Synthesis of 3-(polyfluoroalkyl) thiophenes

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Abstract

Synthese of new thiophenes having various perfluorinated alkyl groups attached via alkyl spacers to the 3-position are described. These compounds are potential monomers for the electrosynthesis of new organic conductors.

Introduction

Interest in the synthesis of 3-substituted thiophenes has increased recently since the electrosynthesis of 3-substituted polythiophenes has shown industrial potential [1]. Thus, taking into account the application of fluorinated polymers as materials in electronics [2], it is not surprising that publications concerning the synthesis of thiophenes having fluorinated substituents have started to appear.

Cowell and Tamborsky [3] have described the copyrolysis of thiophene and perfluoroalkyl iodides as a method of obtaining a mixture of 2- and 3-perfluoroalkyl thiophenes and Wakselman *et al.* used Ullmann-type reactions between 3-iodothiophene and perfluoroalkyl iodides with copper [4]. Although Wakselman's method exhibited a much higher selectivity for the synthesis of 3-substituted products, the formation as major or by-product amounts in these two methods of 2-substituted thiophenes decreases their practical interest: 2-substituted thiophenes are difficult to separate from 3-substituted isomers and are known to have a negative effect on the polymerization and on the properties of the resulting polymers [5]. More recently, Yoshida *et al.* [6] proposed the use of trimethylsilyl substituents as protective groups for the 2,5-positions of the thiophene ring. This strategy permits the preparation of a desired pure 3-perfluoroalkyl thiophene, but unfortunately a low yield make the synthesis unattractive on a preparative scale.

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Thus, development of new, efficient and selective methods of synthesis of monomers is required for the evaluation of the effect of fluorinated substituents on the properties of poly(thiophene). In addition, the introduction of fluorinated substituents may have a dramatic influence on the physical properties of thiophene monomers, particularly on both oxidation potentials and solubilities. Study of the effect of polyfluorinated groups required the synthesis and the evaluation of monomers **1** having a methylene spacer between the thiophene ring and the electron-withdrawing fluorinated moiety [7]. Here we describe the synthesis of monomers **1** having a methylene spaces of length *n*, where n = 0–3, and perfluoroalkyl chains of different lengths (*m* = 3–5) (Scheme 1); 3-(difluoromethyl) thiophene (**2**) has also been prepared by fluorinating thiophene-3-carboxaldehyde with diethylaminosulfur trifluoride (DAST) [8], the fluorinating agent used by Middleton to convert benzaldehyde to difluoromethylbenzene [9].

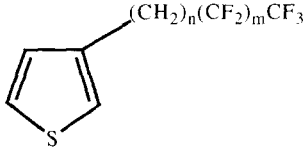
Contrary to the results described by Kitazume and Ishikawa [10] in the benzenic series, the use of perfluorinated zinc reagents in the presence of a transition metal catalyst and/or ultrasound does not produce a coupling reaction with 3-bromo- or 3-iodo-thiophene.

Discussion

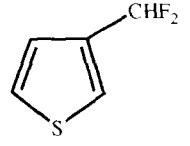
Synthesis of 3-polyfluoroalkylated thiophenes (1) where n = *1*

The introduction of a perfluorinated chain can be performed via the reaction of perfluorinated zinc compounds with thiophene-3-carboxaldehyde, in a Barbier [11] procedure, as previously described for benzaldehyde [12] (Scheme 2). Activation of zinc appears to be the main factor controlling the reaction and trimethylsilyl chloride in pyridine is the best activating system (Table 1).

Attempts to hydrogenate the carbinol **3**, obtained with molecular hydrogen or a metallic hydride in the presence of a catalyst and under various conditions, were unsuccessful. However, the desired product was synthesized by the formation of the chloro derivative and then the use of $LiAlH_4$ in the presence of palladium dichloride (Scheme 2). Conditions which avoid the formation of the olefinic compound **5** were shown to be the use of a large excess of palladium chloride at low temperature. Nevertheless, the required monomer **6** exhibited low stability and gave rise to the elimination product **5** (mixture of *E* and *Z* isomers) at room temperature in polar solvents.

