

Fluorinated Thiophenes and Their Analogues

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Contents

1	Introduction	234
2	Synthesis of Fluorothiophenes	235
2.1	Functionalization of the Thiophene Ring	235
2.2	Heterocyclization	239
3	Synthesis of Fluorobenzothiophenes	240
4	Synthesis of Perfluoroalkylthiophenes	242
4.1	Functionalization of the Thiophene Ring	242
4.2	Heterocyclization and Cycloaddition	250
5	Synthesis of Perfluoroalkylbenzothiophenes	255
6	Synthesis of Perfluoroarylthiophenes	258
6.1	Organometallic Synthesis	258
6.2	Cross-Coupling	260
6.3	Heterocyclization	264
7	Synthesis of Perfluoroarylbenzothiophenes	265
8	Benzothiophenes with Perfluorinated Carbocycle	266
9	Conclusion	268
	References	268

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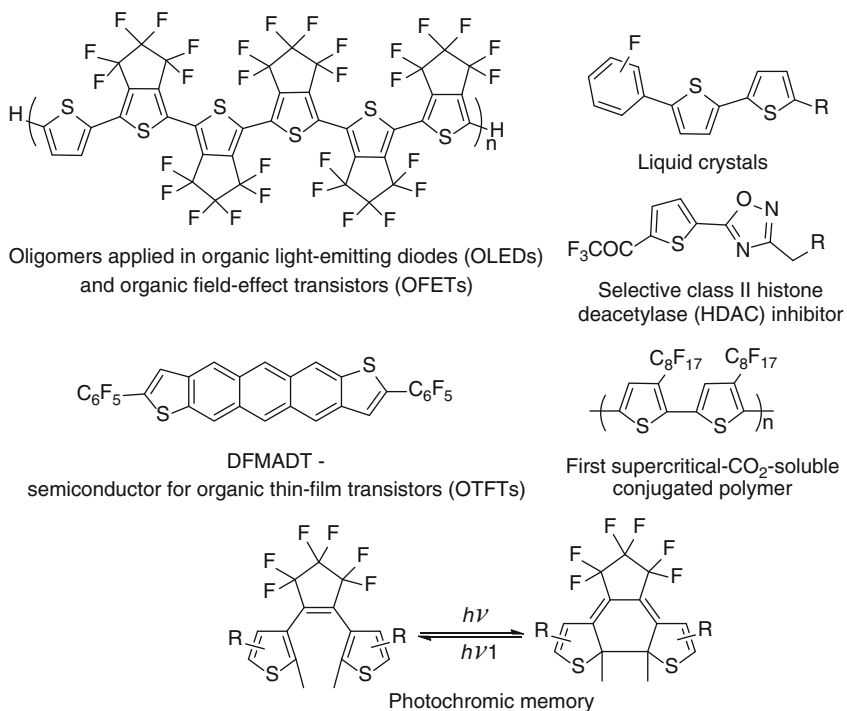
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Abstract The chapter is devoted to the synthesis and application of thiophenes (selenophenes) and benzothiophenes bearing fluorine atoms, CF_3 groups, and perfluorinated aryl fragments.

Keywords Thiophene • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

1 Introduction

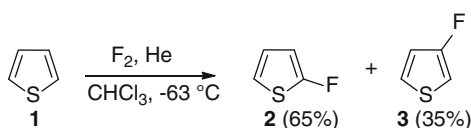
Fluorinated thiophene derivatives are widely used as soluble semiconductors [1], polymers [2], blue light emitting materials [3], and liquid crystals [4]. Some of them represent potent selective class II histone deacetylase (HDAC) inhibitors [5], agonists of sphingosine-1-phosphate (S1P) receptors [6], and some reveal fungicidal properties [7], anti-inflammatory, and immunoregulatory activity [8]. In addition, thiophene-substituted perfluorocyclopentenes are being investigated as thermally irreversible photochromic compounds having a high resistance to fatigue [9]. Herein, we describe methods for the preparation of thiophenes with a fluorine atom in the 2- and 3-position, and polyfluorothiophenes. These methods are classified into functionalization of the thiophene ring and heterocyclizations. This principle of classification is also applied for thiophenes with a perfluoroalkyl group, their benzo analogues, and benzothiophenes with four fluorine atoms on the carbocycle.



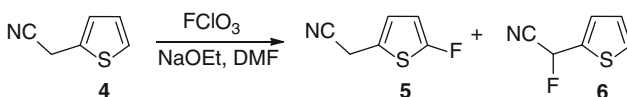
2 Synthesis of Fluorothiophenes

2.1 Functionalization of the Thiophene Ring

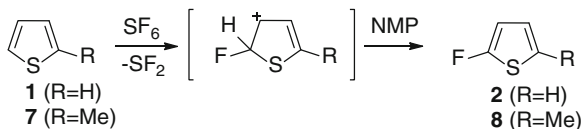
Direct fluorination of thiophene with molecular fluorine (F_2) is inconvenient as it is not selective process, owing to the extreme reactivity of molecular fluorine. For example, the reaction of thiophene **1** with fluorine at $-63\text{ }^\circ\text{C}$ (5 % F_2 in He) gave a mixture of 2- and 3-fluorothiophene **2** and **3** in a 2:1 ratio [10]. The synthesis of 3-fluorothiophene **3** is challenging due to the higher reactivity of the 2-position of thiophene. When a tenfold excess of fluorine was used, the 3-substituted isomer **3** (68 %) was three times more abundant than the 2-substituted product **2**.



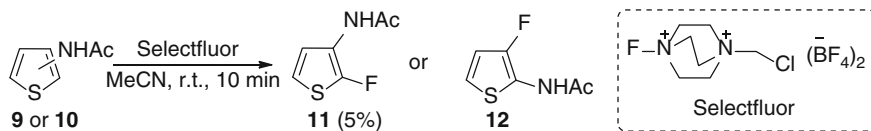
The treatment of 2-(thiophene-2-yl)acetonitrile **4** with perchloryl fluoride ($FCIO_3$) in N,N -dimethylformamide in the presence of sodium ethoxide was also not selective. The formation of 2-(5-fluorothiophen-2-yl)acetonitrile **5** was accompanied by fluorination of the methylene group to give 2-fluoro-(2-thiophen-2-yl)acetonitrile **6** [11].



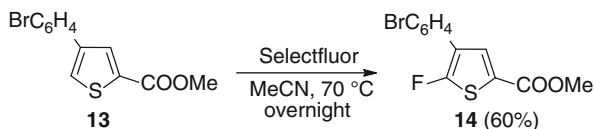
Gaseous SF_3^+ is a gentle and effective electrophilic monofluorinating reagent for five-membered heterocyclic compounds. The reaction of thiophenes **1,7** with gaseous SF_3^+ , generated by electron ionization of sulfur hexafluoride and acting as a source of fluorine cation (F^+), is one more example of a direct fluorination process [12].



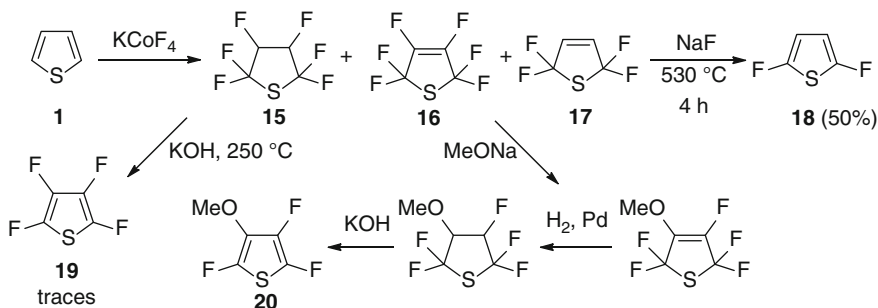
1-(Chloromethyl)-4-fluoro-1,4-diazobicyclo[2.2.2]octane tetrafluoroborate (SelectfluorTM) can also serve as selective fluorinating reagent. Thus 3-acetamidothiophene **9** was fluorinated in the 2-position exclusively on treatment with SelectfluorTM, but the yield of **11** was 5 % [13]. Fluorination of the isomeric 2-acetamidothiophene **10** gave the 3-fluorinated product **12** in low yield.



However, the 60 % conversion was achieved using Selectfluor for the overnight performed fluorination reaction of methyl thiophene-2-carboxylate derivative **13** [14].

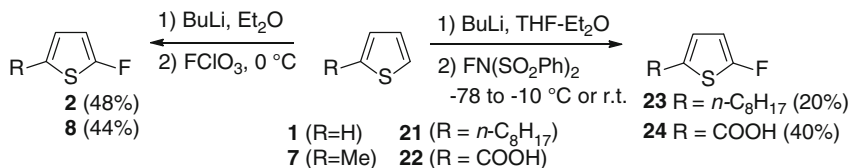


Thiophene **1** was fluorinated with potassium tetrafluorocobaltate(III) (KCoF_4) to give a mixture of hexafluorotetrahydrothiophene **15** and 2,2,5,5-tetrafluoro-2,5-dihydrothiophene **17** as major products. When hexafluorotetrahydrothiophene **15** was bubbled through molten potassium hydroxide, tetrafluorothiophene **19** was formed in low yield. When sodium methoxide was used, substitution of fluoride took place [15]. 2,5-Difluorothiophene **18** was obtained in 50 % yield by heating of 2,2,5,5-tetrafluoro-2,5-dihydrothiophene **17** with sodium fluoride at 530 °C. These conditions were found to be optimal, since the reaction did not occur at moderate temperatures (<480 °C). However, at 530 °C side reactions also took place, thus accounting for the only moderate yield of 2,5-difluorothiophene **18** [16].

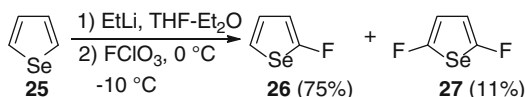


A more convenient approach to the synthesis of fluorothiophenes was based on the reaction of their organolithiums (easily prepared by metallation or halogen-metal exchange) with electrophilic fluorinating reagents such as perchloryl fluoride [17] or *N*-fluorodibenzenesulfonimide [18]. The yields of target fluorinated thiophenes **2**, **8** and **23**, **25** were moderate. This approach was proposed by Gronowitz and Rosén [19] for the preparation of various substituted 2-fluorothiophenes and 3-fluorothiophenes. Complications can arise in the case of halogen-metal exchange: rearrangement can occur if the thienyllithium is thermodynamically unstable. The

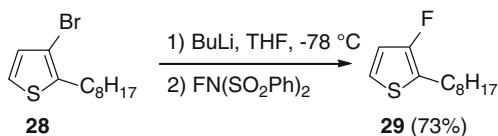
metallation of 2- and 3-fluorothiophenes followed by reaction with electrophiles was found to provide substituted 2-fluorothiophenes and 3-fluorothiophenes, since fluorine does not interfere in the metallation or in the halogen-metal exchange.



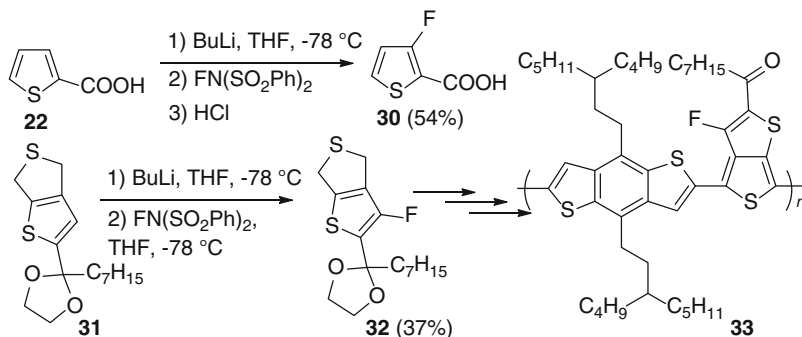
Fluorination of 2-selenophenyllithium **25** with perchloryl fluoride gave a mixture of 2-selenophene **26** and 2,5-difluoroselenophene **27** [20].



