

SYNTHESIS OF 2-FLUORO-3-TRIFLUOROMETHYLTHIOPHENES AND 3-TRIFLUOROMETHYLTHIOPHENES FROM HEXAFLUOROACETONE

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Dedicated to Professor Dr. Arnold Brossi on the occasion of his
70th birthday

Abstract - The transformation of bis(trifluoromethyl)-1-oxabuta-1,3-dienes (1) — available from hexafluoroacetone — into 2-fluoro-3-trifluoromethylthiophenes (9) via 4,4-difluoro-3-trifluoromethyl-3-buten-1-ones (5) is described. The fluorine atom at skeleton position 2 of the thiophenes (9) is readily displaced by various nucleophiles.

INTRODUCTION

Fluorine and/or perfluoroalkyl groups positioned strategically in target molecules may considerably modify chemical reactivity, selectivity, biological activity, and material properties.¹ Therefore, the development of synthetic methodology for the regioselective introduction of fluorine² and short-chain perfluoroalkyl groups³ into organic molecules is of current interest. There are two fundamentally different strategies by which fluorine and/or perfluoroalkyl groups can be introduced into target molecules:

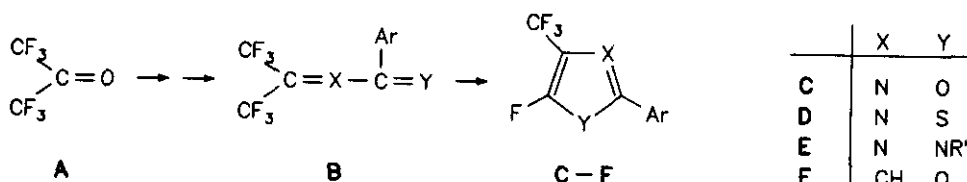
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- 1) Introduction by direct substitution of hydrogen by fluorine and perfluoroalkyl groups or by functional group transformation in a late step of the synthetic sequence;
- 2) Introduction of fluorine and/or perfluoroalkyl groups by application of fluorine-containing building blocks,⁴ derived from readily accessible starting materials.

While the first approach is more straight forward, provided that suitable fluorinating reagents are available, control of regioselectivity is often difficult to achieve. Consequently, the building block strategy represents an useful alternative concept.

For the synthesis of five-membered heteroaromatic compounds some efficient building block concepts have been already developed. Cyclocondensation reactions with fluoro-containing starting materials offer versatile access to partially fluorinated heterocyclic and heteroaromatic compounds.⁵ Trifluoromethyl substituted 1,3-dipoles are especially valuable building blocks for the synthesis of a wide variety of trifluoromethyl substituted five-membered heterocycles.⁶ The introduction of short-chain perfluoroalkyl groups can also be achieved *via* [3+2] cycloaddition reactions using appropriately fluoro substituted dipolarophiles.⁷ Recently ethyl 3,3,3-trifluoro-2-diazopropionate was recognized to be a preparatively useful building block.⁸ 1,5-Electrocyclization of perfluoroalkyl and partially fluorinated heteropentadienyl anions and subsequent heteroaromatization by fluoride elimination offers an elegant route to perfluorinated and partially fluorinated heteroaromatic systems.⁹ Another promising access to five-membered heteroaromatic compounds is a combination of a Diels-Alder reaction of perfluoroalkyl substituted triple bond systems to five-membered heteroaromatic compounds and a thermally induced retro Diels-Alder reaction.¹⁰ In a series of papers we reported on the synthesis of trifluoromethyl substituted oxazoles, thiazoles, and imidazoles¹¹ as well as 3-trifluoromethylfurans¹² starting from 4,4-bis-(trifluoromethyl) substituted 1,3-heterodienes. The latter are readily prepared from hexafluoroacetone (Scheme 1).¹³

Scheme 1

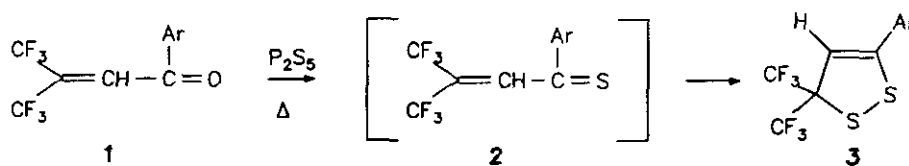


Although numerous synthetic routes to thiophenes have been described,¹⁴ reports on the synthesis of fluorine- and/or perfluoroalkyl substituted thiophenes are still rare.¹⁵ Herein we report on a versatile, preparatively simple route to 2-fluoro-3-trifluoromethylthiophenes and 3-trifluoromethylthiophenes starting from hexafluoroacetone.

RESULTS AND DISCUSSION

Experiments to synthesize 2-fluoro-3-trifluoromethylthiophenes *via* 4,4-bis(trifluoromethyl)-1-thiabuta-1,3-dienes (2), analogous to Scheme 1 were unsuccessful so far, since a transformation of 4,4-bis(trifluoromethyl)-1-oxabuta-1,3-dienes (1) into 4,4-bis(trifluoromethyl)-1-thiabuta-1,3-dienes (2) on heating with phosphorus pentasulfide or Lawesson reagent can not be accomplished. 3,3-Bis(trifluoromethyl)-3*H*-1,2-dithioles (3) are formed in high yields.¹⁶ Most likely compounds (2) are the intermediates of the process $1 \rightarrow 2 \rightarrow 3$ (Scheme 2).

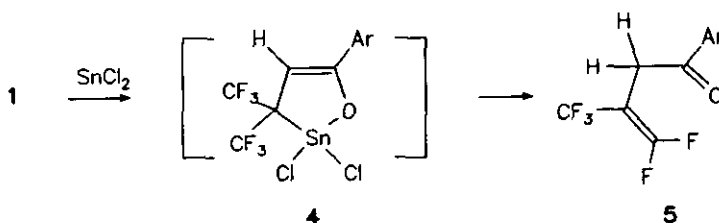
Scheme 2



Ar : **3a** = phenyl; **3b** = 4-fluorophenyl; **3c** = 4-chlorophenyl;
3d = thien-2-yl