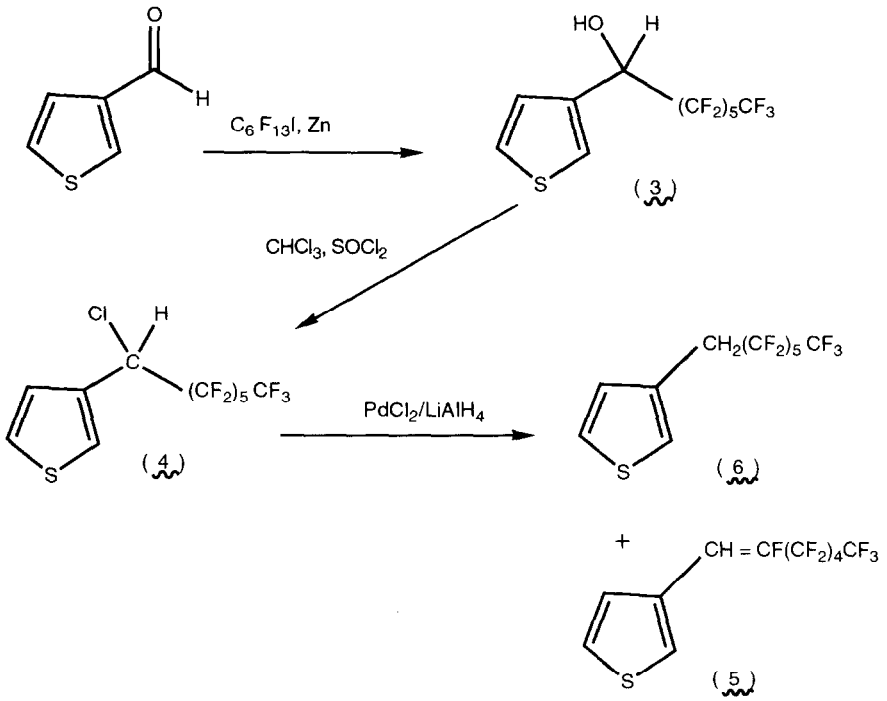


(1)



(2)

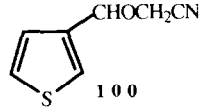
Scheme 1. Thiophenes substituted by 3-polyfluoroalkyl groups.



Scheme 2.

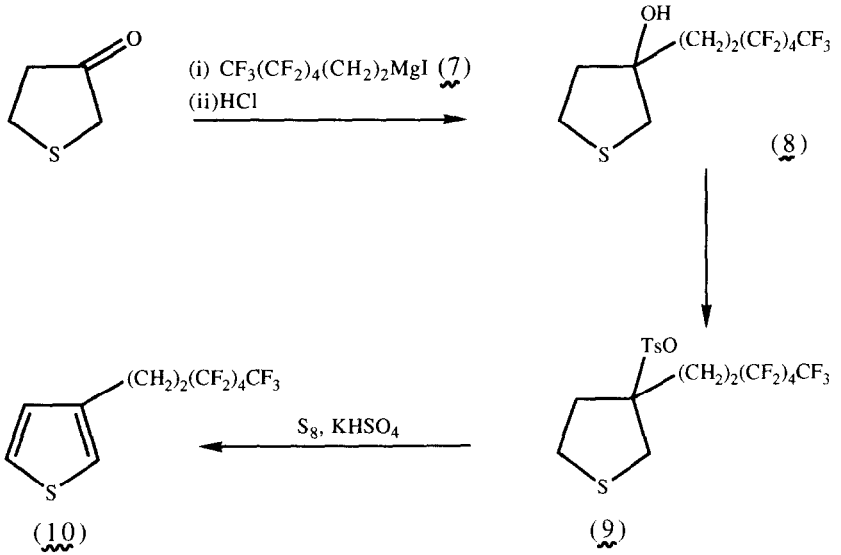
TABLE 1

Activation of zinc in the Barbier reaction

Reaction	Solvent	Activating agent	Product/yield (%)
1	dimethylformamide	ultrasound	0
2	dimethylformamide	$(CH_3)_3SiCl$	decomposition and by-products
3	acetonitrile	$(CH_3)_3SiCl$	 100
4	pyridine	none	(3) 10
5	pyridine	$(CH_3)_3SiCl$	(3) 40

Synthesis of 3-polyfluoroalkylated thiophenes (1) where n = 2

Grignard cross-coupling reactions are widely used to synthesize 3-alkyl thiophenes [13], but proved inefficient when using perfluorinated Grignard reagents. The use of more stable Grignard reagents such as **7** [14] permitted the synthesis of the desired product via reaction with the appropriate tetrahydrothiophenone (Scheme 3).