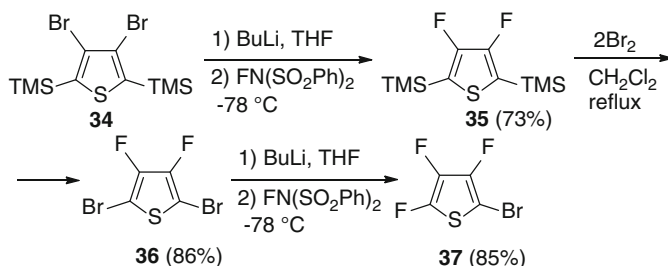
3-Fluorothiophene derivatives were easily obtained starting from the corresponding 3-bromothiophenes (Br-Li exchange). For example, the reactions of 3-thienyllithium obtained from **28** with N-fluorodibenzene-sulfonimide as electrophilic fluorinating reagent led to the 3-fluorosubstituted thiophene **29** [18, 21].



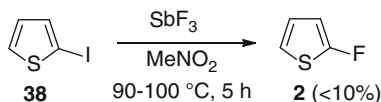
In some cases, the direct metallation was also applied for the synthesis of 3-fluorothiophenes. Thus, 3-fluorothiophene-2-carboxylic acid **30** was prepared in two steps from the corresponding thiophene-2-carboxylic acid **22** by treatment with *n*-butyllithium followed by reaction with N-fluorodibenzene-sulfonimide [22]. This approach was applied to the synthesis of monomer **32** for thieno[3,4-*b*]thiophene polymers **33** used in organic solar cells [23].



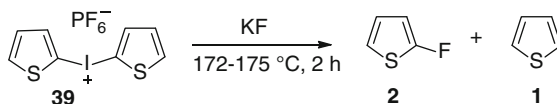
Another convenient approach is based on the use of *N*-fluorodibzenzenesulfonimide. 2,3-Difluoro-, 2,4-difluoro- [18], 3,4-difluoro-, and 2,3,4-trifluorothiophenes can be prepared by this method. Thus, lithiation of 2,5-di(trimethylsilyl)-3,4-dibromothiophene **34** with *n*-BuLi followed by treatment with *N*-fluorodibzenzenesulfonimide provides 3,4-difluoro-2,5-bis(trimethylsilyl)-thiophene **35**. The latter was transformed into 2,5-dibromo-3,4-difluorothiophene **36**. 1-Bromo-2,3,4-trifluorothiophene **37** was prepared similarly [24].



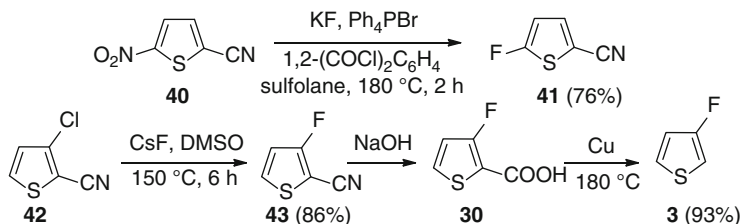
The first reported method for the preparation of 2-fluorothiophene **2** was the reaction of 2-iodothiophene **38** with SbF₃ in nitromethane. However, the method was inconvenient since it gave the target 2-fluorothiophene **2** in less than 10 % yield [25].



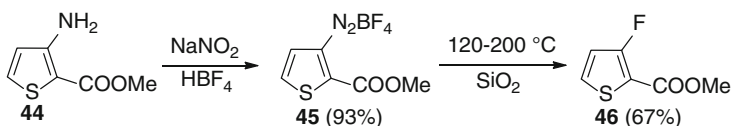
A more useful approach to fluorothiophenes was based on transformations of iodonium salts. 2-Thienyliodonium salts, for example dithiophen-2-ylidonium hexafluorophosphate **39**, afford 2-fluorothiophene **2** (37 %) and thiophene **1** (20 %) after treatment with potassium fluoride and heating at 172–175 °C [26].



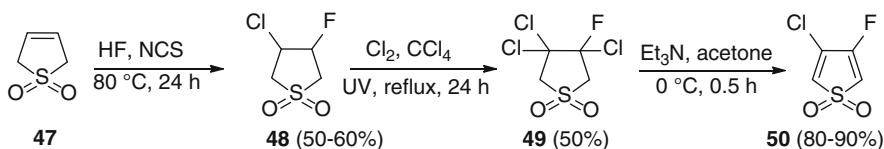
It is known that nitro group is a good leaving group for aromatic nucleophilic substitution and can be substituted by fluoride. For example, 5-nitrothiophene-2-carbonitrile **40** reacted with potassium fluoride in the presence of tetraphenylphosphonium bromide and phthaloyl dichloride in sulfolane at 180 °C providing 5-fluoro-2-cyanothiophene-2-carbonitrile **41** in 76 % yield [14, 27]. The reaction of 2-cyano-3-chlorothiophene **42** with CsF in dimethylsulfoxide gave 2-cyano-3-fluorothiophene **43** in 86 % yield. Subsequent hydrolysis by sodium hydroxide and decarboxylation gave 3-fluorothiophene **3** in 93 % yield [28].



One more method for the synthesis of 3-fluorothiophene is based on the thermal decomposition of a diazonium tetrafluoroborate (Schiemann reaction), which has been successfully used in the synthesis of a variety of fluorobenzenes. The reaction was carried out by heating of thiophene diazonium salt **45** in dry xylene (48 %) [29] or in a mixture with silica gel under vacuum (67 %) [13, 30].

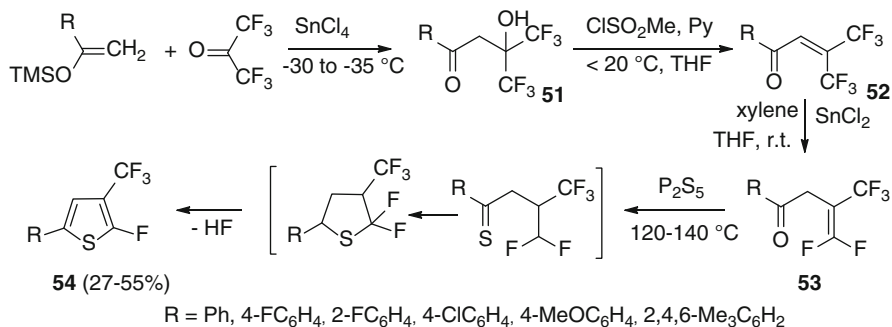


The straightforward synthetic route to 3-chloro-4-fluorothiophene-1,1-dioxide **50** involved chlorofluorination of 3-sulfolene **47**, photochemical chlorination, and dehydrochlorination of 3,3,4-trichloro-4-fluorosulfolene **49** [31].

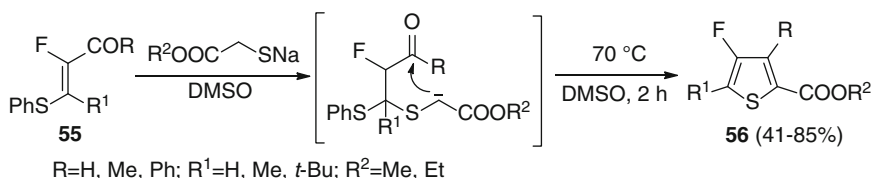


2.2 Heterocyclization

The transformation of 4,4-difluoro-3-trifluoromethylbut-3-ene-1-ones **53**, easily prepared from hexafluoroacetone (HFA), into 2-fluoro-3-trifluoromethylthiophenes **54** proceeded on heating with phosphorus pentasulfide [32]. Yields of 2-fluoro-3-trifluoromethylthiophenes **54** depend on the reaction conditions and the progress of the transformation should be monitored by ^{19}F NMR spectroscopy. The starting compounds were formed by elimination of water from hexafluoroacetone aldols **51** obtained by reaction of HFA with enol silyl ethers in the presence of Lewis acid such as SnCl_4 . The unsaturated ketones **52** were reduced with SnCl_2 and **53** were cyclized to the desired thiophenes **54** with phosphorus pentasulfide [33].

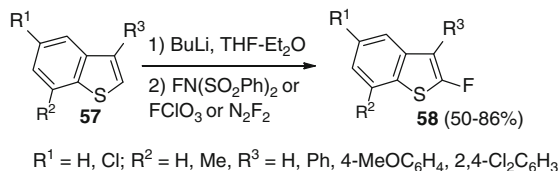


The reaction of (*Z*)- α -fluoro- β -(phenylthio)butanones **55** with methyl or ethyl thioglycolate in dimethylsulfoxide led to substituted 3-fluorothiophenes **56** in moderate to high yields. The authors proposed nonclassical nucleophilic vinylic substitution mechanism, occurring through an enolate intermediate. The first step of the sequence is the Michael addition that gives enolate; subsequent cyclization and aromatization leads to the target 3-fluorothiophenes **56** [34].



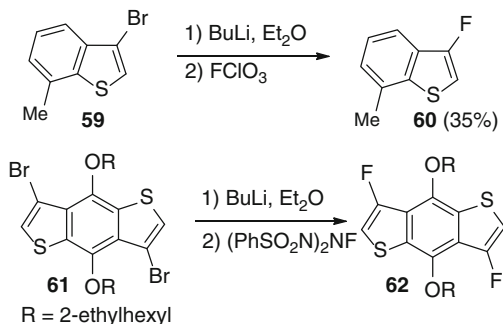
3 Synthesis of Fluorobenzothiophenes

Methods for the synthesis of fluorobenzothiophenes are rare. A lithiation-fluorination sequence by treatment of benzothiophenes **57** with *n*-BuLi followed by fluorination with perchloryl fluoride [35], N_2F_2 [36], or *N*-fluorodibzenzenesulfonimide afforded 2-fluorobenzo[*b*]thiophenes **58** in good yields [37].

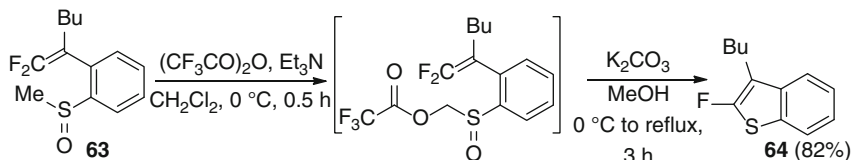


3-Fluorobenzo[*b*]thiophenes **60** and **62** were synthesized from the lithiated precursors by treatment with perchloryl fluoride [35] or *N*-fluorodibzenzenesulfonimide

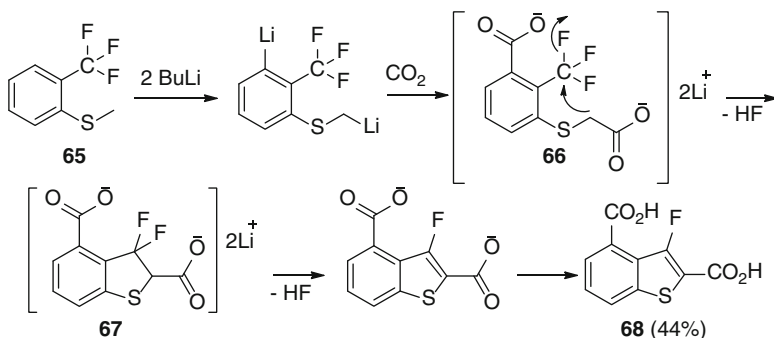
in good yields [38]. The lithium derivatives were obtained from 3-bromobenzo[*b*]thiophene derivatives **59** and **61** and *n*-butyllithium.