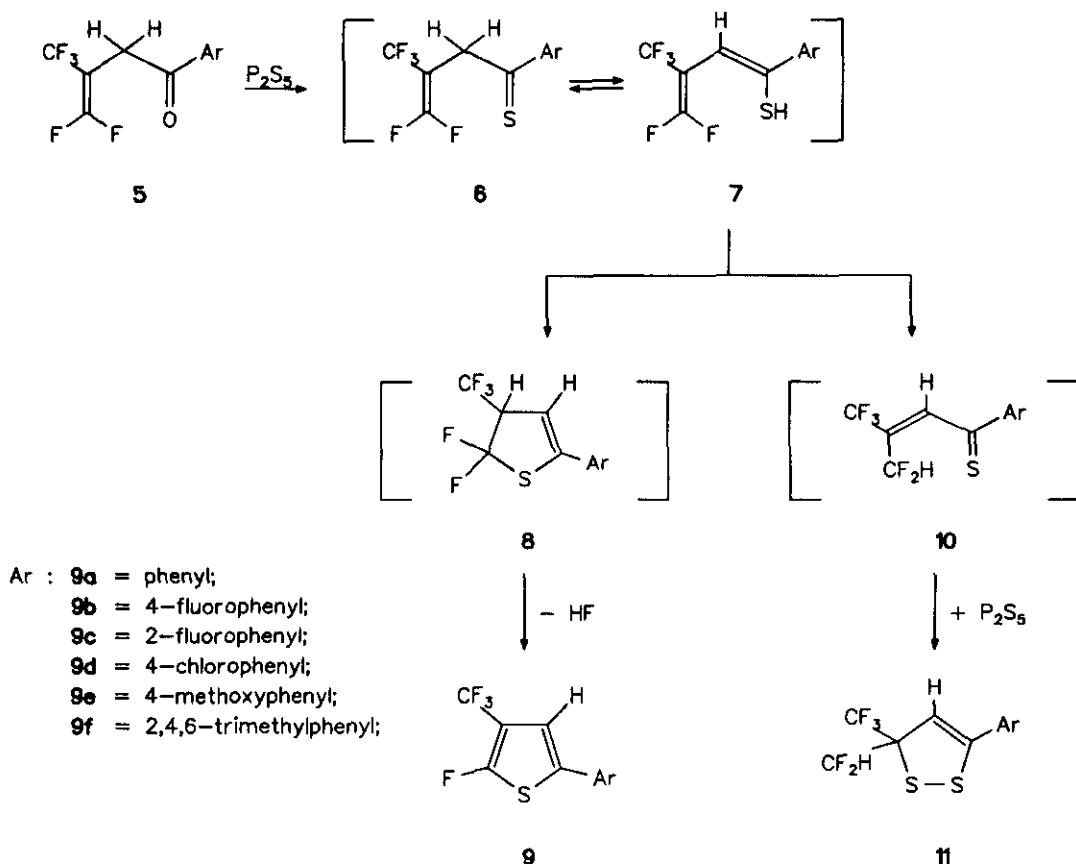
Therefore, we decided to use the partially fluorinated β,γ -unsaturated ketones of type 5 which are intermediates of a recently described 2-fluoro-3-trifluoromethylfuran synthesis¹⁷ as starting materials. Compounds (5) can be prepared in high yields from 4,4-bis(trifluoromethyl)-1-oxabuta-1,3-dienes (1) on treatment with tin(II) chloride in a one-pot procedure (Scheme 3).

Scheme 3



When compounds (5) and phosphorus pentasulfide are heated up to 120 - 140 °C without solvent an oxygen/sulfur exchange reaction takes place (Scheme 4). The β,γ -unsaturated thioketones (6) formed, exist in an equilibrium with their tautomers - thioenols (7) - which under the reaction conditions applied, spontaneously undergo an 1,5-electrocyclization process $7 \rightarrow 8$. Elimination of HF from 8 results in heteroaromatization to give 2-fluoro-3-trifluoromethylthiophenes (9). The structure of compounds (9) was proved by 1H , ^{13}C and ^{19}F nmr spectroscopy as well as by mass spectrometry and elemental analysis.

Scheme 4

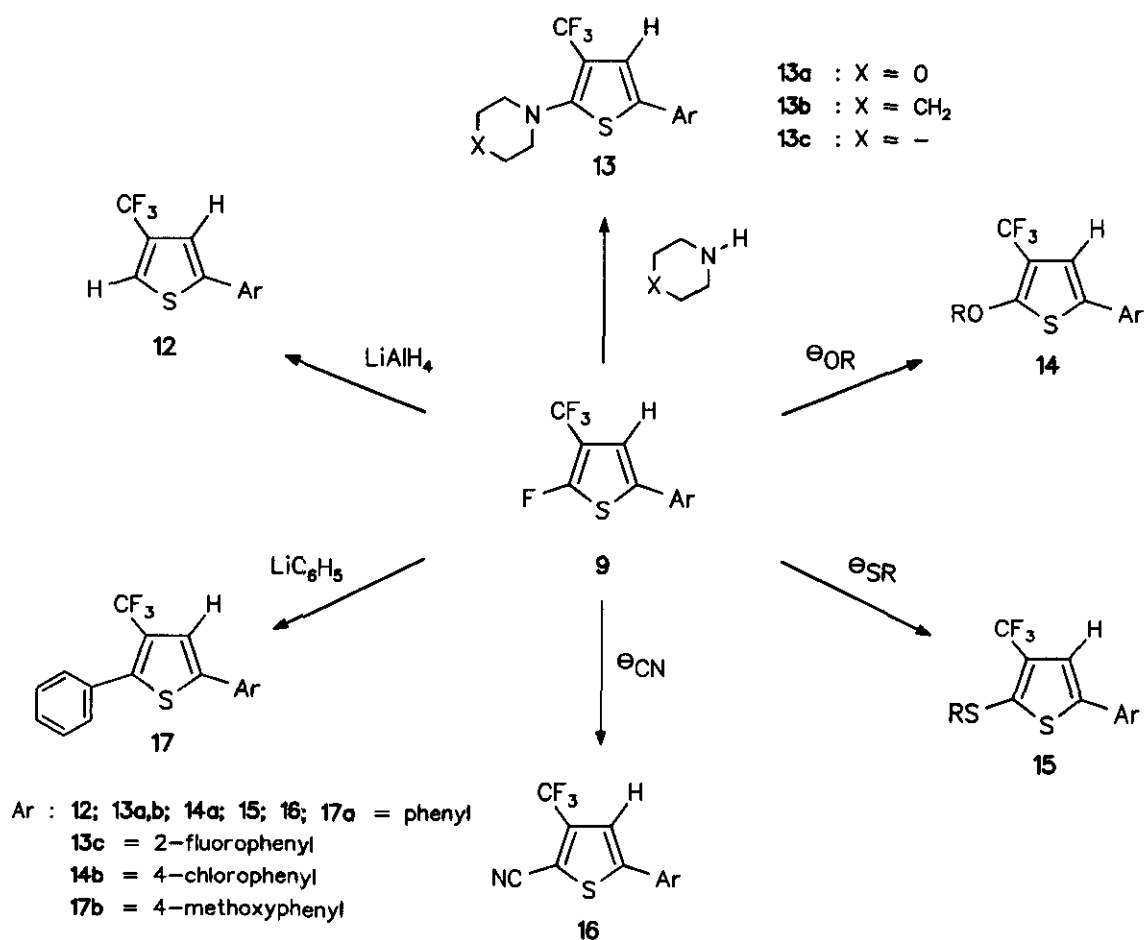


The yields of compounds (**9**) very much depend on the reaction conditions applied. Optimum yields were obtained when the progress of the reaction was carefully controlled by ^{19}F nmr spectroscopy. When higher reaction temperatures and longer reaction times are applied the yields of **9** decrease considerably, as they do when Ar represents a sterical demanding group (Ar = 2,4,6-trimethylphenyl). Based on the ^{13}C nmr data we ascribe the by-product the structure of a 3H-1,2-dithiophene (**11**). Besides the expected trifluoromethyl group the spectra of compounds (**11**) surprisingly show the presence of a difluoromethyl group. A [1,5] hydrogen shift $7 \rightarrow 10$ followed by a [4+1] cycloaddition of sulfur to the 1-thiabuta-1,3-diene (**10**) to form the five-membered ring system (**11**) offers a plausible mechanistic interpretation for the experimental findings.