Scheme 3.

Aromatization of the product **8** can be performed by adaptation of a method proposed by Kagan *et al.* [15], via the tosyl derivative **9**. Product **10** was obtained in a relatively good overall yield (50%) and was found to be much more stable than **6**.

Synthesis of 3-polyfluoroalkylated thiophenes (1) where n=*3*

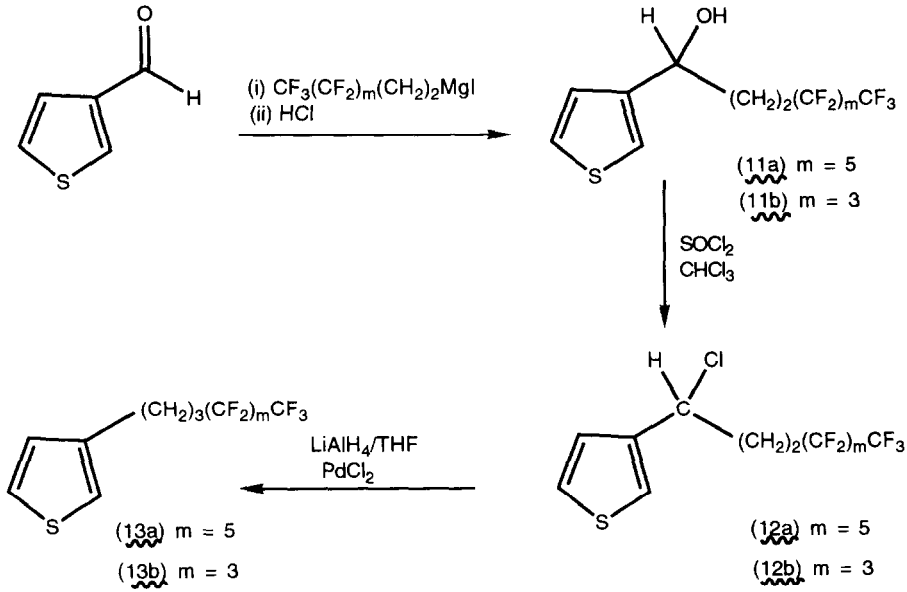
The stability of Grignard reagents such as **7** was also the key to the synthesis of thiophenes having a trimethylene spacer between the thiophene nucleus and the perfluorinated group. Combination of the strategies exemplified in Schemes 2 and 3 permitted the synthesis of the desired products in a three-step route (Scheme 4) with relatively good overall yields (40–45%).

The product with a perfluorohexyl group (**13a**) exhibited low solubility [16] in the polar solvents used during electropolymerization; thus, the product having a perfluorobutyl group (**13b**) and with a much higher solubility in nitrobenzene and acetonitrile was synthesized.

For reasons of cost, the final reduction was studied in some detail and $NiCl_2$ was found to be an efficient catalyst while copper and various homogeneous catalysts were unsuitable (Table 2).

Experimental

^1H NMR spectra were obtained on a Perkin-Elmer R32 spectrometer (90 MHz) or a Bruker AC 200 spectrometer (200 MHz) using $CDCl_3$ as the



Scheme 4.

TABLE 2

Effect of catalyst on the reduction of the chloro derivative **12b**

Entries	Catalyst	Cat./**12b** (mol/mol)	**13b** (% yield)
1	none		0
2	$PdCl_2$	0.2	90
3	$PdCl_2$	2	98
4	Dppp–$PdCl_2$	0.2	0
5	Dppp–$NiCl_2$	0.2	0
6	$CuCl_2$	0.2	0
7	$NiCl_2$	0.2	90
8	$NiCl_2$	1	95

[a]Dppp = 1,3-bis(diphenylphosphino)propane.

solvent and TMS as the internal standard. ^{19}F NMR spectra were obtained with a WP80 (75.4 MHz) Bruker instrument using $CFCl_3$ as the internal standard. Chemical shifts quoted are in ppm (− for deshielded). IR spectroscopy was performed on a Perkin-Elmer 457 spectrometer. Distillation pressures are given in mmHg, i.e. E_{25} = boiling point under 25 mmHg pressure.