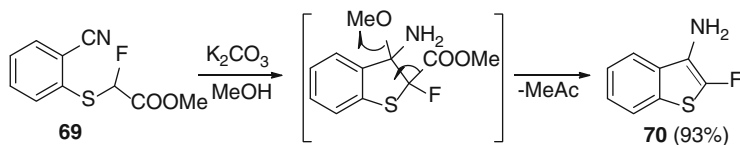
Fluorobenzo[*b*]thiophenes synthesis was also accomplished through a 5-*endo-trig* cyclization. Successive reaction of β,β -difluoro-*o*-methylsulfinylstyrene **63** first with trifluoroacetic anhydride and triethylamine in dichloromethane and then with potassium carbonate provided 2-fluorobenzo[*b*]thiophene **64** in 82 % yield [39].



3-Fluorobenzo[*b*]thiophene derivative **68** was prepared in 44 % yield starting from 4-(methylthio)-1-(trifluoromethyl)benzene **65** by double metallation with *n*-BuLi and subsequent reaction with CO₂. The primary intramolecular cyclization of **66** was anchimerically assisted by the carboxylate anion in *ortho* position and gave rise to a nucleophilic substitution of the fluorine atom by the SCH⁻ anion. The resulting intermediate **67** aromatized after acidification into 3-fluorobenzo[*b*]thiophene **68** [40].



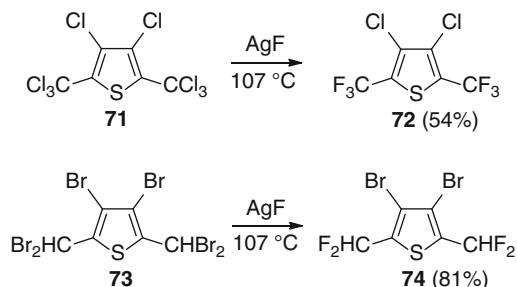
Fluorinated benzo[*b*]thiophene derivative **70** was synthesized in 93 % yield by the intramolecular cyclization of anodically fluorinated open-chain sulfide **69** containing the 2-cyanophenyl group [41].



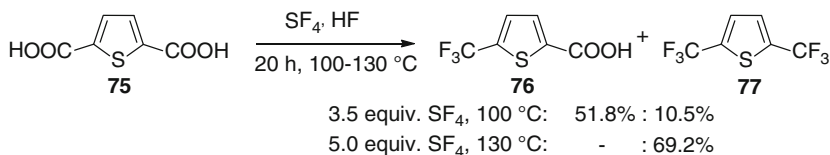
4 Synthesis of Perfluoroalkylthiophenes

4.1 Functionalization of the Thiophene Ring

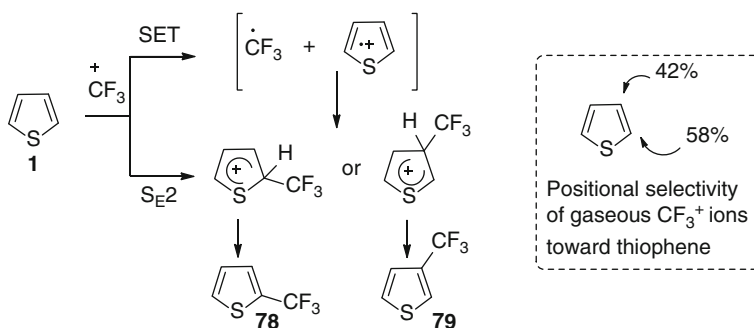
A perfluoroalkyl group can be incorporated onto the thiophene ring directly, or a haloalkyl substituent can be transformed into a perfluoroalkyl moiety. For example, treatment of 2,5-bis(trichloromethyl)-3,4-dichlorothiophene **71** with AgF resulted in exchange of chlorine by fluorine in the CCl₃-groups. It should be noted that no exchange took place for the chlorine atoms attached directly to the thiophene ring. In a similar way, brominated 2,5-dimethylthiophene **73** gave a 2,5-bis(difluoromethyl) thiophene derivative **74** under the same conditions [42].



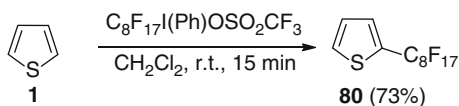
A very useful method for the introduction of a CF₃ group onto the thiophene ring is the transformation of a carboxylic group with SF₄. Depending on the conditions, thiophene-2,5-dicarboxylic acid **75** reacted with SF₄ and HF to produce 5-(trifluoromethyl)thiophene-2-carboxylic acid **76** and 2,5-bis(trifluoromethyl)-thiophene **77**. At lower temperature, the compound **76** was the major product, while **77** was obtained at 130 °C with five equivalents of SF₄ [43].



The direct trifluoromethylation of thiophene can be performed under electrophilic and radical conditions. The electrophilic reaction proceeded in the gas phase using trifluoromethyl cations obtained from CF_4 under radiolysis (^{60}Co γ -rays) [44]. The selectivity trend for thiophene in the gas phase follows the order $\text{C}2 > \text{C}3 > \text{S}1$. The major products of this transformation were found to be monosubstituted trifluoromethylthiophenes **78** and **79** (<20 % yield) [45]. It has been proposed that the trifluoromethylation proceeds through electrophilic substitution and single-electron transfer mechanisms.

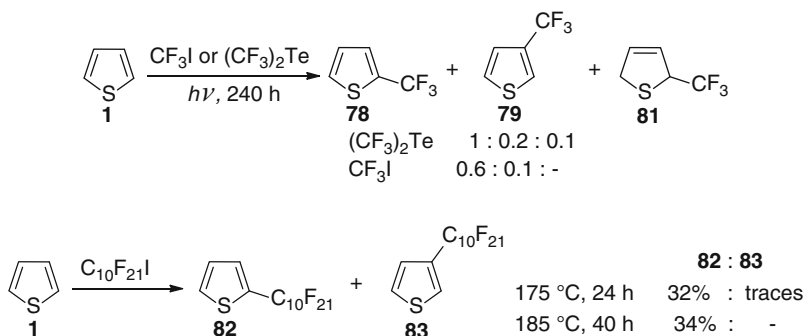


Electrophilic perfluoroalkylation has been performed with the use of iodonium salts $\text{R}_f\text{I}(\text{Ar})\text{X}$, where the perfluoroalkyl group is bonded with a positively charged heteroatom. The trifluoromethylation of thiophene **1** with $\text{C}_8\text{F}_{17}\text{I}(\text{Ph})\text{OSO}_2\text{CF}_3$ in dichloromethane at room temperature proceeds in 73 % yield in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as a base [46].

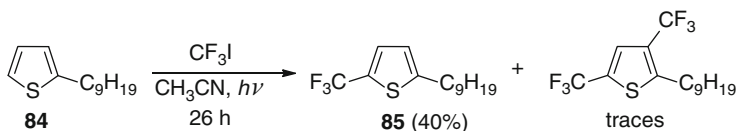


Radical perfluoroalkylation is more versatile because it can be performed under thermal, photolytic, oxidative, and reductive conditions. For example, the photochemical reaction of thiophene **1** with bis(trifluoromethyl)tellurium or trifluoromethyl iodide yields 2-trifluoromethylthiophene **78** as the major product. The most suitable reagent in this case was found to be bis(trifluoromethyl)tellurium. Similarly, perfluoroalkylation of thiophene with perfluorodecyl iodide under thermal

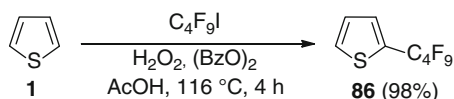
conditions (175 °C, 24 h, steel bomb) provided predominantly the 2-substituted isomer **82**. The latter was the sole product when the reaction was carried out at higher temperature [47].



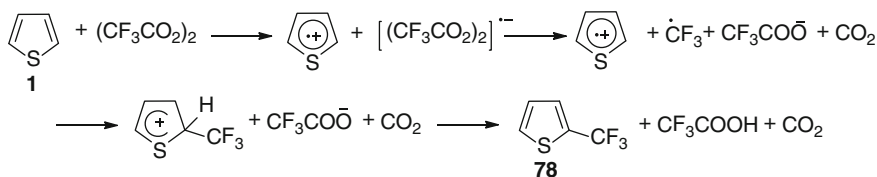
2-Nonylthiophene **84** was trifluoromethylated with trifluoromethyl iodide in acetonitrile under irradiation to produce 2-nonyl-5-trifluoromethylthiophene **85**. A trace amount of 3,5-bis(trifluoromethyl)-2-nonylthiophene was also formed in this reaction. However, the conversion was not complete and starting thiophene (25 %) was recovered [48].



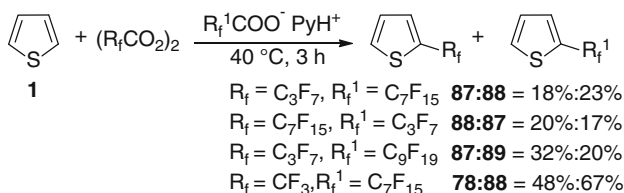
Nonfluoro-4-iodobutane can serve as a source of nonfluorobutyl radical under oxidative conditions. The reaction with thiophene **1** was carried out under reflux in AcOH in the presence of hydrogen peroxide and benzoyl peroxide. Other solvents appeared to be less effective, probably because hydrogen abstraction from the solvent by nonfluorobutyl radical competes with the attack of thiophene [49].



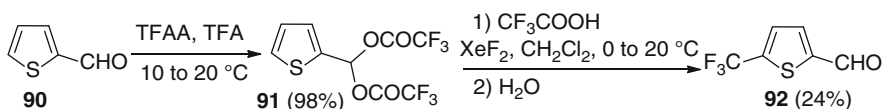
Perfluoroalkylation is often performed with bis(perfluoroalkanyl)peroxides, e.g. bis(trifluoroacetyl)peroxide and bis(heptafluorobutyl)peroxide, which are thermally stable, convenient to use, and can be obtained from the corresponding anhydrides and hydrogen peroxide in Freon 113 (CFCl₂CF₂Cl) as a solvent. Perfluoroalkoxyperoxides provide the same reactivity. The mechanism of the transformation includes oxidation of thiophene to radical cation, followed by reaction with perfluoro radical to produce 2-perfluoroalkylthiophenes [50].



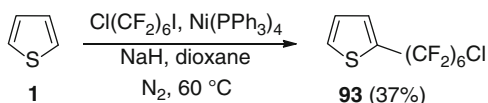
Interestingly, the perfluoroalkyl group can be incorporated onto the thiophene ring even if the corresponding peroxide cannot be synthesized. For example, when thiophene was treated with bis(perfluoroalkanoyl)peroxide in the presence of pyridinium perfluoroalkanoate, not only the perfluoroalkyl group of the peroxide, but also the perfluoroalkyl group of perfluoroalkanoate was incorporated [51].



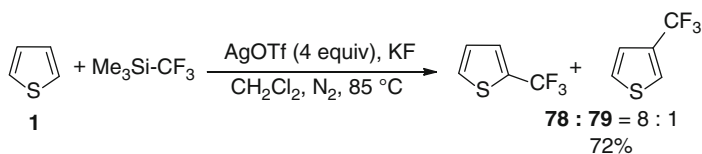
It is well known that xenon fluoride trifluoroacetate, obtained from XeF₂ and trifluoroacetic acid, is able to generate trifluoromethyl radicals which allow introduction of the trifluoromethyl group onto the aromatic ring at room temperature. The trifluoromethylation of thiophene-2-carbaldehyde bistrifluoro-acetate **91** gave 5-trifluoromethyl-thiophene-2-carbaldehyde **92** in 24 % yield [7].