Because of the electron-withdrawing properties of the trifluoromethyl group positioned at C-3 of the thiophene ring, the fluorine atom attached to C-2 is readily susceptible to nucleophilic displacement reactions.^{12,18} Therefore, the reaction sequence $1 \rightarrow 5 \rightarrow 9 \rightarrow 12 - 17$ (Scheme 5) offers a preparatively simple, highly flexible synthetic route to 3-trifluoromethylthiophenes. Depending

on the priority of the substituents present at the thiophene ring, some compounds of this type have to be named 4-trifluoromethylthiophenes (see compound 12). In particular the option of introducing various side chains into ring position 2 in the final step of the reaction sequence, in order to enhance and/or modify biological activity¹⁹ and to improve material properties makes this strategy especially useful.

Scheme 5



EXPERIMENTAL

Materials and methods:

Melting points are determined in a Büchi capillary mp apparatus and are uncorrected. The ^1H , ^{13}C and ^{19}F nmr spectra are taken on a Bruker AC-250 instrument (^1H : 250.1 MHz; ^{13}C : 62.9 MHz; ^{19}F : 235.3 MHz). Chemical shifts are calculated from tetramethylsilane (internal standard) for ^1H and ^{13}C , and from trifluoroacetic acid (external standard) for ^{19}F . Ir spectra are measured on a Perkin-Elmer 237 apparatus. Mass spectra are obtained on an AEI MS 9 spectrometer at 70 eV. Column chromatography is performed on silica gel 60 F₂₅₄ (0.063-0.200, Merck).

S-Aryl-3,3-bis(trifluoromethyl)-3H-1,2-dithioles (3)

General Procedure: A stirred mixture of the 4,4-bis(trifluoromethyl)-1-oxabuta-1,3-diene (1)¹³ (50 mmol) and phosphorus pentasulfide (11.10 g, 50 mmol) was heated up to 120 - 140 °C for 24 - 48 h. The reaction was monitored by ^{19}F nmr spectroscopy. Products (3) were directly distilled from the crude reaction mixture in vacuo.

S-Phenyl-3,3-bis(trifluoromethyl)-3H-1,2-dithiole (3a)

Yield 11.54 g (73%); bp 66 °C/0.2 torr; ir (CHCl₃): ν = 1610 cm⁻¹; ^1H nmr (CDCl₃): δ = 5.75 (s, 1H, dithiole C(4)-H), 7.43 (m, 5H, phenyl H); ^{13}C nmr (CDCl₃): δ = 77.75 (sept., ^2J = 30 Hz, dithiole C-3), 106.98 (dithiole C-4), 123.21 (q, ^1J = 285 Hz, CF₃), 127.40, 129.01, 130.78, 130.94 (phenyl C), 153.42 (dithiole C-5); ^{19}F nmr (CDCl₃): δ = 7.04 [s, 6F, C(CF₃)₂]. Anal. Calcd for C₁₁H₆F₆S₂: C, 41.77; H, 1.91. Found: C, 41.72; H, 1.78. Ms (m/z): 316 [M]⁺, 247 [M-CF₃]⁺, 183 [M-CF₃-S₂]⁺.

S-(4-Fluorophenyl)-3,3-bis(trifluoromethyl)-3H-1,2-dithiole (3b)

Yield 10.05 g (60%); bp 58 °C/0.1 torr; ir (film): ν = 1605 cm⁻¹; ^1H nmr (CDCl₃): δ = 5.70 (s, 1H, dithiole C(4)-H), 7.06 (m, 2H, aryl H), 7.46 (m, 2H, aryl H); ^{13}C nmr (CDCl₃): δ = 77.79 (sept., ^2J = 30 Hz, dithiole C-3), 107.20 (dithiole C-4), 116.14 (d, ^2J = 22 Hz, aryl C-3, C-5), 123.22 (q, ^1J = 285 Hz, CF₃), 127.20 (d, ^4J = 4 Hz, aryl C-1), 129.47 (d, ^3J = 9 Hz, aryl C-2, C-6), 152.27 (dithiole C-5), 164.09 (d, ^1J = 252 Hz, aryl C-4); ^{19}F nmr (CDCl₃): δ = -30.88 (m, 1F, aryl C(4)-F), 6.91 [s, 6F, C(CF₃)₂]. Anal. Calcd for C₁₁H₅F₇S₂: C, 39.52; H, 1.51. Found: C, 39.86; H, 1.54. Ms (m/z): 334 [M]⁺, 265 [M-CF₃]⁺, 201 [M-CF₃-S₂]⁺.

S-(4-Chlorophenyl)-3,3-bis(trifluoromethyl)-3H-1,2-dithiole (3c)

Yield 11.40 g (65%); bp 59 °C/0.1 torr; ir (film): ν = 1605 cm⁻¹; ^1H nmr (CDCl₃): δ = 5.75 (s, 1H, dithiole C(4)-H), 7.39 (m, 4H, aryl H); ^{13}C nmr (CDCl₃): δ = 77.77 (sept., ^2J = 30 Hz, dithiole C-3), 107.67 (dithiole C-4), 123.13 (q, ^1J = 285 Hz, CF₃), 128.64, 129.25, 129.39, 136.94 (aryl C), 152.21 (dithiole C-5); ^{19}F nmr (CDCl₃): δ = 7.08 [s, 6F, C(CF₃)₂]. Anal. Calcd for C₁₁H₅ClF₆S₂: C, 37.67; H, 1.44. Found: C, 38.08; H, 1.50. Ms (m/z): 352/350 [M]⁺, 283/281 [M-CF₃]⁺, 219/217 [M-CF₃-S₂]⁺, 69 [CF₃]⁺.

S-(Thien-2-yl)-3,3-bis(trifluoromethyl)-3H-1,2-dithiole (3d)

Yield 8.38 g (52%); bp 64 °C/0.1 torr; mp 44 °C; ir (KBr): ν = 1610 cm⁻¹; ^1H nmr (CDCl₃): δ =

5.73 (s, 1H, dithiole C(4)-H), 7.03 (m, 1H, thienyl H), 7.21 (m, 1H, thienyl H), 7.37 (m, 1H, thienyl H); ^{13}C nmr (CDCl_3): δ = 77.23 (sept., 2J = 30 Hz, dithiole C-3), 106.23 (dithiole C-4), 123.14 (q, 1J = 285 Hz, CF_3), 128.02, 128.48, 129.00, 132.83 (thienyl C), 145.57 (dithiole C-5); ^{19}F nmr (CDCl_3): δ = 7.29 [s, 6F, $\text{C}(\text{CF}_3)_2$]. Anal. Calcd for $\text{C}_9\text{H}_4\text{F}_6\text{S}_3$: C, 33.54; H, 1.25. Found: C, 33.81; H, 1.33. Ms (m/z): 322 $[\text{M}]^+$, 253 $[\text{M}-\text{CF}_3]^+$, 189 $[\text{M}-\text{CF}_3-\text{S}_2]^+$, 69 $[\text{CF}_3]^+$.

