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A CONVENIENT SYNTHESIS OF 3-FLUOROTHIOPHENE

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ABSTRACT : 2-bromo-3-chlorothiophene **2** underwent nucleophilic aromatic substitution using cyanocupper to give 2-cyano-3-chlorothiophene **3** which, after fluoration with CsF, hydrolysis and decarboxylation gave 3-fluorothiophene **6** in good yield. The electropolymerisation of **6** is also described.

Synthesis of 3-substituted thiophenes had received increasing interest last few years due to the numerous potential applications of substituted poly(thiophenes) as organic conductors[1]. Particularly, the polymerisation of 3-methylthiophene gave rise to a high conductive and stable material, if compared to other poly(3-alkylthiophenes). Therefore,

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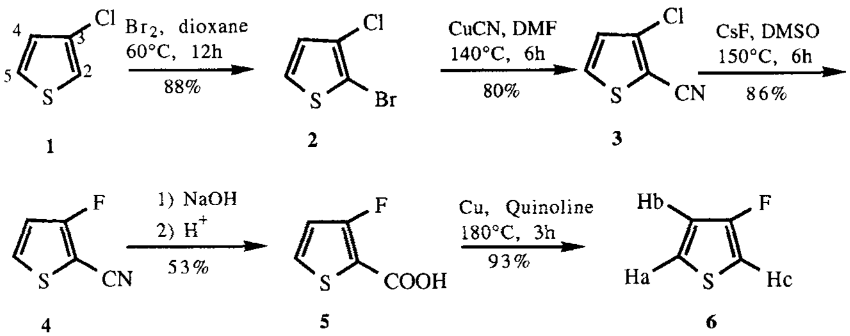

The reported yields are GC yields

Figure 1 : Synthesis of 3-fluorothiophene

3-fluorothiophene has a potential interest due to the small steric hindrance of the fluorine atom. Nevertheless, the poly(3-fluorothiophene) has never been reported so far, because the monomer is not easily accessible. In the literature, very few examples of monofluoration of the thiophene ring has been published. Thus, Gronowitz[2] has obtained the 3-fluorothiophene from 3-bromothiophene with a good chemical yield (77%), but he did not reported the yield of isolated pure product, purified by preparative gas chromatography. Moreover, in this method the fluorinating agent is the perchloryl fluoride, which is dangerous to handle and then cannot be used in preparative scale. 2-fluorothiophene from 2-iodothiophene[3] was also described, using antimony trifluoride but with a 10% yield. Recently[4], a japanese patent revendicated the synthesis and polymerisation of poly(3-fluorothiophene) but without further experimental details.

We report here a convenient preparation of gram amount of the title compound by cesium fluoride mediated fluoration of 2-cyano-3-chlorothiophene **3** (figure 1).

This last compound was obtained by nucleophilic aromatic substitution on 2-bromo-3-chlorothiophene **2** with cupper cyanide in DMF at 140°C (GC yield 80%) , with 3-chlorothiophene as a side product, due to trace amount of water. The cyano group was selectively introduced at the 2-position, as no 2-bromo-3-cyanothiophene was detected. Treatment of compound **3** with excess of cesium fluoride in DMSO gave 2-cyano-3-fluorothiophene **4** in good yield (GC yield 86%) which was hydrolyzed by sodium hydroxide into 2-carboxy-3-fluorothiophene **5**. The hydrolysis in acidic medium was less selective and led to only 20% of the desired compound **5**. This one was decarboxylated following the method of Nishimura[5], with cupper in quinoline at 180°C for 3h to give 93% of the title compound **6**. 60% of 3-fluorothiophene of adequate purity for polymerisation (99%) were easily obtained by distillation from the solvant.

The polymerisation of the 3-fluorothiophene was performed electrochemically in nitrobenzene using NBu_4PF_6 (0.1M) as electrolyte and a current density of $1.8 mA.cm^{-2}$. A free standing film exhibiting a conductivity of $10 S.cm^{-1}$ and a doping level value of 14.5% was obtained. Further studies are in progress in our laboratory to determine the characteristics of this new material and to compare it with other poly(halogeno-thiophenes).

2-bromo-3-chlorothiophene 2

To a solution of 3-chlorothiophene **1** (125g, 1.05mol) in dioxane (300ml) bromine (183g, 1.14mol) was added dropwise at 0°C and the mixture was heated at 60°C for 12h. The solution was washed with water saturated with $NaHCO_3$ (3x100ml) and the organic layer dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting crude product was purified by distillation to give **2** as an oil in 88% yield.

bp : 194°C/760mm Hg, 47°C/0.1mm Hg[6]; ^1H NMR ($CDCl_3$, TMS) δ 7.22 (d, J=5.8 Hz, Ha), 6.85 (d, J=5.7 Hz, Hb); ^{13}C NMR ($CDCl_3$, TMS) δ 127.57 C5, 127.09 C3, 125.88 C4, 108.50 C2. Structure confirmed by comparison with commercial product.