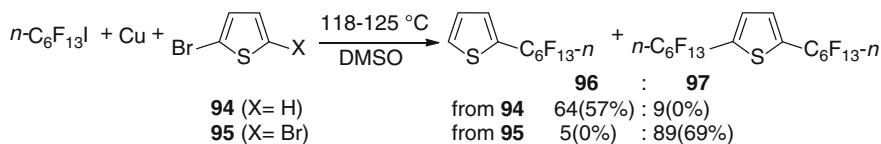
Fluoroalkylation reaction can also be performed using transition-metals catalysis. In the presence of a catalytic amount of tetrakis(triphenylphosphine)nickel, polyfluoroalkyl iodide reacted with thiophene to produce the 2-substituted isomer **93** as the sole product. To complete the reaction, addition of sodium hydride was required to absorb hydroiodic acid by-product [52].



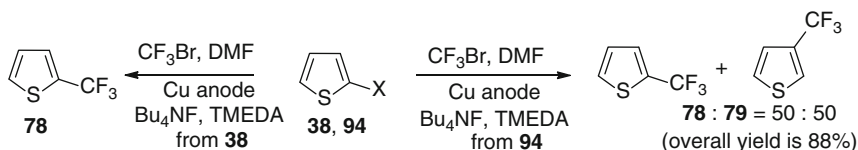
The silver-mediated trifluoromethylation of thiophene with TMSCF₃ gave 2- and 3-trifluoroderivatives **78** and **79** in 72 % total yield. The authors proposed that the reaction proceeds via AgCF₃ intermediates [53].



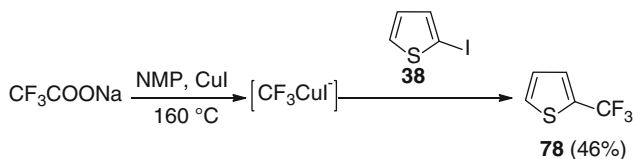
The copper-promoted substitution of halogen atoms on the thiophene ring provides another method for perfluoroalkylation. For example, 2-perfluorohexylthiophene **96** and 2,5-bis(perfluorohexyl)-thiophene **97** were obtained from the corresponding bromothiophenes **94** and **95** and perfluorohexyl iodide in dimethylsulfoxide (isolated yields are given in parentheses) through reaction with the organocopper intermediate, perfluorohexyl copper(I) [54]. More detailed information about fluorinated organometallics and their use in organic synthesis was presented in a review [55], and some examples of copper-promoted perfluoroalkylation of halothiophenes are also described in papers [2b, 8, 56].



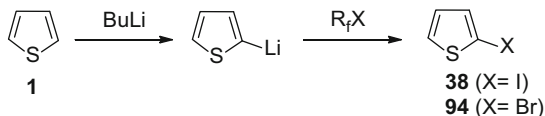
Another method of trifluoromethylation was based on the electrochemical reaction (copper anode) of 2-bromothiophene **94** with bromotrifluoromethane in DMF. In comparison to usual methods leading to trifluoromethylcopper, this one offered an advantage because it allowed the use of CF_3Br instead of the more expensive CF_3I . However, the reaction was not selective and gave a mixture of 2- and 3-isomers **78** and **79**. The use of 2-iodothiophene **38** as a starting material was found to be more effective: 2-trifluoromethylthiophene **78** was obtained in 60% yield [57].



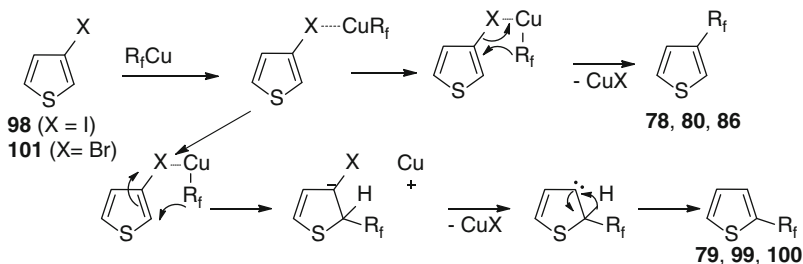
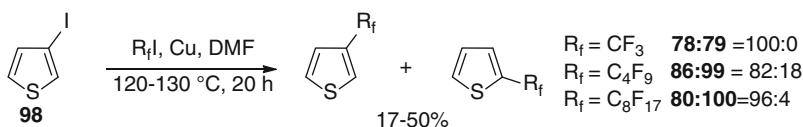
Sodium trifluoroacetate, in the presence of copper(I) iodide, was also used as trifluoromethyl source to replace halogen by trifluoromethyl group in the thiophene system. Sodium trifluoroacetate was decarboxylated, forming fluoroform, when heated alone in aqueous N-methylpyrrolidin-2-one. The addition of copper(I) iodide increased the rate of decarboxylation dramatically. The mechanism of this process was explored and an intermediate $[\text{CF}_3\text{CuI}]^-$ was proposed. Introduction of higher perfluoroalkyl groups from their corresponding sodium perfluoroalkane carboxylates was also shown to be possible [58].



The reaction of 2-thienyllithium with perfluoroalkyl iodides and bromides gave 2-halothiophenes **38**, **94** rather than corresponding perfluoroalkylated thiophene [59].

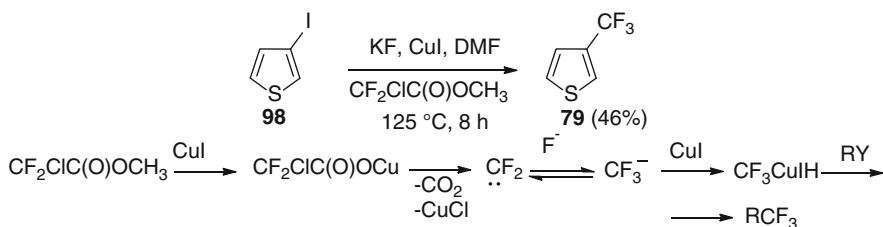


The copper-catalyzed substitution of a halogen atom was used for the preparation of 3-perfluoroalkylthiophenes. Usually, the reaction involves the heating of 3-iodothiophene **98** with perfluoroalkyl iodide in *N,N*-dimethylformamide or dimethylsulfoxide [54]. In some cases, however, it was not possible to obtain useful quantities of the three-substituted products. When the perfluoroalkyl group was not trifluoromethyl, two isomers were formed due to the addition of the perfluoroalkyl anion to the C(2)–C(3) double bond. The ratio of isomers was also influenced by the nature of halogen: iodine, which is better leaving group than bromine, gave a lower percentage of rearrangement [60].

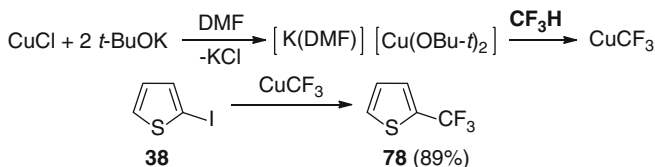


An improved method of 3-trifluoromethylthiophene **79** synthesis was the reaction of methyl-2-chloro-2,2-difluoroacetate with 3-iodothiophene **98** in the presence of copper(I) iodide and potassium fluoride in *N,N*-dimethylformamide. The reaction was carried out at 125 °C and gave 3-trifluoromethylthiophene **79** in 46 % as the sole product [61]. The proposed mechanism includes the formation of the copper(I)

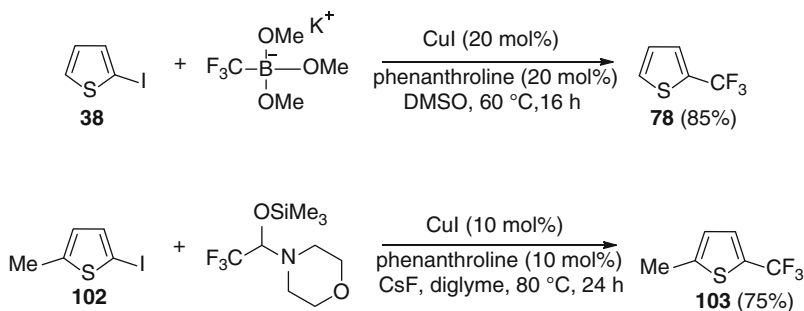
iodide salt or a complex, followed by its decarboxylation to yield difluorocarbene; the latter then reacts with fluoride to establish an equilibrium with trifluoromethyl anion. In the presence of copper(I) iodide, the equilibrium was readily shifted to give trifluoromethyl copper species CF_3CuI^- , which reacted with halides to afford the final products [62].



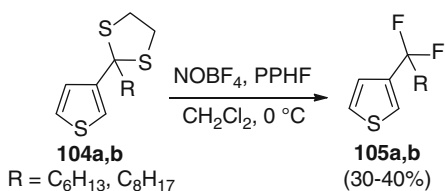
The reaction of direct cupration of fluoroform provides a source for the introduction of the trifluoromethyl group into organic molecules, including thiophene [63].



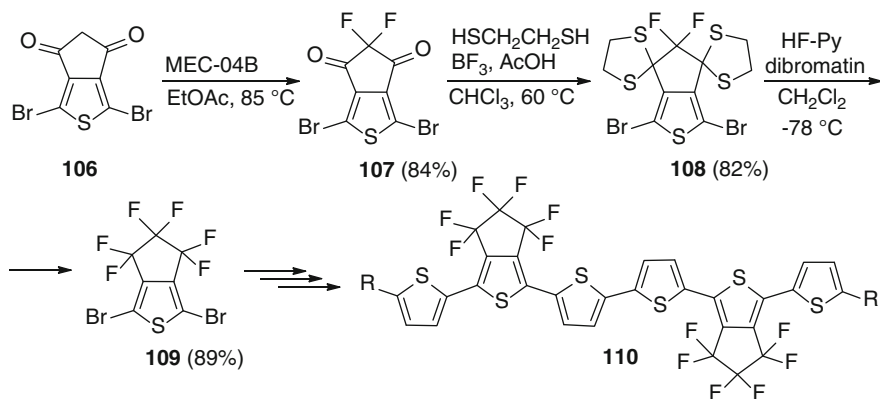
Recently, it was demonstrated that a small amount of copper(I) iodide-phenanthroline complex efficiently catalyzes aromatic trifluoromethylation of 2-iodothiophenes **38** and **102** leading to 2-trifluoromethylated products **78** and **103** in 75–85 % yields [64].



Dithioacetals **104** have been transformed into difluoromethyl derivatives **105**: a one-pot desulfurative fluorination of dithiolane led to the synthesis of difluoroalkylthiophene. Treatment of the dithioacetals **104a, b** with pyridinium polyhydrogen fluoride (PPHF) and nitrosyl tetrafluoroborate at 0°C led to 3-(1,1-difluoroheptyl) thiophene **105a** (40 %) or 3-(1,1-difluorononyl)thiophene **105b** (30 %) [65].

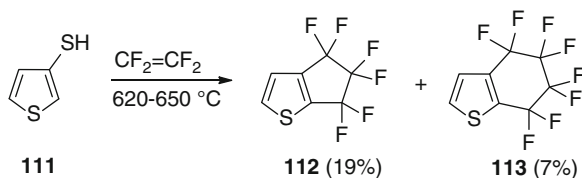


Fluorination of a carboxylic group with sulfur tetrafluoride was applied to the incorporation of the trifluoromethyl and difluoromethyl group onto the thiophene ring [43, 66]. As it was mentioned, 2,5-bis(trifluoromethyl)thiophene **77** was obtained by the reaction of thiophene-2,5-dicarboxylic **75** acid with five equivalents of sulfur tetrafluoride at 130 °C. This approach can also be used for the synthesis of oligothiophenes annelated with hexafluorocyclopentene **110**. The latter have good electron-donating properties and inherently low electron affinities, and have widespread applications as hole-transporting materials to various electronics such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs), and organic solar cells. The synthesis of such thiophenes includes three steps.



