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Ring fluorinated thiophenes: applications to liquid crystal synthesis

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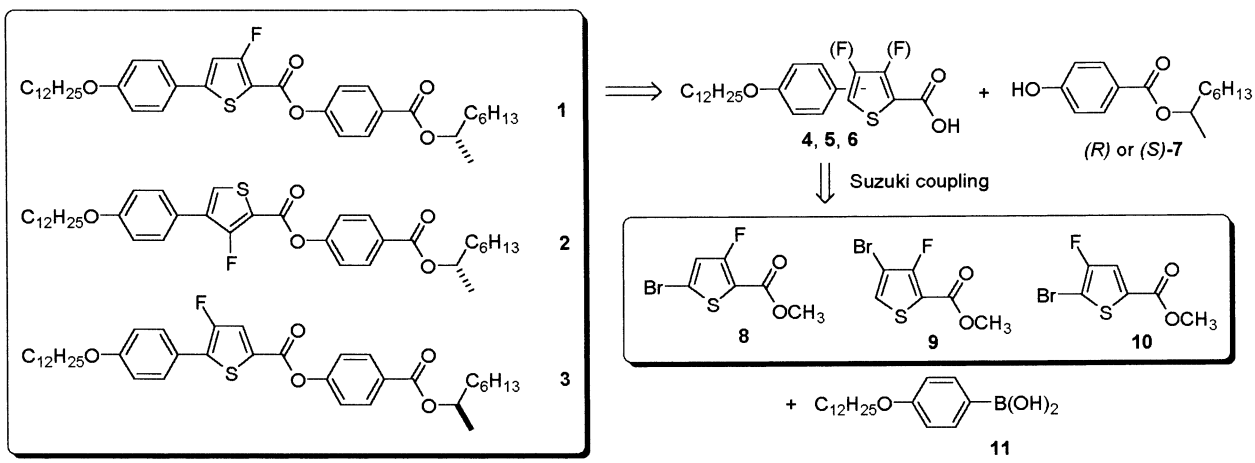
Abstract—Ring fluorinated thiophenes were synthesized via a Balz–Schiemann fluorination approach and were successfully employed in the synthesis of liquid crystals using regioselective electrophilic bromination and regioselective Suzuki coupling chemistry.

While the introduction of lateral fluorine into *phenyl* ring-containing liquid crystals has proven very beneficial for the desirable lowering of melting point whilst maintaining broad mesophase ranges,[1] no studies on laterally fluorinated *thiophene*-containing analogs have been reported in the open literature.[2] Thiophene-containing liquid crystals often show better physical characteristics than those of their phenyl counterparts, such as lower viscosity, high birefringence and faster switching times.[3] Therefore, fluorinated thiophene-based materials are of exceptional promise for ferroelectric displays, including the latest ferroelectric liquid crystal over silicon devices that require highly birefringent materials to effect optimum light transmission.[4] The present paper[5] communicates our initial synthetic efforts toward the synthesis of 3- and 4-fluorothiophene-containing mesogens **1**–**3**, which were chosen based on the known ferroelectric non-fluorinated analog MHDDOPTCOB.[6] Very few viable synthetic approaches exist for the synthesis of 3- and 4-fluorothiophenes; our approach to these systems exploits a Balz–Schiemann fluorination protocol.[7]

We considered that mesogens **1**–**3** should be accessible via esterification of the corresponding carboxylic acids **4**–**6** with readily available (*S*)-(+) or (*R*)-(−)-phenol **7**[8] (Scheme 1). These carboxylic acids should, in turn, be available via Suzuki coupling[9] of bromothiophenes **8**–**10** with boronic acid **11**[10] followed by saponification. Therefore, our initial goal was to obtain the three



Scheme 1. Retrosynthetic analysis.