5-Aryl-2-fluoro-3-trifluoromethylthiophenes (9)

General Procedure: 1-Aryl-4,4-difluoro-3-trifluoromethyl-3-buten-1-ol (5)^{17,20} (10 mmol) and phosphorus pentasulfide (2.22 g, 10 mmol) were heated up to 120 - 140 °C with stirring until no 5 could be identified by ^{19}F nmr spectroscopy. The reaction mixture was extracted with 50 ml pentane. The pentane layer was filtered and evaporated in vacuo. The residue was purified by column chromatography (eluant: hexanes).

2-Fluoro-5-phenyl-3-trifluoromethylthiophene (9a)

Yield 1.35 g (55%); oil; ir (film): ν = 1600, 1520, 1490, 1450, 1410 cm^{-1} ; ^1H nmr (CDCl_3): δ = 6.98 (d, 4J = 3 Hz, 1H, thiophene C(4)-H), 7.36 (m, 3H, phenyl H), 7.44 (m, 2H, phenyl H); ^{13}C nmr (CDCl_3): δ = 113.11 (dq, 2J = 4 Hz, 2J = 36 Hz, thiophene C-3), 116.40 (m, thiophene C-4), 120.94 (dq, 3J = 3 Hz, 1J = 270 Hz, CF_3), 125.52 (d, 4J = 1 Hz), 128.53, 129.16, 132.42 (phenyl C), 132.65 (d, 3J = 2 Hz, thiophene C-5), 163.39 (dq, 1J = 301 Hz, 3J = 3 Hz, thiophene C-2); ^{19}F nmr (CDCl_3): δ = -46.0 (dq, 4J = 3 Hz, 4J = 12 Hz, 1F, C(2)-F), 19.30 (d, 4J = 12 Hz, 3F, CF_3). Anal. Calcd for $\text{C}_{11}\text{H}_6\text{F}_4\text{S}$: C, 53.66; H, 2.46. Found: C, 53.52; H, 2.52. Ms (m/z): 246 $[\text{M}]^+$, 227 $[\text{M}-\text{F}]^+$, 226 $[\text{M}-\text{HF}]^+$, 207 $[\text{M}-\text{F}-\text{HF}]^+$, 182 $[\text{M}-\text{HF}-\text{CS}]^+$, 133 $[\text{M}-\text{CF}_3-\text{CS}]^+$.

2-Fluoro-5-(4-fluorophenyl)-3-trifluoromethylthiophene (9b)

Yield 1.22 g (46%); mp 33 °C; ir (film): ν = 1600, 1530, 1495, 1425, 1405 cm^{-1} ; ^1H nmr (CDCl_3): δ = 6.92 (d, 4J = 3 Hz, 1H, thiophene C(4)-H), 7.07 (m, 2H, aryl H), 7.42 (m, 2H, aryl H); ^{13}C nmr (CDCl_3): δ = 113.18 (dq, 2J = 4 Hz, 2J = 36 Hz, thiophene C-3), 116.23 (d, 2J = 22 Hz, aryl C-3, C-5), 116.48 (m, thiophene C-4), 120.89 (dq, 3J = 3 Hz, 1J = 270 Hz, CF_3), 127.41 (dd, 5J = 1 Hz, 3J = 8 Hz, aryl C-2, C-6), 128.70 (d, 4J = 3 Hz, aryl C-1), 131.57 (d, 3J = 2 Hz, thiophene C-5), 162.91 (d, 1J = 249 Hz, aryl C-4), 163.32 (dq, 1J = 302 Hz, 3J = 3 Hz, thiophene C-2); ^{19}F nmr (CDCl_3): δ = -45.92 (dq, 4J = 3 Hz, 4J = 12 Hz, 1F, thiophene C(2)-F), -34.81 (m, 1F, aryl C(4)-F), 19.21 (d, 4J = 12 Hz, 3F, CF_3). Anal. Calcd for $\text{C}_{11}\text{H}_5\text{F}_5\text{S}$: C, 50.00; H, 1.91. Found: C, 49.33; H, 1.93. Ms (m/z): 264 $[\text{M}]^+$, 245 $[\text{M}-\text{F}]^+$, 244 $[\text{M}-\text{HF}]^+$, 225 $[\text{M}-\text{F}-\text{HF}]^+$, 201 $[\text{M}-\text{F}-\text{CS}]^+$, 151 $[\text{M}-\text{CF}_3-\text{CS}]^+$, 132 $[\text{M}-\text{CF}_3-\text{F}-\text{CS}]^+$.

2-Fluoro-5-(2-fluorophenyl)-3-trifluoromethylthiophene (9c)

Yield 0.85 g (32%); oil; ir (film): ν = 1600, 1515, 1485, 1450, 1405 cm^{-1} ; ^1H nmr (CDCl_3): δ = 7.17 (m, 3H, aryl H, thiophene C(4)-H), 7.27 (m, 1H, aryl H), 7.47 (m, 1H, aryl H); ^{13}C nmr (CDCl_3): δ = 112.88 (dq, 2J = 4 Hz, 2J = 37 Hz, thiophene C-3), 116.57 (d, 2J = 22 Hz, aryl C-3), 119.71 (m, thiophene C-4), 120.35 (d, 2J = 12 Hz, aryl C-1), 121.06 (dq, 3J = 3 Hz, 1J = 270 Hz, CF_3), 124.83 (d, 3J = 4 Hz, aryl C-6), 127.95 (dd, 3J = 2 Hz, 3J = 3 Hz, thiophene C-5), 129.88 (d, 3J = 8 Hz, aryl

C-4), 130.26 (d, $^4J = 2$ Hz, aryl C-5), 159.20 (dd, $^1J = 250$ Hz, $^5J = 1$ Hz, aryl C-2), 164.46 (ddq, $^1J = 301$ Hz, $^5J = 3$ Hz, $^3J = 3$ Hz, thiophene C-2); ^{19}F nmr (CDCl_3): $\delta = -46.4$ (dq, $^4J = 3$ Hz, $^4J = 12$ Hz, 1F, thiophene C(2)-F), -36.4 (m, 1F, aryl C(2)-F), 19.3 (d, $^4J = 12$ Hz, 3F, CF_3). Anal. Calcd for $\text{C}_{11}\text{H}_5\text{F}_5\text{S}$: C, 50.00; H, 1.91. Found: C, 49.72; H, 2.01. Ms (m/z): 264 $[\text{M}]^+$, 245 $[\text{M}-\text{F}]^+$, 244 $[\text{M}-\text{HF}]^+$, 200 $[\text{M}-\text{HF}, -\text{CS}]^+$, 151 $[\text{M}-\text{HF}, -\text{C}_3\text{F}_3]^+$, 132 $[\text{M}-\text{HF}, -\text{C}_3\text{F}_4]^+$, 131 $[\text{M}-\text{HF}, -\text{CS}, -\text{CF}_3]^+$, 69 $[\text{CF}_3]^+$.