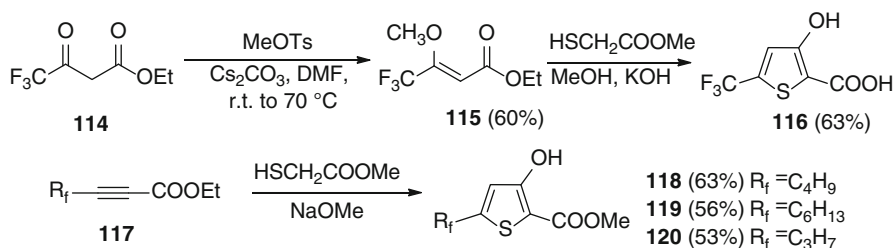
The first is fluorination of cyclopenta[*c*]thiophene-4,6-dione **106** by treatment with *N*-fluoro-6-(trifluoromethyl)pyridinium-2-sulfonate (MEC-04B) in ethyl acetate to give 1,3-dibromo-5,5-difluorocyclopenta[*c*]thiophene-4,6-dione **107** in 84 % yield. Then, conversion of the two carbonyl groups to difluoromethylene groups was accomplished via formation of the bis-1,3-dithiolane derivative **108** followed by desulfurative fluorination with hydrofluoric acid-pyridine complex and dibromatin (1,3-dibromo-5,5-dimethylhydantoin) in dichloromethane to afford 1,3-dibromoheptafluorocyclopenta[*c*]thiophene **109** in a two-step yield of 73 % [1d, 67].

2-Substituted thiophenes were found to react with tetrafluoroethylene (TFE) at high temperatures to produce 4,4,5,5,6,6-hexafluorocyclopenta[*b*]thiophene **112**. In such a reaction, 3-thiophenethiol **111** gave rise to the major product **112**, along with 4,4,5,5,6,6,7,7-octafluorocyclohexa[*b*]thiophene **113**. Yields of the products were low [68].

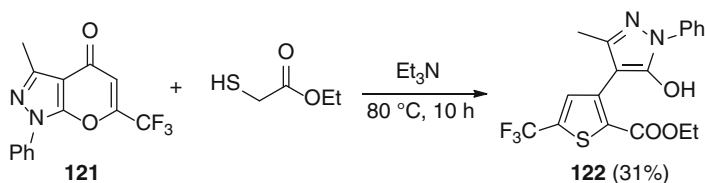


4.2 Heterocyclization and Cycloaddition

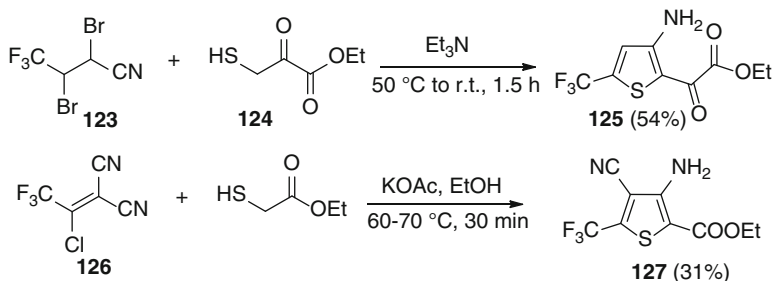
The most versatile method for synthesis of 2-trifluoromethylthiophenes is based on heterocyclizations with the participation of methyl thioglycolate (HSCH₂COOMe). For example, 2-trifluoromethylthiophene **116** was formed as a result of condensation of trifluoromethyl-substituted α,β -unsaturated ester **115** and methyl thioglycolate in the presence of a base. 2-Trifluoromethyl- and (perfluoroalkyl)thiophenes were prepared by reaction with α -fluoroalkylacetates in good yields [69]. A similar transformation took place when fluoroalkylpropynoates **117** were treated with methyl thioglycolate under basic conditions [70].



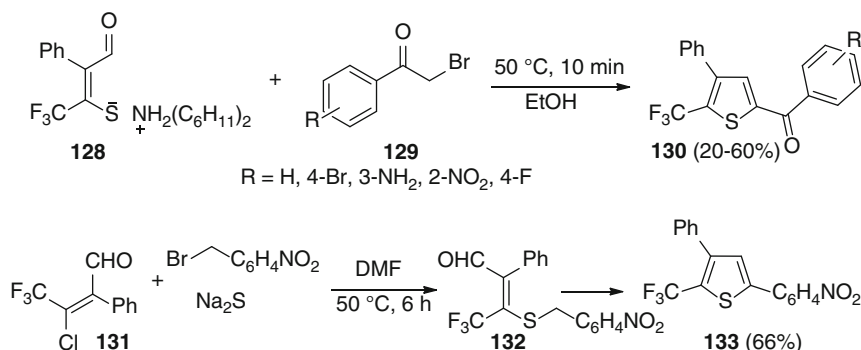
6-Trifluoromethylpyranopyrazole **121** reacted at C(6) atom with excess of methyl mercaptoacetate in the presence of triethylamine to form a derivative **122** of trifluoromethyl thiophene bonded with a pyrazole fragment. The reaction took place via pyran ring opening and intramolecular aldol-type condensation [71].



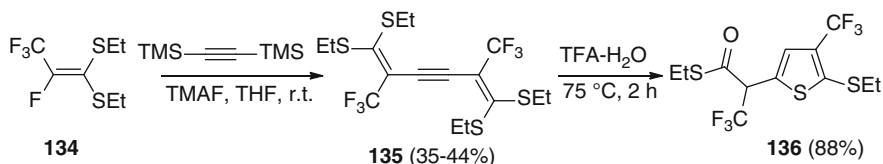
Ethyl mercaptopyruvate **124** was also transformed into 2-trifluoromethylthiophene **125** in 54 % yield by reaction with 2,3-dibromo-4,4,4-trifluorobutanenitrile **123** in the presence of triethylamine at 50 °C [72]. The condensation of a trifluoromethylethylene **126** derivative with ethyl thioglycolate in ethanol proceeded analogously [73].



Additionally, sulfur and perfluoroalkyl functionalities can both be present in the same starting molecule. For example, nucleophilic attack of trifluoromethylated thiolate **128** on phenacyl bromides **129** followed by spontaneous aldol cyclization gave 5-substituted 2-trifluoromethylthiophene **130** in yields of 20–60 % [74]. 4,4,4-Trifluoro-3-(4-nitrobenzylthio)-2-phenylbut-2-enal **132** obtained from trifluoro-substituted β -chlorovinylaldehyde **131** afforded the trifluoromethylthiophene product **133** in 66 % yield on heating in *N,N*-dimethylformamide [75].

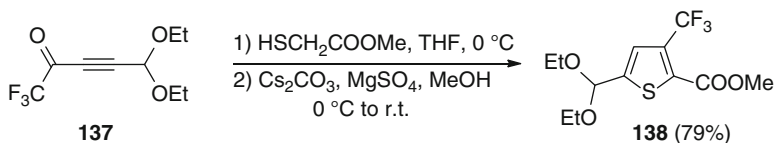


Some heterocyclizations have been used for the preparation of 3-perfluoroalkylthiophenes. As an illustration, treatment of 1,1,6,6-tetrakis(ethylsulfanyl)-2,5-bis(trifluoromethyl)-hexa-1,5-dien-3-yne **135** with a mixture of trifluoroacetic acid and water for 2 h at 75 °C led to the thiophene derivative **136** in high yield. The starting compound **135** was obtained by reaction of perfluoroketene dithioacetal **134** with bis(trimethylsilyl)acetylene [76].

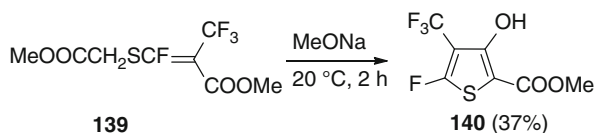


2,3,5-Trisubstituted thiophene **138** was synthesized in good yields using a tandem Michael addition and intramolecular Knoevenagel condensation strategy starting

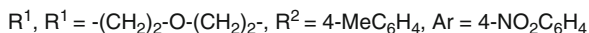
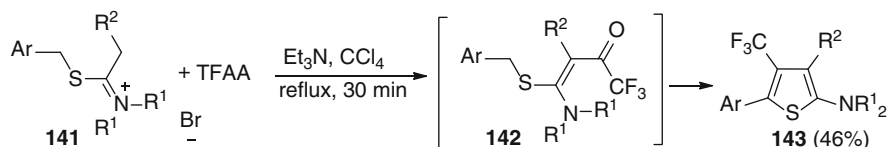
from readily available acetylenic ketone **137** in the presence of cesium carbonate and magnesium sulfate as a base to initiate the reaction [77].



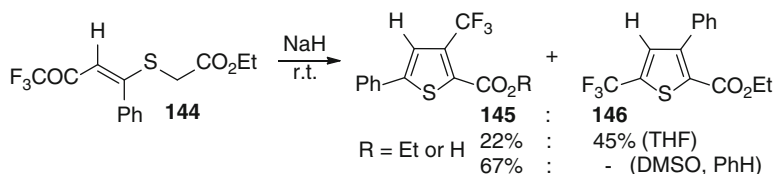
1,3,3,3-Tetrafluoro-2-(methoxycarbonyl)propenyl methoxycarbonylmethyl sulfide **139**, with its activated α -methylene group, underwent intramolecular cyclocondensation in the presence of sodium methoxide as a catalyst to form 3-trifluoromethylthiophene **140** in 37 % yield. The fluorine atom at the 2-position was substituted by a methoxy group when an excess of sodium methoxide was used [78].



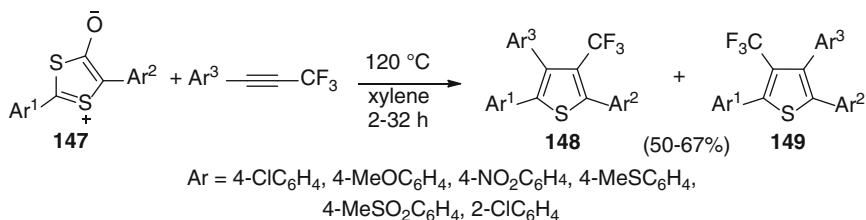
The reaction of mercaptomethyleniminium salts **141** with trifluoroacetic anhydride in the presence of triethylamine yielded substituted 2-aminothiophenes, including 3-trifluoromethyl heterocycle **143**. The starting mercaptomethyleniminium salts were prepared by S-alkylation of thioacetamides. When triethylamine was not used in the reaction, it was possible to isolate the intermediate ketene-S,N-aminals **142** and cyclize them under basic conditions [79].



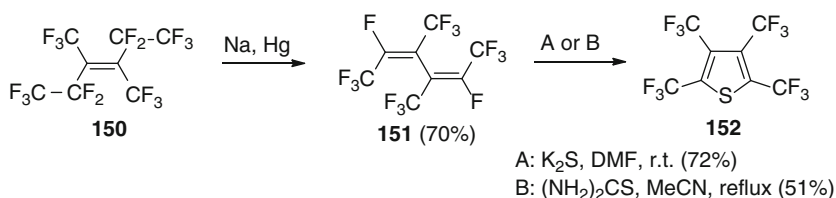
Ethyl-2-(4,4,4-trifluoro-3-oxo-1-phenylbut-1-enylthio)acetate **144** gave 3-trifluoromethylthiophene derivative **145** in moderate yield upon treatment with sodium hydride in benzene in the presence dimethylsulfoxide. The same reaction in tetrahydrofuran yielded a mixture of 2- and 3-trifluoromethylthiophene **146** and **145** with a predominance of the 2-isomer **146** [80].