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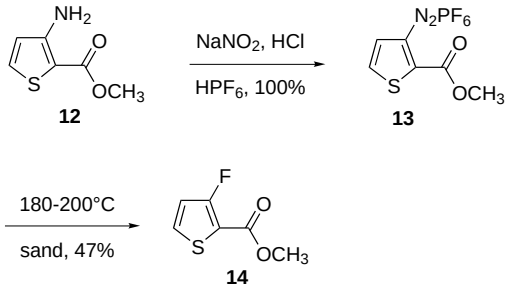
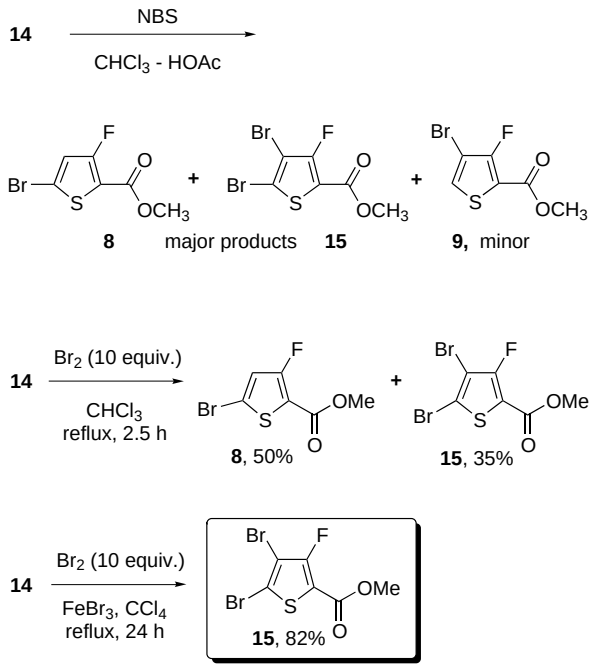
previously unknown regioisomeric methyl bromofluorothiophene-2-carboxylate building blocks **8**–**10**.

Diazotization of 3-aminothiophene **12** provided an excellent yield of the corresponding diazonium hexafluorophosphate **13** (Scheme 2).[11] The use of the literature conditions (160°C) for the Balz–Schiemann reaction[7a] provided us with the corresponding fluorothiophene **14** in 35% yield. In contrast, performing the reaction at ca. 200°C and trapping the reaction product using a cold finger allowed us to obtain **14** in 47% yield.



Scheme 2. Balz–Schiemann fluorination.

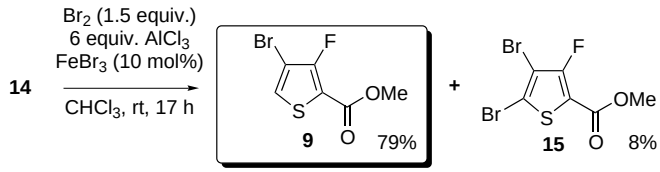
Bromination of **14** with NBS in chloroform–acetic acid afforded a mixture of 5-bromo and 4,5-dibrominated products **8** and **15** along with smaller amounts of the 4-bromo derivative **9** (Scheme 3). Refluxing in $CHCl_3$ for 2.5 h also gave a mixture of **8** and **15**. When using an excess of Br_2 in CCl_4 at reflux, the major product was again **8**, but **9** and **15** were still formed in substantial ($\sim$10% each) quantities. Chromatographic separation of **8** and **9** has proven very problematic, precluding the efficient preparation of **8**. Therefore, an alternative approach was taken that targeted the 4,5-dibrominated thiophene **15**, addressing the problem of regioselectivity



Scheme 3. Bromination of **14**.

at the later stage of Suzuki coupling. We found that addition of 1.8 mol% $FeBr_3$ accelerated the bromination reaction and afforded 4,5-dibromothiophene **15** in 82% yield.

As can be seen from the above results, the 4-bromo derivative **9** could not be obtained by any of the direct bromination methods examined and an alternative entry was sought. 'Catalyst swamping' conditions[12a] for electrophilic chlorination (excess $AlCl_3$, $CHCl_3$) are known to lead cleanly to 4-substitution in thiophenes bearing carbonyl functionality at C(2) with[12b] or without[12c] a chlorine substituent at C(3). When these conditions were applied to the bromination of **14**, virtually no reaction was observed; however, on addition of 10 mol% $FeBr_3$ the desired 4-bromothiophene **9** was obtained in 79% yield together with 8% of the dibrominated compound **15**, which was easily separable by column chromatography (Scheme 4). The crucial addition of $FeBr_3$ appears to be unprecedented and holds potential for other deactivated substrates to be used under 'catalyst swamping' conditions.