3-Difluoromethyl thiophene (2)

Freshly distilled thiophene-3-carboxaldehyde (Janssen Chemica) (2.24 g, 20 mmol) was added to 10 ml CH_2Cl_2, followed by 2.7 ml (20 mmol) of a solution of DAST (Aldrich). The solution was reacted for 3 h at room

temperature and then washed with water. The organic layer was dried and distilled at atmospheric pressure. The crude product was purified by distillation under reduced pressure. Isolated yield, 30%; E_{25}, 65 °C. ^{1}H NMR δ: 6.1–6.7 (1H, dd); 7.3–7.6 (3H, m) ppm.

Activation of zinc

Zinc (Janssen) (2 g, 30 mmol) was added to 20 ml dried THF under an argon atmosphere. Trimethysilyl chloride (Janssen) (0.2 ml) in 2 ml THF was then slowly added at room temperature. The zinc was filtered under argon and dried under vacuum.

*3-(1-Hydroxy-1-hydro-tridecafluoroheptyl) thiophene (**3**)*

Activated zinc (2 g, 30 mmol) was added to a solution of 2.26 g (20 mmol) of freshly distilled thiophene-3-carboxaldehyde. To this suspension, 9.4 g (21 mmol) of perfluorohexyl iodide (Aldrich) was added under an argon atmosphere. The suspension was reacted for 15 h at room temperature, filtered and precipitated in 40 ml of 1 N HCl at 0 °C. The suspension was then extracted three times with 50 ml diethyl ether. The organic layers were washed with sodium monosulfite and then with water, dried and evaporated under vacuum. The crude product was distilled under vacuum. Isolated yield 37%; $E_{0.5}$, 130 °C; m.p., 50 °C. ^{1}H NMR δ: 2.9 (1H, m); 5.32 (1H, dd); 7.15 (3H, m) ppm. IR (neat) cm^{-1}: 3350 (OH); 1230–1350 (C–F).

*3-(1-Chloro-1-hydro-tridecafluoroheptyl) thiophene (**4**)*

Thionyl chloride (Aldrich) (2 ml, 27 mmol) was added to a solution of 4.3 g (10 mmol) of alcohol **3** in 5 ml chloroform. The solution was refluxed for 1 h and evaporated under vacuum. The colourless oil was washed with chloroform/water until neutral. The resulting oil was used in the next step without further purification. Crude yield, 95%. ^{1}H NMR δ: 5.44 (1H, t); 7.35 (3H, m) ppm.

*3-(1-Dihydro-tridecafluoroheptyl) thiophene (**6**)*

$LiAlH_4$ (0.4 g) was added to a suspension of 3 g of dried $PdCl_2$ and 4.5 g (10 mmol) of **4** in 10 ml THF at −15 °C under an argon atmosphere. The suspension was allowed to react for 1 h at 20 °C and was then quenched with ethyl acetate and water. The suspension was filtered and the filtrate washed with water. The organic layer was then dried and evaporated. The crude product was purified by distillation under vacuum. Isolated yield, 73%; E_{18}, 170 °C. ^{1}H NMR δ: 3.43 (2H, t); 7.3 (3H, m) ppm.

*3-(1,2-Tetrahydro-undecafluoroheptyl)-3-hydroxy-tetrahydrothiophene (**8**)*

The required fluorinated Grignard reagent [14] (20 mmol in 30 ml diethyl ether) was added to a solution of 2.2 g (21.6 mmol) of tetrahydrothio-

phen-3-one (Aldrich) in 10 ml diethyl ether. The solution was warmed to reflux for 2 h and then poured on to ice. The organic layer was washed with 1 N HCl and then with water. After evaporation of the solvent, the crude product was purified by distillation under vacuum. Isolated yield, 39%; $E_{0.2}$, 150 °C; m.p., 50 °C. ^{1}H NMR δ: 2.0 (8H, m); 2.85 (3H, m) ppm. IR (KBr) cm^{-1}: 3420 (OH); 1240–1160 (C–F).

*3-(1,2-Tetrahydro-undecafluoro)-3-toluenesulfonyl tetrahydrothiophene (**9**)*

Tosyl chloride (Janssen) (1.2 g) was added to a solution of 2.5 g of **8** in 1.6 g (20 mmol) of pyridine and 50 mg of dimethyl aminopyridine (Janssen). The solution was reacted for 17 h at room temperature and poured on to ice. The precipitate was filtered and washed with 1 N HCl and then with water. The crude product was dried under vacuum and used for the next step without further purification.