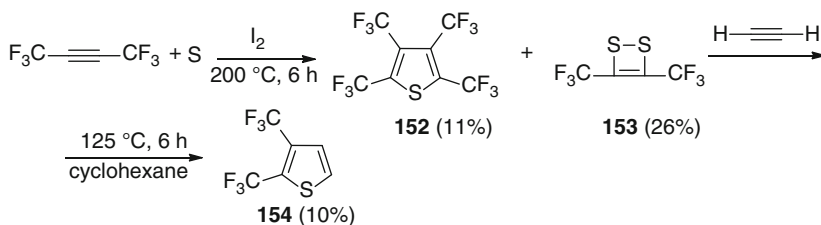
Triaryl- β -trifluoromethylthiophenes **148**, **149** were synthesized from 1,3-dithiolium-4-olates **147** and various 1-aryl-3,3,3-trifluoro-1-propynes. The 1,3-dipolar cycloaddition was carried out by heating in xylene at 120 °C. Interestingly, when the substituents Ar¹ and Ar² in the mesoionic 1,3-dithiolium-4-olates were swapped, the isomer ratio was completely reversed. The observed regioselectivity was explained by HOMO-LUMO interactions of the reacting species [81].



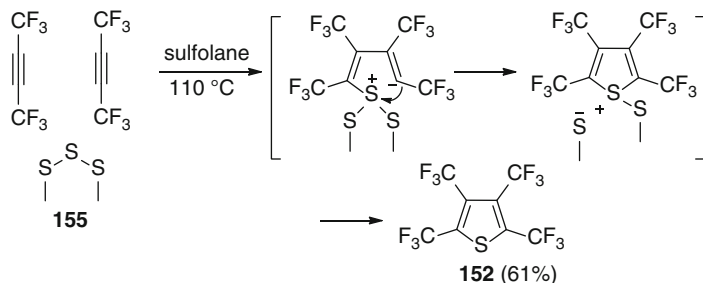
1,2,3,4-Tetrakis(trifluoromethyl)buta-1,3-diene **151** was employed for the preparation of 2,3,4,5-tetrakis(trifluoromethyl)thiophene **152**. The transformation can be performed by treatment of the diene with potassium sulfide in *N,N*-dimethylformamide at room temperature [82] or by heating at reflux with thiourea in acetonitrile [83]. The starting diene **151** was obtained from perfluoro-3,4-bis(trifluoromethyl)hex-3-ene **150**.



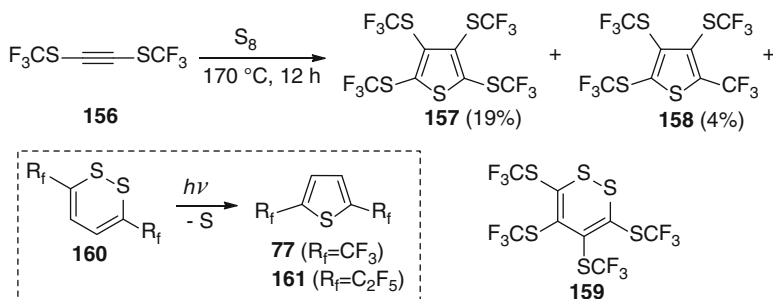
2,3,4,5-Tetrakis(trifluoromethyl)thiophene **152** was also obtained by addition of sulfur to hexafluoro-2-butyne at 110–200 °C [84]. The process is supposed to involve reaction of an intermediate dithietene **153** with starting hexafluoro-2-butyne at high temperature. This mechanism was supported by the preparation of 2,3-bis(trifluoromethyl)thiophene **154** and tetrakis(trifluoromethyl)thiophene **152** from dithietene **153** and the corresponding alkynes [85].



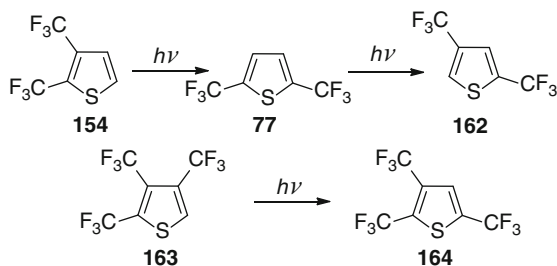
The reaction with dimethyltrisulfide **155** as sulfur source occurred at 110 °C in sulfolane giving tetrakis(trifluoromethyl)thiophene **152**. No other sulfur heterocycles were detected and the authors presumed that a different process was taking place under these conditions. They concluded that a nucleophilic cyclisation process operates with the *cis*-addition occurring because sulfur is both a bulky and a neutral nucleophile [84].



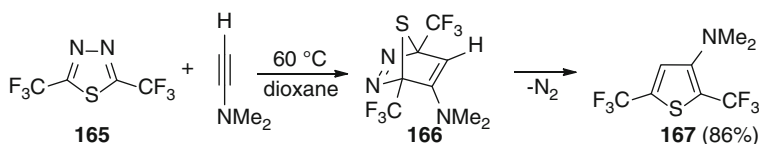
Photolysis or heating of bistrifluoromethylthioacetylene **156** with sulfur afforded 2,3,4,5-tetrakis(trifluoromethylthio)thiophene **157** in low yield. The transformation was determined to proceed via an intermediate 1,2-dithiin derivative **159**; this was supported by the reaction of 3,6-bis(perfluoroalkyl)-1,2-dithiins **160** that produced 2,5-bis(perfluoroalkyl)thiophenes **77**, **161** under irradiation [86].



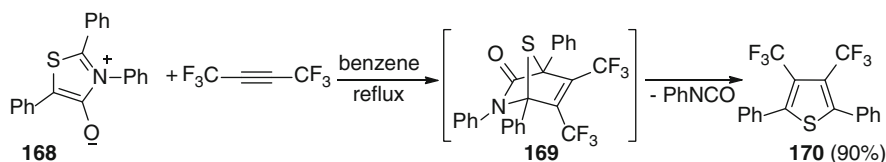
The photolysis of bis(trifluoromethyl)thiophenes **154** and **77** and tristrifluoromethylated thiophene provides a simple way to produce isomeric structures, but usually these procedures are not synthetically useful for the preparation of thiophene derivatives [87].



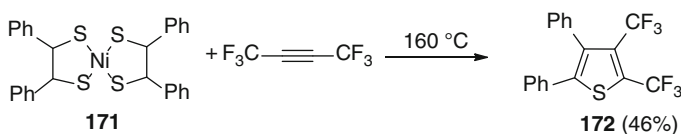
A convenient synthesis of 2,5-bis(trifluoromethyl)thiophene **167** involved the [4+2]-cycloaddition reaction of acetylenes to 2,5-bis(trifluoromethyl)-1,3,4-thiadiazole **165** and subsequent elimination of nitrogen. The reaction proceeded under sufficiently mild conditions and led to 2,5-bis(trifluoromethyl)thiophene **167** in high yield [88].



Another type of cycloaddition used to produce, in this case, 3,4-bis(trifluoromethyl)thiophene **170** was the reaction of hexafluoro-2-butyne with mesoionic thiazolium system **168**. Phenyl isocyanate was eliminated from the initial adduct, giving the substituted thiophene in more than 90 % yield [89].

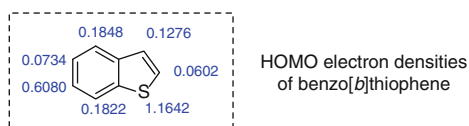


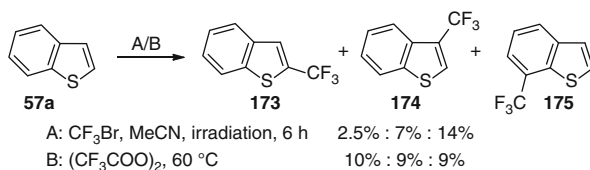
The reaction of bis(dithiobenzyl)nickel **171** with alkynes yielded thiophene derivative **172**. In view of the improved method of preparation of the complexes, this reaction has been applied to the synthesis of difficult-to-access substituted thiophene derivatives. Complexes are air-stable and easily available from benzoin and phosphorus pentasulfide [90].



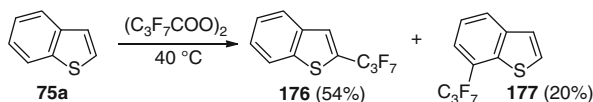
5 Synthesis of Perfluoroalkylbenzothiophenes

Direct trifluoromethylation of benzo[*b*]thiophene is not selective. For instance, photochemical reaction with bromotrifluoromethane yielded a mixture of 3-, 4- and 7-trifluoromethylbenzo[*b*]thiophenes (**173**, **174** and **175**), which correlates with the values of electron density in the molecule [91].

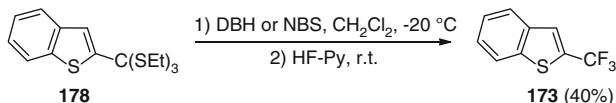




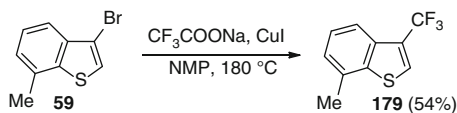
Oxidative trifluoromethylation with bis(trifluoroacetyl)peroxide provided a similar result, while the reaction with bis(heptafluorobutyryl)peroxide afforded 3-heptafluoropropylbenzo[*b*]thiophene **176** as a major product (54 %) with some 7-substituted isomer **177** [50].



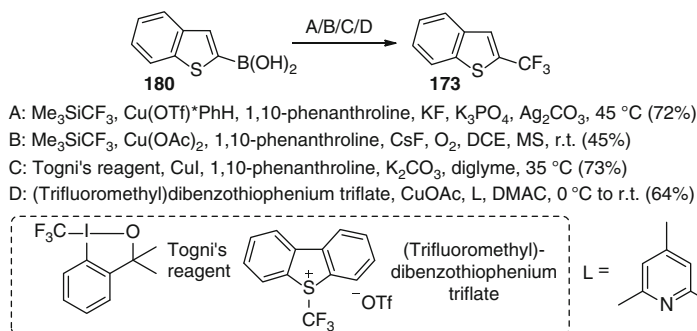
A more effective method for the preparation of 2-trifluoromethylbenzo[*b*]thiophene **173** involved the treatment of orthothioester **178** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) or *N*-bromosuccinimide (NBS) followed by hydrofluoric acid-pyridine complex. The target compound was obtained by this method in 40 % yield [92].



Through direct trifluoromethylation, 7-methyl-3-trifluoromethylbenzo[*b*]thiophene **179** was prepared in 54 % yield from 7-methyl-3-bromobenzo[*b*]thiophene **59**. The reaction took place with sodium trifluoroacetate and copper(I) iodide in *N*-methylpyrrolidone at 180 °C [35].

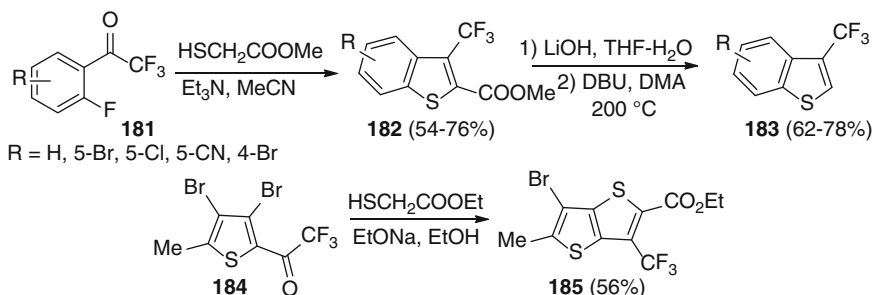


Recently, simple copper-catalyzed trifluoromethylation of aryl boronic acids under mild conditions was developed. Using (trifluoromethyl)trimethylsilane (Me_3SiCF_3) [93], trifluoromethyldibenzothiophenium triflate [94], or Togni's reagent [95], 2-trifluoromethylbenzo[*b*]thiophene **173** was prepared in 45–73 % yields.