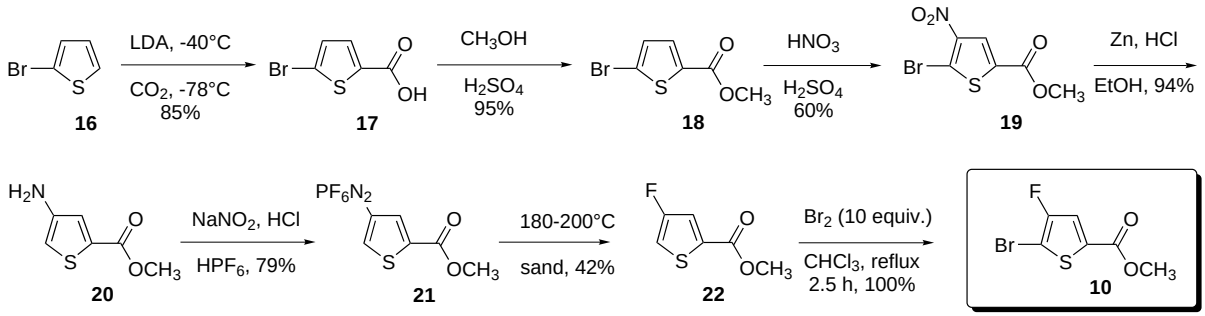


Scheme 4. 'Catalyst swamping' bromination of **14**.

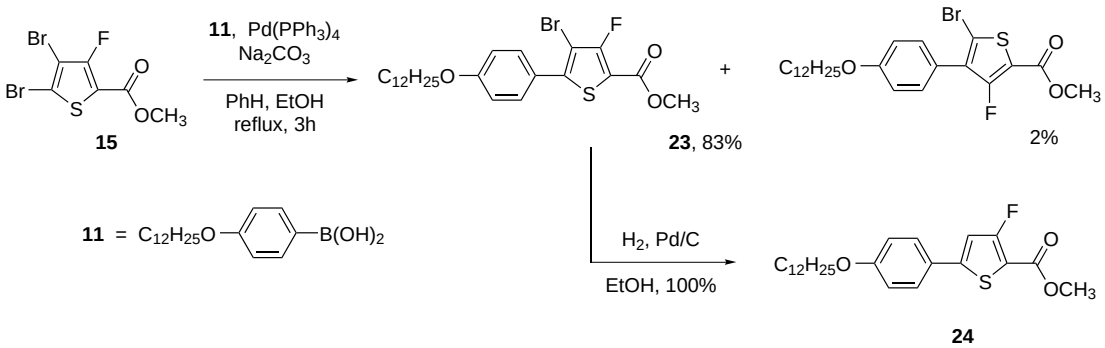
In the synthesis of the third bromofluorothiophene regioisomer **10**, the originally planned nitration of thiophene-2-carboxylic acid gave a mixture of 4- and 5-nitro derivatives that would be very tedious to separate on a large scale.[13] Therefore, an alternative approach was taken (Scheme 5).

Commercially available 2-bromothiophene (**16**) was selectively deprotonated at the 5-position with LDA and quenched with excess CO_2 to produce carboxylic acid **17**, which was esterified under standard conditions. The resulting ester **18** was nitrated selectively at the 4-position and the nitro- and bromo-functionalities in **19** were reduced in one pot to provide the amine **20** in excellent yield. During this transformation, the bromo functionality was always reduced faster than the nitro group under several sets of conditions (Fe/HCl, H_2–Pd/C, Zn/HCl). Diazotization of **20** provided hexafluorophosphate salt **21** and the subsequent Balz–Schiemann reaction afforded fluorinated ester **22**[14] in 42% yield. Quantitative regioselective bromination then gave the desired 5-bromo-4-fluorothiophene intermediate **10**.

With the three bromofluorothiophene building blocks **9**, **10** and **15**[14] in hand, the stage was set for the synthesis of liquid crystalline materials **1**–**3**. When **15** was subjected to Suzuki coupling conditions with boronic acid **11**, reaction took place predominantly at C(5), giving the corresponding ester **23** along with a small amount of by-product resulting from reaction at C(4) (Scheme 6). The observed regioselectivity can be



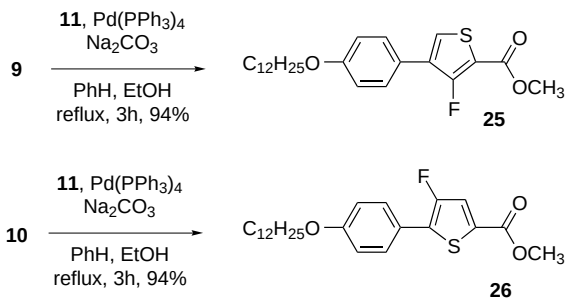
Scheme 5. Synthesis of bromofluorothiophene **10**.



Scheme 6. Regioselective Suzuki coupling of **15**.