5-(4-Chlorophenyl)-2-fluoro-3-trifluoromethylthiophene (9d)

Yield 1.66 g (59%); mp 44 °C; ir (KBr): $\nu = 3460, 1600, 1520, 1480, 1420, 1400$ cm^{-1} ; ^1H nmr (CDCl_3): $\delta = 6.99$ (d, $^4J = 3$ Hz, 1H, thiophene C(4)-H), 7.39 (m, 4H, aryl H); ^{13}C nmr (CDCl_3): $\delta = 113.31$ (dq, $^2J = 4$ Hz, $^2J = 36$ Hz, thiophene C-3), 116.89 (m, thiophene C-4), 120.81 (dq, $^3J = 3$ Hz, $^1J = 270$ Hz, CF_3), 126.71, 129.36, 130.92 (aryl C), 131.34 (d, $^3J = 3$ Hz, thiophene C-5), 134.53 (aryl C), 163.50 (dq, $^1J = 302$ Hz, $^3J = 4$ Hz, thiophene C-2); ^{19}F nmr (CDCl_3): $\delta = -45.15$ (dq, $^4J = 3$ Hz, $^4J = 12$ Hz, 1F, C(2)-F), 19.27 (d, $^4J = 12$ Hz, 3F, CF_3). Anal. Calcd for $\text{C}_{11}\text{H}_5\text{ClF}_4\text{S}$: C, 47.07; H, 1.80. Found: C, 47.11; H, 1.73. Ms (m/z): 282/280 $[\text{M}]^+$, 263/261 $[\text{M}-\text{F}]^+$, 262/260 $[\text{M}-\text{HF}]^+$, 225 $[\text{M}-\text{HF}, -\text{Cl}]^+$, 218/216 $[\text{M}-\text{HF}, -\text{CS}]^+$, 201 $[\text{M}-\text{Cl}, -\text{CS}]^+$.

2-Fluoro-5-(4-methoxyphenyl)-3-trifluoromethylthiophene (9e)

Yield 0.75 g (27%); mp 43 °C; ir (KBr): $\nu = 1615, 1605, 1470, 1425, 1405$ cm^{-1} ; ^1H nmr (CDCl_3): $\delta = 3.83$ (s, 3H, OCH_3), 6.86 (d, $^4J = 4$ Hz, 1H, thiophene C(4)-H), 6.91 (m, 2H, aryl H), 7.38 (m, 2H, aryl H); ^{13}C nmr (CDCl_3): $\delta = 55.34$ (OCH_3), 112.85 (dq, $^2J = 4$ Hz, $^2J = 36$ Hz, thiophene C-3), 114.53 (aryl C), 118.82 (d, $^3J = 2$ Hz, thiophene C-4), 120.96 (dq, $^3J = 3$ Hz, $^1J = 270$ Hz, CF_3), 125.10, 126.92, 126.95 (aryl C), 132.62 (d, $^3J = 2$ Hz, thiophene C-5), 159.95 (aryl C), 162.66 (dq, $^1J = 301$ Hz, $^3J = 4$ Hz, thiophene C-2); ^{19}F nmr (CDCl_3): $\delta = -47.15$ (dq, $^4J = 4$ Hz, $^4J = 12$ Hz, 1F, thiophene C(2)-F), 19.31 (d, $^4J = 12$ Hz, 3F, CF_3). Anal. Calcd for $\text{C}_{12}\text{H}_8\text{OF}_4\text{S}$: C, 52.17; H, 2.92. Found: C, 52.09; H, 2.97. Ms (m/z): 276 $[\text{M}]^+$, 261 $[\text{M}-\text{CH}_3]^+$, 233 $[\text{M}-\text{CH}_3, -\text{CO}]^+$, 213 $[\text{M}-\text{CH}_3, -\text{CO}, -\text{HF}]^+$, 169 $[\text{M}-\text{CH}_3, -\text{CO}, -\text{HF}, -\text{CS}]^+$, 69 $[\text{CF}_3]^+$.

2-Fluoro-3-trifluoromethyl-5-(2,4,6-trimethylphenyl)thiophene (9f)

Yield 0.87 g (30%); oil; ir (film): $\nu = 2920, 1600, 1525, 1400$ cm^{-1} ; ^1H nmr (CDCl_3): $\delta = 2.16$ (s, 6H, $\text{o}-\text{CH}_3$), 2.31 (s, 3H, $\text{p}-\text{CH}_3$), 6.54 (d, $^4J = 3$ Hz, 1H, thiophene C(4)-H), 6.93 (s, 2H, aryl H); ^{13}C nmr (CDCl_3): $\delta = 20.61$ (2x $\text{o}-\text{CH}_3$), 21.11 ($\text{p}-\text{CH}_3$), 112.17 (dq, $^2J = 4$ Hz, $^2J = 36$ Hz, thiophene C-3), 120.32 (m, thiophene C-4), 121.17 (dq, $^3J = 4$ Hz, $^1J = 270$ Hz, CF_3), 128.44, 128.63 (aryl C), 130.14 (thiophene C-5), 138.65, 139.13 (aryl C), 163.93 (dq, $^1J = 301$ Hz, $^3J = 4$ Hz, thiophene C-2); ^{19}F nmr (CDCl_3): $\delta = -45.83$ (dq, $^4J = 3$ Hz, $^4J = 12$ Hz, 1F, thiophene C(2)-F), 19.66 (d, $^4J = 12$ Hz, 3F, CF_3). Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{F}_4\text{S}$: C, 58.32; H, 4.20. Found: C, 57.91; H, 4.35. Ms (m/z): 288 $[\text{M}]^+$, 273 $[\text{M}-\text{CH}_3]^+$, 253 $[\text{M}-\text{CH}_3, -\text{HF}]^+$, 219 $[\text{M}-\text{CF}_3]^+$, 69 $[\text{CF}_3]^+$.

