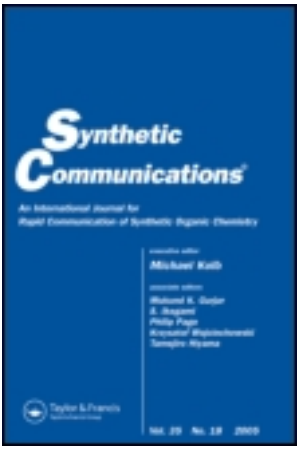

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A SHORT, PRACTICAL SYNTHESIS OF 3-THIOPHENECARBOXALDEHYDE

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ABSTRACT

The compound 3-thiophenecarboxaldehyde (**2**) was prepared in multi-kilogram quantities by a novel two-step process involving the condensation of acrolein with 1,4-dithiane-2,5-diol, followed by sulfuryl chloride-mediated oxidation.

During development of a process for the synthesis of an HIV protease inhibitor, we required large amounts of the deceptively simple-looking material 3-thiophenecarboxaldehyde (**2**). The commercial cost of **2** was prohibitive, and, unfortunately, in our hands none of the published procedures[1–8] (cf. Scheme 1) were suitable for large-scale preparation of material. The first synthesis of note[1,2] employs the relatively inexpensive 3-methylthiophene (**1**) and produces the aldehyde in a modest 38% yield. We were dissuaded from using this process because of (1) the use of CCl_4 as solvent; (2) some capricious results on scale-up; and (3) safety concerns surrounding the radical peroxide reaction. An alternative approach[3–6] begins with thiophene and produces the 3-thiophenecarboxaldehyde after four steps in 38% yield. This route was unattractive, both because of the number of steps, as well as

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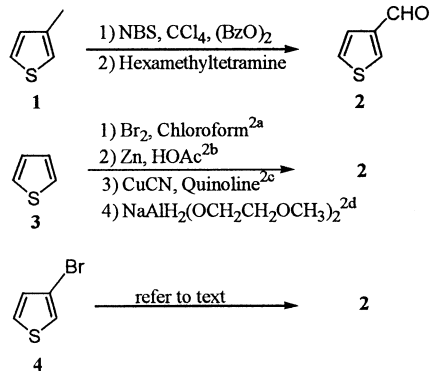
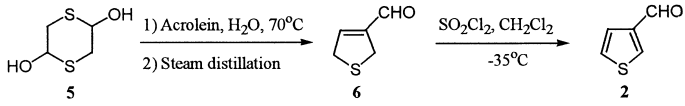


Scheme 1.

the cost of the final material produced. We also examined approaches that rely on metal-bromine exchange of 3-bromothiophene (**4**), which is a relatively costly material, followed by quenching with an appropriate electrophile such as triethylorthoformate[7] or DMF.[8] We found that, even at low temperatures (−78°C), some migration of the anion to the more stable C-2 position occurred, and that this produced hard-to-remove impurities in the product. At warmer temperatures, the C-2 aldehyde became the sole product.

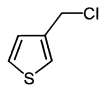
Our synthesis (cf. Scheme 2) involves very inexpensive reagents and has been demonstrated to be reliable at the multi-kilogram scale. The initial step is a modification of an abandoned European patent[9] and involves the condensation of thioacetaldehyde (sold commercially as the dimer, 1,4-dithiane-2,5-diol, **5**) with acrolein. The crystalline dihydrothiophene product **6** can be steam-distilled from the reaction solution. The product is crystallized from the aqueous distillate and further MTBE extractions are performed on the mother liquors in order to maximize yield.



Scheme 2.

After attempting a number of more common aromatization techniques, we found that using a slight excess of sulfuryl chloride[10] afforded the highest yield of material and was also the most economical choice (cf. Scheme 2). We found that running the oxidation reaction at

temperatures warmer than −30°C produced two minor chlorinated by-products (determined to be **7** and **8**). Cooling to −35°C was sufficient to fully suppress their formation. We also found that if the dihydro-thiophene intermediate **6** was not fully dried prior to aromatization, then the stable hydrate **9** was formed to a corresponding degree in the subsequent reaction.



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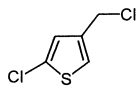

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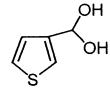

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Aqueous work-up of the final material resulted in substantial loss of product, even when highly concentrated aqueous salt solutions were used. However, our anhydrous triethylamine quench, as detailed in the experimental section, served to remove the hydrochloric acid that was generated and afforded a 92% recovered yield of high quality material.

EXPERIMENTAL

2,5-Dihydrothiophene-3-carboxaldehyde (6)

To a suspension of 1,4-dithiane-2,5-diol (1250 g, 8.21 mol) in water (2.5 L) was added acrolein (1088 g, 19.4 mol) over a period of 30 min while maintaining a temperature of approximately 70°C. The reaction was heated at 70°−80°C for 1 h. The reaction mixture was steam distilled[11] (while collecting the distillate in a flask cooled by a dry ice/isopropanol bath) until the reaction flask solution became clear. The product crystals, which formed in the distillate, were collected by filtration. The aqueous liquors were extracted with 1 L of *tert*-butyl methylether. The organic layer was concentrated and the material was combined with the previously obtained crystals to afford 1.2 Kg (64%) of 99% pure material.[12] The material was dried in vacuo at 30°C; m.p. 45°−46°C (lit. m.p. 41°−43°C);[9] ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.8 (1H, s), 6.9 (1H, s), 4.0 (2H, m), 3.9 (2H, m).

3-Thiophenecarboxaldehyde (2)

A solution of 2,5-dihydrothiophene-3-carboxaldehyde (20 g, 0.25 mol) in methylene chloride (160 mL) was cooled to −35°C. To this was added a solution of sulfuryl chloride (34.75 g, 0.258 mol) in methylene chloride

(40 mL) over a period of 45 min, maintaining the temperature between −35° and −30°C. After the addition was complete, the reaction was stirred for 30 min. To the solution was added triethylamine (52.6 g, 0.520 mol), maintaining the temperature at less than −20°C. The resulting slurry was transferred to a flask containing hexanes (300 mL). The triethylamine salts were removed by filtration and the filtrate was concentrated under vacuum to afford 17.4 g (92% yield) of a 97% pure[12] oil. ^{1}H NMR[13] (200 MHz,$CDCl_3$) δ 9.9(s, 1H), 8.1 (dd, 1H, J = 1,3 Hz), 7.5 (dd, 1H, J = 1,4 Hz), 7.4 (dd, 1H, J = 3,4 Hz); ^{13}C NMR[13] (100 MHz, $CDC1_3$) δ 185.0, 136.5, 143.1, 125.7, 127.4.

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11. Distillation time was about 5 h. The process was greatly expedited through use of a steam trap that "dries" the steam prior to addition to the flask; this prevents the flask from filling with water and removes particulates from the steam line.
12. The compounds were analyzed by GC using a DB-5 30 m column; 50°C for 5 min, then 10°C per minute to 250°C. Retention times are 8.5 min for thiophene **2**, 11.02 min for dihydrothiophene **6**, 9.5 min for chloride **7**, and 12.2 min for dichlorinated thiophene **8**.
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