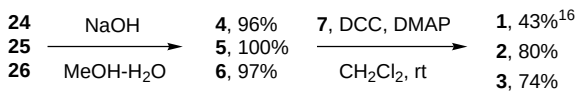
attributed to a faster oxidative addition of Pd(0) to the C(5)–Br bond, which is more activated by the presence of an electron-withdrawing ester functionality at C(2) than the C(4)–Br bond, and possibly steric or other reasons. The remaining bromine was then conveniently removed from C(4) in quantitative yield by hydrogenolysis with H_2–Pd/C to afford **24**. Overall, the 4,5-dibromo derivative **15** has proven to be an effective substitute for the monobromo derivative **8** en route to this advanced building block.

Suzuki coupling reactions of the two other bromothiophene intermediates **9** and **10** were also efficient and gave the corresponding biaryl esters **25** and **26** in 94% yields (Scheme 7).



Scheme 7. Suzuki coupling of **9** and **10**.

Saponification of the resulting esters **24**–**26** was accomplished under standard conditions to give the carboxylic acids **4**–**6** in virtually quantitative yield (Scheme 8), whence DCC–DMAP esterification[15] with phenol **7** provided the target molecules **1** (43%),[16] **2** (80%) and **3** (74%).



Scheme 8. Synthesis of liquid crystals **1**–**3**.

In conclusion, a strategy involving Balz–Schiemann fluorination followed by regioselective bromination and Suzuki coupling was successfully employed for the construction of several fluorothiophene-containing mesogens. The liquid crystalline properties of these compounds are under investigation and will be reported in due course.

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5. This work was presented at the 222nd ACS National Meeting, August 26–30, 2001, Chicago, IL (P-152).
6. MHDDOPTCOB is a non-fluorinated analog of **1** and **3**. See: Lagerwall, S. T. In *Ferroelectric and Antiferroelectric Liquid Crystals*; Wiley-VCH: Weinheim, 1999; p. 370.
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14. ^{1}H, ^{13}C and ^{19}F NMR data for new fluorothiophene building blocks **9**, **10**, **15** and **22** are presented below. Compound **9**: ^{1}H NMR δ 3.91 (s, 3H), 7.42 (d, $J_{H-F}=3.9$ Hz, 1H); ^{13}C NMR δ 52.5, 101.9 (d, $J_{C-F}=26.2$ Hz), 113.2 (d, $J_{C-F}=10.2$ Hz), 127.3 (d, $J_{C-F}=3.2$ Hz), 156.4 (d, $J_{C-F}=276.9$ Hz), 160.1 (d, $J_{C-F}=4.5$ Hz); ^{19}F NMR δ −112.3 (d, $J=3.5$ Hz, 1F). Compound **10**: ^{1}H NMR δ 3.89 (s, 3H), 7.42 (d, $J_{H-F}=1.2$ Hz, 1H); ^{13}C NMR δ 52.8, 100.3 (d, $J_{C-F}=24.8$ Hz), 122.2 (d, $J_{C-F}=24.8$ Hz), 131.2 (d, $J_{C-F}=7.0$ Hz), 155.7 (d, $J_{C-F}=263.9$ Hz), 161.2 (d, $J_{C-F}=2.5$ Hz); ^{19}F NMR δ −124.3 (d, $J=1.2$ Hz, 1F). Compound **15**: ^{1}H NMR δ 3.91 (s, 3H); ^{13}C NMR δ 52.7, 106.6 (d, $J_{C-F}=26.3$ Hz), 113.8 (d, $J_{C-F}=9.8$ Hz), 117.9 (d, $J_{C-F}=4.6$ Hz), 155.3 (d, $J_{C-F}=279.9$ Hz), 159.4 (d, $J_{C-F}=3.8$ Hz); ^{19}F NMR δ −105.6 (s, 1F). Compound **22**: ^{1}H NMR δ 3.89 (s, 3H), 6.96 (dd, $J=1.8$, 0.8 Hz, 1H), 7.50 (dd, $J=1.8$, 0.9 Hz, 1H); ^{13}C NMR δ 52.5, 110.9 (d, $J_{C-F}=20.3$ Hz), 122.5 (d, $J_{C-F}=25.4$ Hz), 132.0 (d, $J_{C-F}=7.6$ Hz), 157.4 (d, $J_{C-F}=260.0$ Hz), 161.9 (d, $J_{C-F}=2.5$ Hz); ^{19}F NMR δ −126.3 (app t, $J_{F-H}=0.7$ Hz, 1F) (it should be noted that $^{3}J_{H-F}$ is very small between vicinal H and F substituents at the C(3) and C(4) positions on the thiophene ring).
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16. The lower yield for **1** was due to the extensive purification required to obtain highly pure material.