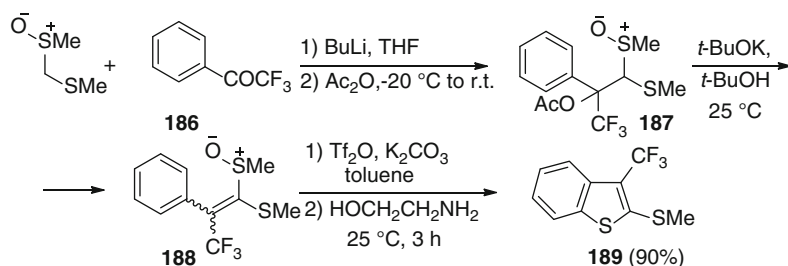


A straightforward method for the synthesis of 5- or 6-substituted 2-trifluoromethylbenzo[*b*]thiophenes involved the reaction of *ortho*-fluorinated trifluoroacetophenones **181** with methyl thioglycolate [96]. The starting trifluoroacetophenones **181** were prepared from fluorobenzenes and ethyl trifluoroacetate. The key transformation proceeded in the presence of triethylamine at room temperature in acetonitrile and produced methyl 3-trifluoromethylbenzo[*b*]thiophene-2-carboxylates **182** in good yields. The products **182** were easily transformed into their corresponding 3-trifluoromethylbenzo[*b*]thiophenes **183**.

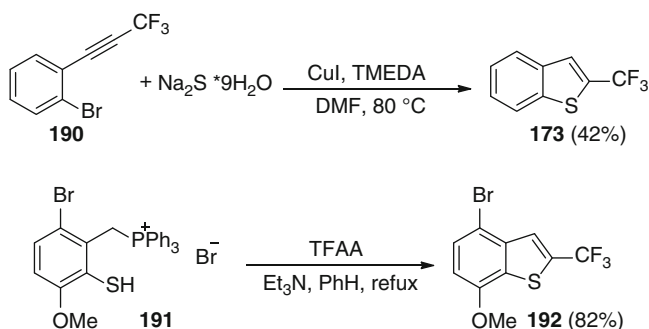
A similar approach was used for the preparation of the thienothiophene derivative **185**: the treatment of the trifluoroacetyl-substituted thiophene **184** with ethyl thioglycolate gave the condensed thiophene [97] bearing a trifluoromethyl group [98].



An alternative approach to benzo[*b*]thiophene derivatives includes treatment of an aryl-substituted ketene dithioacetal monoxide **188** with trifluoromethanesulfonic anhydride [99] (Tf_2O) in the presence of K_2CO_3 in toluene at 25°C , followed by addition of ethanolamine to the reaction mixture, provided benzo[*b*]thiophenes, including 3-trifluoromethylbenzo[*b*]thiophene **189**, in good yields. The cyclization proceeded through formation of reactive sulfonium electrophile [100]. The synthesis of the starting material **188** was also facile and scalable, starting from aryl ketone **186** and formaldehyde dimethyl dithioacetal S-oxide (FAMSO) [101].



In 2011 a copper-catalyzed thiolation annulation reaction of 2-bromo alkynylbenzenes **190** with sodium sulfide has been developed. This approach provided 2-substituted benzo[*b*]thiophenes in moderate to good yields [102]. Also, synthesis of the 2-trifluoromethyl benzothiophene **192** was carried out in high yield using the thiophenol equivalent of the phenolic phosphonium bromide salt **191** [103].

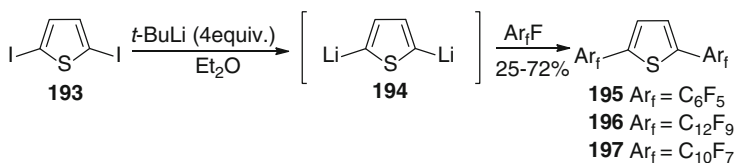


6 Synthesis of Perfluoroarylthiophenes

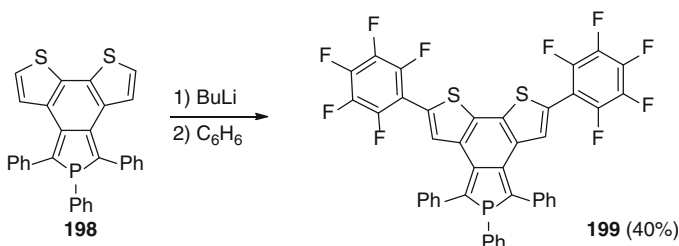
Usually, methods used for the synthesis of 2-perfluoroarylthiophenes synthesis are also applicable for the preparation of 3-perfluoroarylthiophenes. Although not numerous, they include reactions with organometallic reagents, cross-coupling reactions, and heterocyclization.

6.1 Organometallic Synthesis

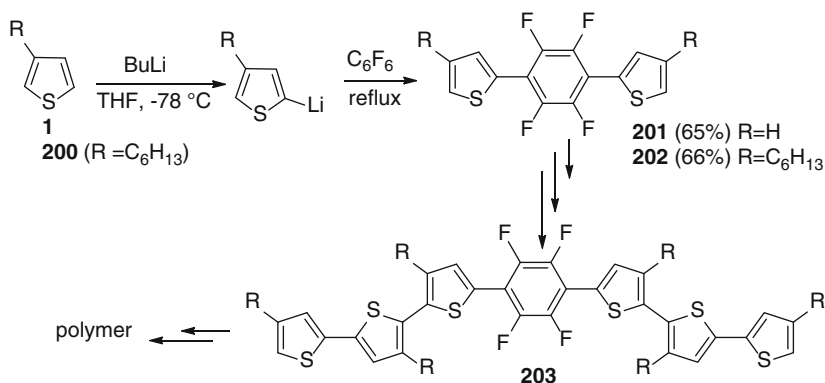
Perfluoroaryl thiophene derivatives **195**–**197** were obtained by nucleophilic aromatic substitution via thienyllithium intermediates **194**. The reaction is quite simple and is widely used for the preparation of various fluoroaromatics [59].



Lithiated bithiophene also gave rise to pentafluorophenyl derivative **199** in moderate yield. The S_NAr-type reaction proceeded with hexafluorobenzene in 8 h. The starting compound was obtained from the corresponding thiophene on treatment with *n*-butyllithium [104].

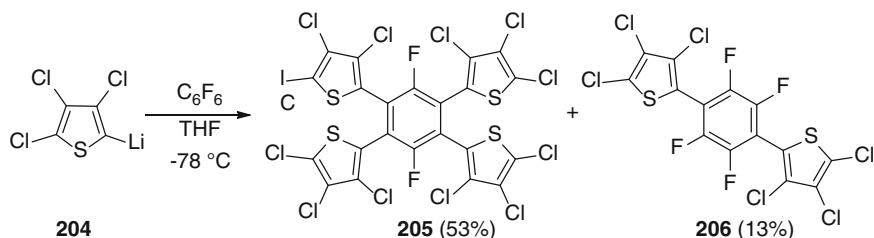


2-Thienyllithium and 4-hexyl-2-thienyllithium reacted with hexafluorobenzene to give the triaryl derivatives **201** (65 %) and **202** (66 %), respectively. The procedure is noteworthy since the lithiation of 3-hexylthiophene was regioselective and resulted in the isolation of a single isomer. The compounds **201**, **202** have been used as precursors for oligothiophene **203** synthesis and preparation of polymeric materials [105].

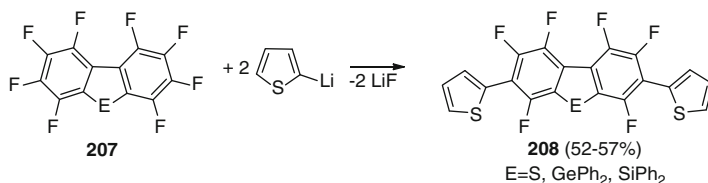


Similarly, lithiated chlorothiophenes reacted with hexafluorobenzene to produce fluoroaryl derivatives. Addition of hexafluorobenzene to trichloro-2-thienyllithium **204** in tetrahydrofuran at $-78\text{ }^\circ\text{C}$ gave 1,2,4,5-tetrakis(trichloro-2-thienyl)difluorobenzene **205** and 1,4-bis(trichloro-2-thienyl)tetrafluorobenzene **206**. A

similar reaction in diethyl ether at -15 to -20 °C also gave both **205** (44 %) and **206** (20 %) products [106].

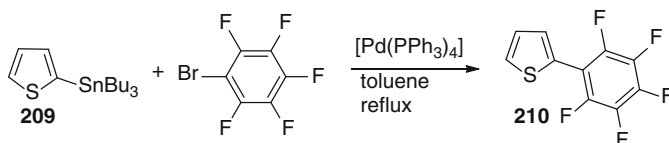


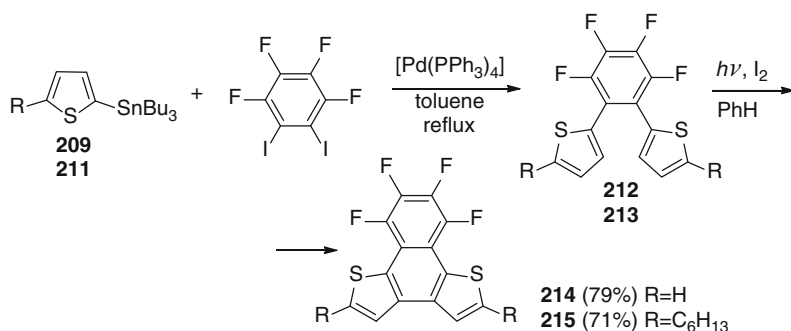
2,7-Disubstituted hexafluoro-9-heterofluorenes **208** were synthesized via nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) reactions of 2-thienyllithium with various octafluoroheterofluorenes **207**. These compounds are of interest as possible building blocks for materials with useful electron-transport properties, since they possess relatively low LUMO energy levels [107].



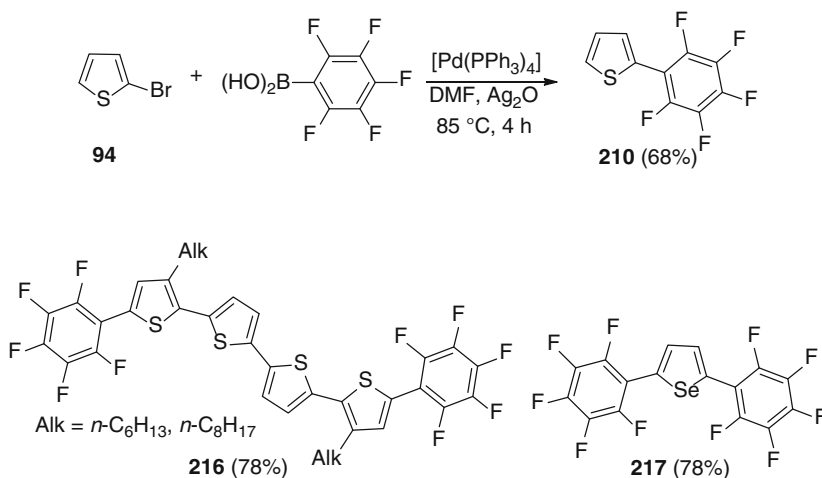
6.2 Cross-Coupling

More often, cross-coupling reactions are applied for the preparation of perfluoroarylthiophenes. Copper and palladium catalysts are common for arylation. For example, palladium-catalyzed Stille coupling with iodo- and bromosubstituted fluoroarenes gave the fluoroarene-modified thiophenes which can act as organic semiconductors [108]. The palladium-catalyzed reaction was performed with the corresponding stannylated thiophenes (e.g. **209**, **211**) in toluene under reflux. Numerous thiophene derivatives have been obtained by this method. Product yields for these transformations ranged from moderate to good (45–80 %) [109].