3-Difluoromethyl-3-trifluoromethyl-5-(2,4,6-trimethylphenyl)-3H-1,2-dithiol (11)

Yield 0.82 g (24%); oil; ir (film): $\nu = 1610$ cm^{-1} ; ^1H nmr (CDCl_3): $\delta = 2.27$ (s, 3H, $\text{p}-\text{CH}_3$), 2.33 (s, 6H, 2x $\text{o}-\text{CH}_3$), 5.25 (s, 1H, dithiole C(4)-H), 6.08 (ddq, $^2J = 55$ Hz, $^2J = 55$ Hz, $^4J = 0.5$ Hz, 1H, CF_2H), 6.87 (m, 2H, aryl H); ^{13}C nmr (CDCl_3): $\delta = 19.30$ (2x $\text{o}-\text{CH}_3$), 21.09 ($\text{p}-\text{CH}_3$), 77.67 (m,

dithiole C-3), 111.64 (dithiole C-4), 112.44 (t, $^1J = 251$ Hz, CF_2H), 124.11 (q, $^1J = 284$ Hz, CF_3), 126.58, 128.57, 137.28, 139.49 (aryl C), 151.30 (dithiole C-5); ^{19}F nmr ($CDCl_3$): $\delta = -45.12$ (m, 1F, CF_2H), -43.79 (m, 1F, CF_2H), 6.72 (t, $^4J = 9$ Hz, 3F, CF_3). Anal. Calcd for $C_{14}H_{13}F_5S_2$: C, 49.40; H, 3.85. Found: C, 49.85; H, 4.11. MS (m/z): 340 $[M]^+$, 325 $[M-CH_3]^+$, 289 $[M-CF_2H]^+$, 271 $[M-CF_3]^+$, 205 $[M-CH_3-CF_2H-CF_3]^+$, 187 $[M-CF_3-S_2-HF]^+$, 156 $[M-CF_2H-CF_3-S_2]^+$, 69 $[CF_3]^+$.

2-Phenyl-4-trifluoromethylthiophene (12)

9a (0.25 g, 1 mmol) and $LiAlH_4$ (0.11 g, 3 mmol) were stirred at room temperature in 10 ml dioxane for 3 days. The reaction was quenched with 10 ml water, acidified with 0.1 N H_2SO_4 , and extracted with 10 ml ether (3x). The ethereal solution was dried ($MgSO_4$) and evaporated in vacuo. The white solid was purified by sublimation. Yield 0.18 g (80%); mp $54^\circ C$; ir (KBr): $\nu = 3440, 1560, 1465, 1410$ cm^{-1} ; 1H nmr ($CDCl_3$): $\delta = 7.37$ (m, 4H, phenyl H, thiophene H), 7.56 (m, 2H, phenyl H), 7.60 (m, 1H, phenyl H); ^{13}C nmr ($CDCl_3$): $\delta = 119.92$ (q, $^3J = 2$ Hz, thiophene C-3), 121.99 (q, $^1J = 270$ Hz, CF_3), 125.31 (q, $^3J = 5$ Hz, thiophene C-5), 126.04, 128.47, 129.09 (phenyl C), 132.40 (q, $^2J = 36$ Hz, thiophene C-4), 133.07 (phenyl C), 146.79 (thiophene C-2); ^{19}F nmr ($CDCl_3$): $\delta = 17.90$ (s, 3F, CF_3). Anal. Calcd for $C_{11}H_7F_3S$: C, 57.89; H, 3.09. Found: C, 57.89; H, 2.80. MS (m/z): 228 $[M]^+$, 209 $[M-F]^+$, 207 $[M-HF-H]^+$, 189 $[M-F-HF]^+$, 183 $[M-H-CS]^+$, 115 $[M-CF_3-CS]^+$.

2-Amino-5-phenyl-3-trifluoromethylthiophenes (13)

General Procedure: A solution of **9a** (0.25 g, 1 mmol) and of a secondary amine (2 mmol) in 4 ml dioxane was stirred at room temperature for 12 days. After addition of 10 ml water, the reaction mixture was extracted three times with 10 ml ether (3x). The ether solution was dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue was purified by column chromatography (eluant: chloroform/hexanes).

2-Morpholino-5-phenyl-3-trifluoromethylthiophene (13a)

Yield 0.29 g (93%); mp $70^\circ C$; ir (KBr): $\nu = 3450, 1575, 1520, 1490, 1465, 1415$ cm^{-1} ; 1H nmr ($CDCl_3$): $\delta = 3.07$ (m, 4H, 2x NCH_2), 3.85 (m, 4H, 2x OCH_2), 7.19 (s, 1H, thiophene C(4)-H), 7.33 (m, 3H, phenyl H), 7.51 (m, 2H, phenyl H); ^{13}C nmr ($CDCl_3$): $\delta = 54.82$ (NCH_2), 66.63 (OCH_2), 119.63 (q, $^2J = 33$ Hz, thiophene C-3), 119.65 (q, $^3J = 3$ Hz, thiophene C-4), 122.26 (q, $^1J = 271$ Hz, CF_3), 125.27, 127.71, 128.92, 133.49 (phenyl C), 135.76 (thiophene C-5), 158.50 (q, $^3J = 3$ Hz, thiophene C-2); ^{19}F nmr ($CDCl_3$): $\delta = 20.1$ (s, 3F, CF_3). Anal. Calcd for $C_{15}H_{14}NOF_3S$: C, 57.50; H, 4.50; N, 4.47. Found: C, 57.64; H, 4.49; N, 4.57. MS (m/z): 313 $[M]^+$, 255 $[M-C_3H_6O]^+$.

5-Phenyl-2-piperidino-3-trifluoromethylthiophene (13b)

Yield 0.28 g (90%); oil; ir (film): $\nu = 2940, 2860, 2810, 1600, 1565, 1510, 1450, 1405$ cm^{-1} ; 1H nmr ($CDCl_3$): $\delta = 1.54$ (m, 2H, piperidine C(4)-H), 1.70 (m, 4H, piperidine C(3)-H, C(5)-H), 3.01 (m, 4H, piperidine C(2)-H, C(6)-H), 7.16 (s, 1H, thiophene C(4)-H), 7.23 (m, 1H, phenyl H), 7.32 (m, 2H,

phenyl H), 7.48 (m, 2H, phenyl H); ^{13}C nmr (CDCl_3): δ = 23.75, 25.85, 56.20 (piperidine C), 118.04 (q, ^2J = 33 Hz, thiophene C-3), 119.80 (q, ^3J = 3 Hz, thiophene C-4), 122.61 (q, ^1J = 271 Hz, CF_3), 125.21, 127.44, 128.93, 133.91, 134.38 (phenyl C, thiophene C-5), 160.37 (q, ^3J = 3 Hz, thiophene C-2); ^{19}F nmr (CDCl_3): δ = 20.20 (s, 3F, CF_3). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{NF}_3\text{S}$: C, 61.72; H, 5.18; N, 4.50. Found: C, 61.55; H, 5.34; N, 4.37. Ms (m/z): 311 $[\text{M}]^+$, 228 $[\text{M}-\text{C}_5\text{H}_9\text{N}]^+$, 183 $[\text{M}-\text{C}_5\text{H}_9\text{N}-\text{CHS}]^+$, 114 $[\text{M}-\text{C}_5\text{H}_9\text{N}-\text{CHS}-\text{CF}_3]^+$, 77 $[\text{C}_6\text{H}_5]^+$, 69 $[\text{CF}_3]^+$.

