137°C).

3-Nitrothiophene. The acid (1.55 g) was dissolved in quinoline (20 ml) and copper(1) oxide (1.5 g) was added. The mixture was heated at 100-110°C in an oil bath for 1 hour. The cooled reaction mixture was poured into 4M hydrochloric acid (100 ml) and stirred for 10 min. The filtrate obtained after passage of the mixture through kieselguhr was extracted with ether (3x) and the combined ether layers were washed with 4M hydrochloric acid (3x), water (2x), saturated brine (1x), dried ($MgSO_4$), filtered and evaporated to give an orange/brown solid (1.16 g) . Recrystallisation from ethanol (charcoal) afforded a pale brown solid (0.87g, 75%, mp 76-77°C). Lit.[2a] mp 73-74°C.

3-Aminothiophene. Methyl 3-aminothiophene-2-carboxylate (6.4 g) was refluxed with 2M sodium hydroxide solution (40 ml) for 30 min.

The solution was then cooled, acidified to Congo Red with concentrated hydrochloric acid and the thick precipitate was filtered off. It was pressed as dry as possible under a rubber dam before being dissolved in acetone (50 ml). The solution was dried ($MgSO_4$), filtered and evaporated at 20°C (the acid decomposes quite rapidly, especially on warming, so it must be used at once). The resulting thick paste (it is not necessary to remove all traces of acetone for the next step) was treated with 1-propanol (12 ml) and anhydrous oxalic acid (4 g) at 38°C for 45 min. The mixture was cooled, diluted with ether and the solid was filtered off and washed with ether. The resulting white crystalline solid weighed 5.64 g and became pale lilac on exposure to light and air. The solid, which has no definite melting point, is made into the free base when required as follows. The salt (1g) was dissolved in water (20 ml) and basified with concentrated ammonia. The mixture was extracted with dichloromethane (3 x 10 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to give a brown oil with an aniline-like odour (0.47 g; δ_H ($CDCl_3$, 270 MHz) 3.56 (br s, 2H, NH_2) 6.07 (dd, 1H, J = 1.65, 2.97 Hz, H2) 6.56 (dd, 1H, J = 1.65, 4.95 Hz, H4) 7.06 (dd, 1H, J = 3.3, 4.95 Hz, H5) δ_C ($CDCl_3$, 67.8 MHz) 99.96 (C2) 121.13 (C4) 125.19 (C5) 145.17 (C3)). On this basis the yield of crude free base (substantially pure by pmr) is about 60%.

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