2-cyano-3-chlorothiophene 3

To a solution of **2** (131.5g, 666mmol) in anhydrous dimethylformamide (230ml) stirred under argon was added dried cupper cyanide (71.5g, 799mmol). The mixture was refluxed for 5h, then cooled at 100°C and poored into a solution of $FeCl_3.6H_2O$ (275g) in water (360ml) and HCl (10N, 82ml). After 20mn heating at 60°C, the reaction medium ,was cooled and extracted with CH_2Cl_2 (6x250ml). The organic layer was washed with HCl 6N (2x250ml), water (2x300ml) and water saturated with $NaHCO_3$ (150ml), and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was chromatographed on a column of silica gel (eluent : CH_2Cl_2/heptane : 1/1) to give **3** as a solid in 51% yield.

mp = 62°C; ^1H NMR ($CDCl_3$, TMS) δ 7.59 (d, J=5.3 Hz, Ha), 7.06 (d, J=5.4, Hb); ^{13}C NMR ($CDCl_3$, TMS) δ 136.18 C3, 132.60 C5, 128.28 C4, 112.00 CN, 105.97 C2; LRMS (m/z, relative intensity) 143 (100, M^+), 145 (37), 108 (9), 45 (14); HRMS calculated for C_5H_2ClNS 142.9596 found 142.9595; Anal. calculated for C_5H_2ClNS:

C 41.81; H 1.39; N 9.75; S 22.29; Cl 24.7. Found: C 41.96; H 1.38; N 9.60; S 21.90; Cl 24.6.

2-cyano-3-fluorothiophene 4

A solution of **3**, first dried by lyophilization (22g, 153mmol) in which is added dried cesium fluoride (65g, 428mmol) in anhydrous DMSO (108ml) was refluxed for 5h. After cooling, the reaction medium was diluted in CH_2Cl_2 (250ml), carbon black was added and the mixture was stirred for 10min and filtered. The liquid phase was washed with water (4x200ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and a mixture of **4** and 2-cyanothiophene (9/1) was obtained (57% yield of crude product). It was not possible to separate them, even by distillation.

^{1}H NMR ($CDCl_3$, TMS) δ 7.55 (dd, J_{ab}=5.6 Hz, J_{aF}=3.9 Hz, Ha), 6.92 (dd, J_{bF}=0.6, J_{ab}=5.6 Hz, Hb); ^{13}C NMR ($CDCl_3$, TMS) δ 163.87 (J=277.2 Hz, C3), 132.18 (J=9.0 Hz, C5), 117.32 (J=22.3 Hz, C4), 110.69 (J=2.7 Hz, CN), 91.27 (J=15.7 Hz, C2); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -113.90 (J_{bF}=3.9 Hz); LRMS (m/z, relative intensity) 127 (100, M^+), 100 (17), 82 (29), 70 (70), 57 (71), 45 (61); HRMS calculated for C_5H_2FNS: 126.9892, found: 126.9891.

2-carboxy-3-fluorothiophene 5

4 (4g, 31.5mmol) was added to a solution of NaOH (2.54g, 63mmol) in water (35ml) and refluxed 11h. The reaction medium was extracted with ether (2x15ml). The aqueous phase was cooled and HCl 10N (10ml) was added dropwise. The resulting aqueous phase was reextracted with ether (5x20ml). The combinated organic layers were dried ($MgSO_4$) and after removal of the solvent, the crude product **5** was purified by crystallization in water (yield 53%).

mp=158°C; ^1H NMR ($CDCl_3$, TMS) δ 7.85 (dd, $\underline{J}_{ab}$=5.5 Hz, $\underline{J}_{aF}$=4.2 Hz, Ha), 7.12 (dd, $\underline{J}_{ba}$=5.6 Hz, Hb); ^{13}C NMR ($CDCl_3$, TMS) δ 161.94 (<u>COOH</u>), 158.96 ($\underline{J}$=245.7 Hz, C3), 131.43 ($\underline{J}$=10.5 Hz, C5), 118.81 ($\underline{J}$=22.5 Hz, C4), 113.41 ($\underline{J}$=10.3 Hz, C2); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -115.98 ($\underline{J}_{bF}$=4.1 Hz); LRMS (m/z, relative intensity) 146 (100, M^+), 129 (98), 111 (19), 101 (10), 57 (32); HRMS calculated for $C_5H_3O_2SF$: 145.98378, found 145.98383. Anal. Calculated for $C_5H_3O_2SF$: C 41.09; H 2.05; S 21.91; found: C 41.10; H 2.12; S 21.68.

3-fluorothiophene 6

A solution of **5** (3.6g, 16.1mmol) in quinoline (15ml) was refluxed for 3h. The crude product was purified by distillation of the solvent (**6** : yield 60%).

bp : 85°C, 760mmHg; ^1H NMR ($CDCl_3$, TMS) δ 7.15 (ddd, $\underline{J}_{ab}$=5.4 Hz, $\underline{J}_{ac}$=3.4 Hz, $\underline{J}_{aF}$=3.4 Hz, Ha), 6.85 (ddd, $\underline{J}_{ba}$=5.5 Hz, $\underline{J}_{bc}$=1.1 Hz, $\underline{J}_{bF}$=2.4 Hz, Hb), 6.70 (ddd, $\underline{J}_{ca}$=3.4 Hz, $\underline{J}_{cb}$=1.1 Hz, $\underline{J}_{cF}$=2.4 Hz, Hc); ^{13}C NMR ($CDCl_3$, TMS) δ 158.5 ($\underline{J}$=257.5 Hz, C3), 124.81 ($\underline{J}$=9.2 Hz, C5), 117.25 ($\underline{J}$=26.9 Hz, C4), 103.16 ($\underline{J}$=21.1 Hz, C2); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -131.06 ($\underline{J}_{bF}$=3.2 Hz); LRMS (m/z, relative intensity) 102 (100, M^+); HRMS calculated for C_4H_3SF 101.9939, found: 101.9940.

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