5-(2-Fluorophenyl)-2-pyrrolidino-3-trifluoromethylthiophene (13c)

Yield 0.27 g (85%); oil; ir (film): 2970, 2820, 1555, 1510, 1480, 1460, 1405 cm^{-1} ; ^1H nmr (CDCl_3): δ = 2.02 (m, 4H, pyrrolidine C(3)-H, C(4)-H), 3.44 (m, 4H, pyrrolidine C(2)-H, C(5)-H), 7.10 (m, 3H, aryl H), 7.34 (s, 1H, thiophene C(4)-H), 7.44 (m, 1H, aryl H); ^{13}C nmr (CDCl_3): δ = 26.14, 52.68 (pyrrolidine C), 104.17 (q, ^2J = 35 Hz, thiophene C-3), 116.17 (d, ^2J = 22 Hz, aryl C-3), 122.04 (d, ^2J = 13 Hz, aryl C-1), 123.70 (q, ^1J = 268 Hz, CF_3), 124.38 (d, ^3J = 3 Hz, aryl C-6), 125.59 (dq, ^4J = 8 Hz, ^3J = 4 Hz, thiophene C-4), 127.01, 127.07 (aryl C-5, thiophene C-5), 127.18 (d, ^3J = 8 Hz, aryl C-4), 156.21 (m, thiophene C-2), 158.77 (d, ^1J = 249 Hz, aryl C-2); ^{19}F nmr (CDCl_3): δ = -37.05 (m, 1F, aryl C(2)-F), 28.25 (s, 3F, CF_3). Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{NF}_4\text{S}$: C, 57.14; H, 4.16; N, 4.44. Found: C, 57.17; H, 4.24; N, 4.44. Ms (m/z): 315 $[\text{M}]^+$, 273 $[\text{M}-\text{C}_3\text{H}_6]^+$, 259 $[\text{M}-\text{C}_4\text{H}_8]^+$, 176 $[\text{M}-\text{C}_6\text{H}_4\text{FCS}]^+$, 139 $[\text{C}_6\text{H}_4\text{FCS}]^+$, 120 $[\text{C}_6\text{H}_4\text{CS}]^+$, 95 $[\text{C}_6\text{H}_4\text{F}]^+$, 69 $[\text{CF}_3]^+$, 43 $[\text{C}_3\text{H}_7]^+$.

2-(1-Methylethoxy)-5-phenyl-3-trifluoromethylthiophene (14a)

To 0.25 g (3 mmol) of freshly prepared sodium isopropoxide in 5 ml dioxane **9a** (0.25 g, 1 mmol) was added with stirring. After 1 h the reaction mixture was filtered, 10 ml 1 N NaOH were added, then the mixture was extracted with 10 ml ether (3x). The combined organic layers were dried (MgSO_4) and evaporated to dryness in vacuo. The crude product was purified by column chromatography (eluant: chloroform/hexanes). Yield 0.27 g (93%); mp 57 $^\circ\text{C}$; ir (KBr): ν = 1590, 1525, 1500, 1460, 1420, 1400 cm^{-1} ; ^1H nmr (CDCl_3): δ = 1.43 [d, ^3J = 6 Hz, 6H, $\text{CH}(\text{CH}_3)_2$], 4.44 [sept, ^3J = 6 Hz, $\text{CH}(\text{CH}_3)_2$], 7.05 (s, 1H, thiophene C(4)-H), 7.32 (m, 3H, phenyl H), 7.47 (m, 2H, phenyl H); ^{13}C nmr (CDCl_3): δ = 21.97 $[\text{CH}(\text{CH}_3)_2]$, 80.59 (OCH), 113.79 (q, ^2J = 34 Hz, thiophene C-3), 117.95 (q, ^3J = 3 Hz, thiophene C-4), 122.13 (q, ^1J = 270 Hz, CF_3), 125.04, 127.49, 128.96 (phenyl C), 130.51 (thiophene C-5), 133.52 (phenyl C), 163.36 (q, ^3J = 3 Hz, thiophene C-2); ^{19}F nmr (CDCl_3): δ = 19.73 (s, 3F, CF_3). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{OF}_3\text{S}$: C, 58.73; H, 4.58. Found: C, 58.81; H, 4.58. Ms (m/z): 286 $[\text{M}]^+$, 244 $[\text{M}-\text{C}_3\text{H}_6]^+$, 243 $[\text{M}-\text{C}_3\text{H}_7]^+$, 225 $[\text{M}-\text{C}_3\text{H}_6\text{F}]^+$, 224 $[\text{M}-\text{C}_3\text{H}_7\text{F}]^+$, 196 $[\text{M}-\text{C}_3\text{H}_7\text{F}-\text{CO}]^+$, 121 $[\text{C}_6\text{H}_5\text{CS}]^+$, 77 $[\text{C}_6\text{H}_5]^+$, 43 $[\text{C}_3\text{H}_7]^+$, 42 $[\text{C}_3\text{H}_6]^+$.

5-(4-Chlorophenyl)-2-(4-phenylphenoxy)-3-trifluoromethylthiophene (14b)

A mixture of **9d** (0.34 g, 1.2 mmol), 4-hydroxybiphenyl (0.17 g, 1.2 mmol), and KOH (0.11 g, 2 mmol) in 5 ml dioxane was heated up to 80 $^\circ\text{C}$ for 6 h. After addition of 10 ml of water, the reaction mixture was extracted with 10 ml ether (3x). The combined organic layer was dried (MgSO_4) and evaporated to dryness in vacuo. The crude product was purified by column chroma-

tography (eluant: chloroform/hexanes, 1:1). Yield 0.26 g (51%); mp 140 °C; ir (KBr): ν = 1580, 1515, 1490, 1420, 1400 cm^{-1} ; ^1H nmr (CDCl_3): δ = 7.15 (s, 1H, thiophene C(4)-H), 7.25 (m, 2H, aryl H), 7.39 (m, 7H, aryl H), 7.59 (m, 4H, aryl H); ^{13}C nmr (CDCl_3): δ = 117.41 (q, 2J = 35 Hz, thiophene C-3), 118.34 (q, 3J = 3 Hz, thiophene C-4), 121.62, (q, 1J = 271 Hz, CF_3), 126.57, 127.04, 127.46, 128.67, 128.88, 129.26, 129.41, 131.61 (aryl C), 132.82 (thiophene C-5), 134.01, 138.38, 140.07, 157.72 (aryl C), 160.45 (q, 3J = 3 Hz, thiophene C-2); ^{19}F nmr (CDCl_3): δ = 19.33 (s, 3F, CF_3). Anal. Calcd for $\text{C}_{23}\text{H}_{14}\text{ClO}_2\text{F}_3\text{S}$: C, 64.11; H, 3.28. Found: C, 63.85; H, 3.44. Ms (m/z): 432/430 $[\text{M}]^+$, 279/277 $[\text{M}-\text{C}_{12}\text{H}_9]^+$, 153 $[\text{C}_{12}\text{H}_9]^+$, 152 $[\text{C}_{12}\text{H}_8]^+$.