*3-(1,2-tetrahydro-undecafluoroheptyl) thiophene (**10**)*

Compound **9** (1.5 g, 2.48 mmol), 3.4 g (2.48 mmol) of $KHSO_4$ and 1.2 g of sulphur were heated to 210 °C under argon for 20 min. The crude mixture was distilled under vacuum (18 mmHg). The liquid obtained was purified by flash chromatography (SiO_2/pentane). Isolated yield, 70%; E_{20}, 170 °C. ^{1}H NMR δ: 2.45 (2H, m); 2.97 (2H, m); 7.0 (2H, m); 7.3 (1H, dd) ppm. ^{19}F NMR δ: −80 (3F, t); −113 (2F, m); −121 (6F, m); −124.6 (2H, m) ppm. n_D^{22}, 1.373.

*3-(1-Hydroxyl-1,2,3-pentahydro-fluoroalkyl) thiophenes (**11a**, **11b**)*

Fluorinated Grignard [14] reagent (25 mmol) in 30 ml diethyl ether was added to a solution of 2.9 g of thiophene-3-carboxaldehyde in 20 ml diethyl ether at 0 °C. The suspension was allowed to react for 17 h at room temperature. The resulting suspension was hydrolyzed using 20 ml of 1 N HCl. The organic layer was washed with a solution of $NaHSO_3$ and then with water. The organic phase was evaporated and the crude product purified by flash chromatography.

3-(1-Hydroxy-1,2,3-pentahydro-undecafluorononyl) thiophene (**11a**): Isolated yield, 55%; m.p., 50 °C. ^{1}H NMR δ: 2.08 (4H, m); 2.5 (1H, O–H); 4.83 (1H, t); 7.22 (3H, m) ppm. IR (KBr) cm^{-1}: 3350 (OH); 1350–1230 (C–F).

3-(1-Hydroxy-1,2,3-pentahydro-nonafluoroheptyl) thiophene (**11b**): Isolated yield, 54%. ^{1}H NMR δ: 2.08 (4H, m); 2.26 (1H, O–H); 4.95 (1H, t); 7.06–7.35 (3H, m) ppm. IR (Kbr) cm^{-1}: 3340 (OH); 1350–1220 (C–F).

*3-(1-Chloro-1,2,3-pentahydro-fluoralkyl) thiophenes (**12a**, **12b**)*

Thionyl chloride (2 ml) was added to a solution of 10 mmol of alcohol (**11a**, **b**) in 5 ml chloroform and refluxed for 1 h. The solution was evaporated

under vacuum and the crude product used for the next step without further purification.

3-(1-Chloro-1,2,3-pentahydro-undecafluorononyl) thiophene (**12a**): Crude yield, 95% (oil). ^{1}H NMR δ: 2.4 (4H, m); 5.05 (1H, t); 7.25 (3H, m) ppm.

3-(1-Chloro-1,2,3-pentahydro-nonafluoroheptyl) thiophene (**12b**): Crude yield, 98% (oil). ^{1}H NMR δ: 2.38 (2H, m); 4.95 (1H, m); 7.13 (1H, dd); 7.33 (2H, m) ppm.

*3-(1,2,3-Hexahydro-fluoroalkyl) thiophene (**13a**, **13b**)*

$LiAlH_4$ (10.5 mmol) was slowly added at 0 °C and under an argon atmosphere to a solution consisting of 9.5 mmol of **12a**, **b** in 10 ml THF. Dried $PdCl_2$ (11 mmol) was then added to the suspension which was allowed to react for 2 h. The resulting mixture was quenched with ethyl acetate, filtered and evaporated. The crude product was purified by flash chromatography and vacuum distillation.

3-(1,2,3-Hexahydro-undecafluorononyl) thiophene (**13a**): Isolated yield, 80% (colourless oil). ^{1}H NMR δ: 1.8 (4H, m); 2.64 (2H, t); 6.67 (2H, m); 7.18 (1H, dd) ppm. ^{19}F NMR δ: −79.3 (3F, t); −99.5 (2F, m); −120.5 (2F, m); −121.8 (2F, m); −124 (2F, m) ppm. IR (neat) cm^{-1}: 1350–1240 (C–F).

3-(1,2,3-Hexahydro-nonafluoroheptyl) thiophene (**13b**): Isolated yield, 69% (colourless oil). ^{1}H NMR δ: 2.01 (4H, m); 2.76 (2H, t); 6.38 (2H, m); 7.26 (1H, dd) ppm. IR (neat) cm^{-1}: 1350–1240 (C–F).

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