2-(1-Methylimidazol-2-ylmercapto)-5-phenyl-3-trifluoromethylthiophene (15)

9a (0.25 g, 1 mmol), 2-mercapto-1-methylimidazole (0.23 g, 2 mmol) and KOH (0.05 g, 1 mmol) are heated in 5 ml dioxane until no **9a** could be identified by ^{19}F nmr spectroscopy. After addition of 20 ml water the reaction mixture was extracted with 20 ml ether (3x). The ether solution was dried (MgSO_4) and evaporated in vacuo. The residue was purified by column chromatography (eluant: hexanes/chloroform). Yield 0.33 g (96%); mp 68 °C; ir (KBr): ν = 3450, 1460, 1440, 1420 cm^{-1} ; ^1H nmr (CDCl_3): δ = 3.72 (s, 3H, CH_3), 7.05, 7.18, 7.27 (3x s, 3H, thiophene C(4)-H, imidazole C(4)-H, C(5)-H), 7.29 (m, 3H, phenyl H), 7.43 (m, 2H, phenyl H); ^{13}C nmr (CDCl_3): δ = 33.72 (CH_3), 121.09 (q, 3J = 3 Hz, thiophene C-4), 121.68 (q, 1J = 272 Hz, CF_3), 124.11, 125.43, 128.48, 128.88, 130.31 (phenyl C, imidazole C), 130.77 (q, 2J = 34 Hz, thiophene C-3), 132.22 (phenyl C), 134.52 (q, 3J = 2 Hz, thiophene C-2), 136.80 (imidazole C-2), 146.61 (thiophene C-5); ^{19}F nmr (CDCl_3): δ = 20.20 (s, 3F, CF_3). Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{F}_3\text{S}_2$: C, 52.93; H, 3.26; N, 8.23. Found: C, 52.93; H, 3.18; N, 8.28. Ms (m/z): 340 $[\text{M}]^+$, 271 $[\text{M}-\text{CF}_3]^+$, 195 $[\text{M}-\text{C}_4\text{H}_5\text{N}_2\text{S}_2]^+$, 121 $[\text{C}_6\text{H}_5\text{CS}]^+$, 77 $[\text{C}_6\text{H}_5]^+$.

2-Cyano-5-phenyl-3-trifluoromethylthiophene (16)

9a (0.21 g, 0.8 mmol), potassium cyanide (0.07 g, 1.6 mmol) and catalytical amounts of 18-crown-6 were stirred in 5 ml dioxane at room temperature for 9 days. After addition of 10 ml 1N NaOH the reaction mixture was extracted with 10 ml ether (3x). The ether phase was dried (MgSO_4) and evaporated in vacuo. The residue was sublimed in high vacuo. Yield 0.18 g (89%); mp 69 °C; ir (KBr): ν = 3440, 2220, 1460, 1445, 1410 cm^{-1} ; ^1H nmr (CDCl_3): δ = 7.44 (s, 1H, thiophene C(4)-H), 7.47 (m, 3H, phenyl H), 7.59 (m, 2H, phenyl H); ^{13}C nmr (CDCl_3): δ = 108.16 (q, 3J = 3 Hz, thiophene C-2), 111.12 (CN), 120.48 (q, 1J = 272 Hz, CF_3), 121.22 (q, 3J = 3 Hz, thiophene C-4), 126.48, 129.61, 130.47, 131.07 (phenyl C), 139.64 (q, 2J = 36 Hz thiophene C-3), 152.46 (thiophene C-5); ^{19}F nmr (CDCl_3): δ = 18.17 (s, 3F, CF_3). Anal. Calcd for $\text{C}_{12}\text{H}_6\text{NF}_3\text{S}$: C, 56.91; H, 2.39; N, 5.53. Found: C, 56.92; H, 2.37; N, 5.57. Ms (m/z): 253 $[\text{M}]^+$, 233 $[\text{M}-\text{HF}]^+$, 190 $[\text{M}-\text{CS}, -\text{F}]^+$, 184 $[\text{M}-\text{CF}_3]^+$.

5-Aryl-2-phenyl-3-trifluoromethylthiophene (17)

General Procedure: To a stirred solution of **9** (1 mmol) in 5 ml tetrahydrofuran 1.5 ml of a 2.0 M solution of phenyllithium in tetrahydrofuran was added dropwise. After 10 min the reaction was quenched with water (20 ml) at 0 °C and extracted with 20 ml ether (3x). The ether phase was dried (MgSO₄) and evaporated in vacuo. The crude product was purified by column chromatography (eluant: hexanes).

2,5-Diphenyl-3-trifluoromethylthiophene (17a)

Yield 0.20 g (67%); mp 55 °C; ir (KBr): ν = 1600, 1560, 1490, 1470, 1450, 1400 cm⁻¹; ¹H nmr (CDCl₃): δ = 7.40 (m, 7H, phenyl H, thiophene C(4)-H), 7.59 (m, 4H, phenyl H); ¹³C nmr (CDCl₃): δ = 121.95 (q, ³J = 3 Hz, thiophene C-4), 122.31 (q, ¹J = 271 Hz, CF₃), 127.21 (q, ²J = 34 Hz, thiophene C-3), 125.73, 127.13, 128.33, 128.44, 128.73, 128.96, 129.08, 129.39, 131.95, 132.97 (phenyl C), 143.95 (thiophene C-5), 144.71 (q, ³J = 3 Hz, thiophene C-2); ¹⁹F nmr (CDCl₃): δ = 22.36 (s, 3F, CF₃). Anal. Calcd for C₁₇H₁₁F₃S: C, 67.09; H, 3.64. Found: C, 67.09; H, 3.60. Ms (m/z): 304 [M]⁺, 235 [M-CF₃]⁺, 121 [C₆H₅CS]⁺, 77 [C₆H₅]⁺.

5-(4-Methoxyphenyl)-2-phenyl-3-trifluoromethylthiophene (17b)

Yield 0.23 g (70%); mp 41 °C; ir (KBr): ν = 2975, 1610, 1525, 1475, 1400 cm⁻¹; ¹H nmr (CDCl₃): δ = 3.81 (OCH₃), 6.91 (m, 2H, aryl H), 7.21 (s, 1H, thiophene C(4)-H), 7.40 (m, 3H, aryl H), 7.50 (m, 2H, aryl H), 7.51 (m, 2H, aryl H); ¹³C nmr (CDCl₃): δ = 55.34 (OCH₃), 114.50 (aryl C), 120.92 (q, ³J = 3 Hz, thiophene C-4), 122.38 (q, ¹J = 272 Hz, CF₃), 125.78, 127.10 (aryl C), 127.10 (q, ²J = 34 Hz, thiophene C-3), 128.44, 128.86, 129.39, 129.42, 132.10 (aryl C), 143.68 (q, ³J = 3 Hz, thiophene C-2), 143.99 (thiophene C-5), 159.87 (aryl C); ¹⁹F nmr (CDCl₃): δ = 22.45 (s, 3F, CF₃). Anal. Calcd for C₁₈H₁₃OF₃S: C, 64.66; H, 3.92. Found: C, 64.45; N, 3.96. Ms (m/z): 334 [M]⁺, 319 [M-CH₃]⁺, 291 [M-CH₃-CO]⁺.

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