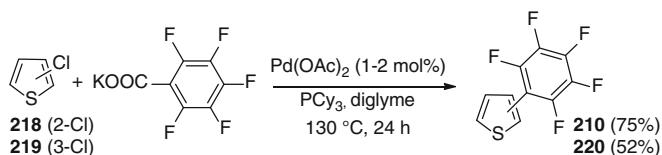




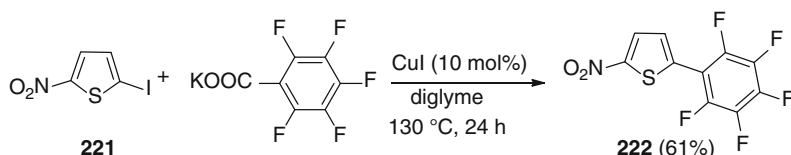
2-(Pentafluorophenyl)thiophene **210** and its derivatives were also synthesized by a palladium catalyzed Suzuki reaction between pentafluoroiodobenzene and thiophene boronic acid derivative. However, considering the ready accessibility of 2-halothiophenes by electrophilic substitutions of thiophenes, commercially available pentafluorophenylboronic acid is the counterpart of choice for the Suzuki coupling. The use of DMF as a solvent and potassium phosphate as a base in the presence of palladium catalyst allowed for the synthesis of a wide range of compounds, including thiophene-fused system and oligothiophenes with various chain lengths, such as **216**, as well as several selenophene homologues, for example **217** [110].



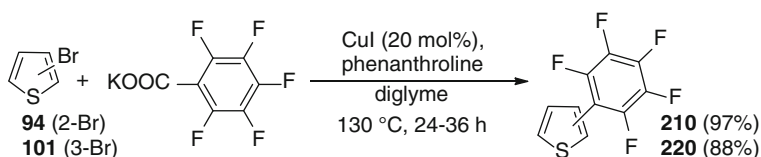
The palladium-catalyzed decarboxylative coupling of potassium pentafluorobenzoate with aryl chlorides, bromides and triflates was shown to be a useful method for the synthesis of polyfluorobiaryls from readily accessible polyfluorobenzoate salts. For instance, 2- and 3-chlorothiophenes **218**, **219** reacted with potassium pentafluorobenzoate to produce pentafluorophenyl derivatives **210** and **220**. The reaction proceeded in refluxed diglyme in the presence palladium acetate(II) [111].



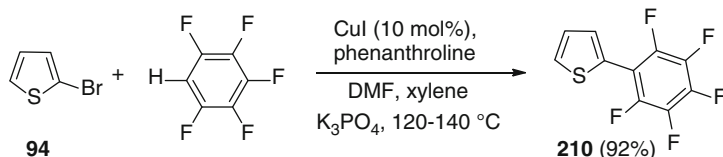
A similar coupling proceeded with 2-iodo-5-nitrothiophene **221** in the presence of a copper catalyst. A possible explanation for the outstanding performance of diglyme is that it can coordinate to K^+ , thereby facilitating the complexation between CuI and pentafluorobenzoate.



This protocol was applicable to aryl iodides but not to less reactive aryl bromides. This problem was solved by using 1,10-phenanthroline as a ligand: 2- and 3-bromothiophenes **94** and **101** formed the corresponding pentafluorophenyl derivatives in good yields in the presence of a copper-phenanthroline catalytic system [112].

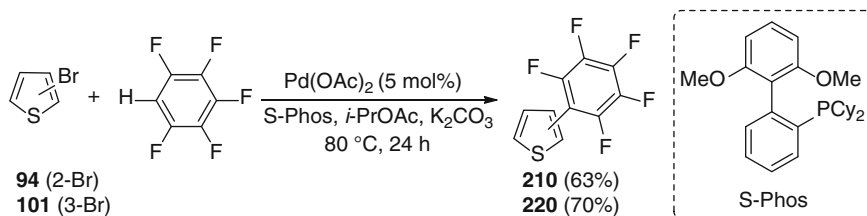


All of the methods presented above are based on cross-couplings of halogenated thiophenes and different pentafluorophenyl derivatives. However, the arylation of polyfluorobenzene C-H bonds can also be used for the synthesis of perfluoroarylthiophenes. For example, 2-bromothiophene **94** and pentafluorobenzene gave 2-(perfluorophenyl)thiophene **210** in 92 % yield in the presence of phenanthroline [113].

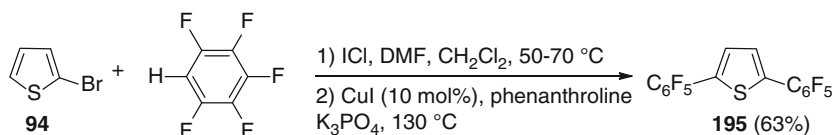


A similar monoarylation was performed with 2- and 3-bromothiophenes **94** and **101** under palladium-catalyzed conditions in good yields. The use of a more

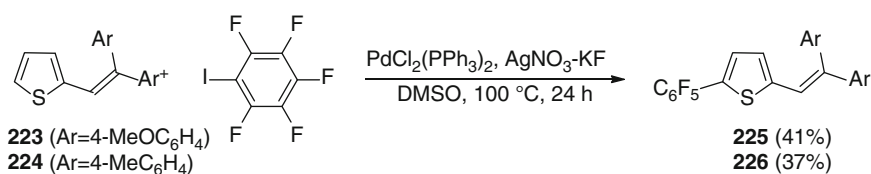
effective palladium catalyst with the phosphine ligand S-Phos allowed for the temperature of this transformation to be reduced to 80 °C [114].



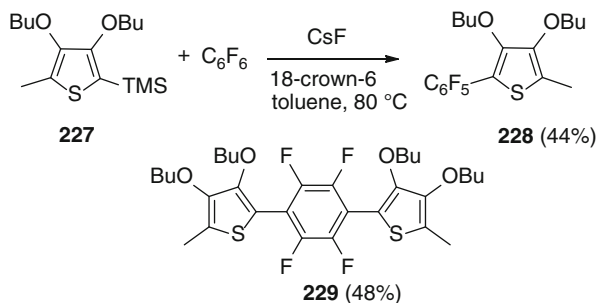
2,5-Bis(perfluorophenyl)thiophene **195** was obtained by a one-pot sequential iodination and copper-catalyzed cross-coupling of arene C–H bonds. The first step was the electrophilic halogenations with incorporation of the iodine atom. Then, copper-catalyzed arylation allowed for a highly regioselective heterocoupling, thereby leading to the diarylated product **195** [115].



The previous three examples involved the couplings of halogenated thiophenes with different substrates. However, it is also possible to perform coupling between thiophene and halogen-substituted arenes. The reaction of thiophene derivatives **223**, **224** with pentafluoroiodobenzene proceeded in the presence of bis(triphenylphosphine)palladium(II) dichloride and silver nitrate [116].

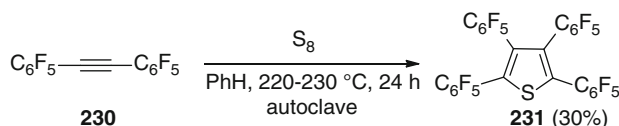


The transition-metal-free carbon-carbon bond formation by fluoride activation of silicon-carbon bonds has been used for coupling of perfluoroarenes and trimethylsilylthiophene derivative **227**. In the case of 2,5-bis(trimethylsilyl)thiophenes, the ratio of isolated products indicated that the first and second attacks on perfluorobenzene proceeded with the same rate, or that conversion of the second TMS group can be more rapid than that of the first [117].

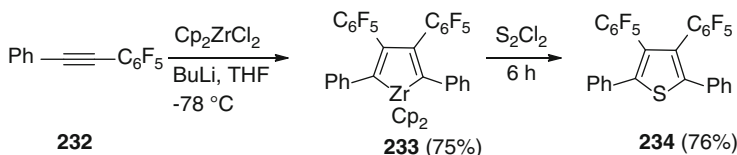


6.3 Heterocyclization

The heterocyclization of substituted alkynes with sulfur was also shown to be applicable for the preparation of perfluoroarylthiophenes. When a mixture of 1,2-bis(perfluorophenyl)ethyne **230** and sulfur was heated in benzene at $220\text{--}230\text{ }^\circ\text{C}$ the tetrakis(perfluorophenyl)thiophene **231** was formed in 30 % yield [118].

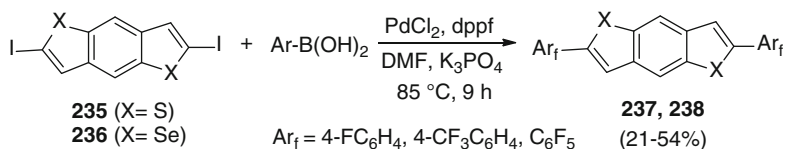


Another pathway to perfluoroalkylthiophenes involved the cyclization of zirconocene obtained from pentafluorophenyl-substituted alkynes. The fluorophenyl-substituted alkynes was synthesized by coupling of the appropriate fluoroaryl iodide with a terminal alkyne catalyzed by tetrakis(triphenylphosphine)-palladium(0) and CuI . Reaction of the resulting alkyne **232** with Negishi's zirconocene synthon at low temperature followed by warming to room temperature afforded zirconacyclopentadienes **233** in high yields. The reaction of the latter with S_2Cl_2 gave thiophene **234** in high yield [119].

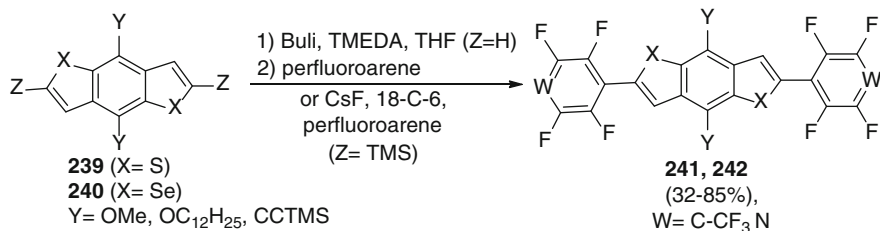


7 Synthesis of Perfluoroarylbenzothiophenes

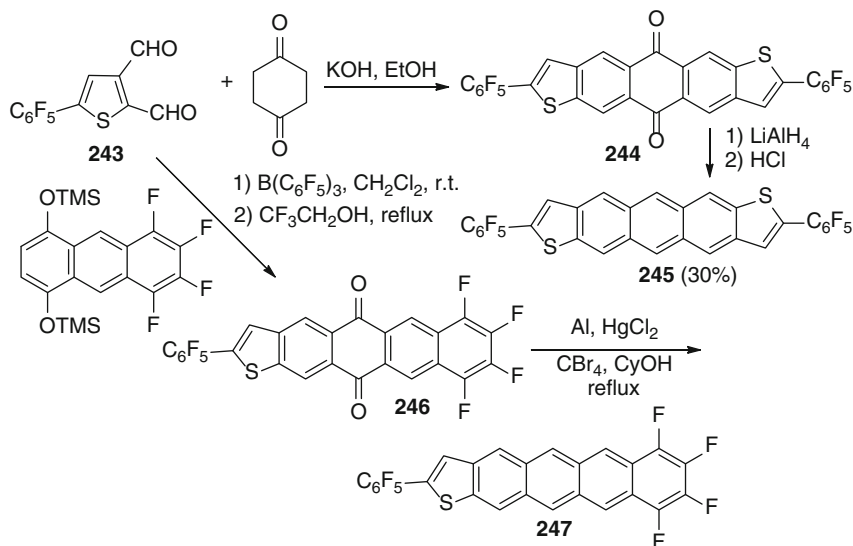
The known approaches to perfluoroarylbenzothiophenes are generally based on the cross-couplings and reactions with organometallic reagents. For example, benzo[1,2-*b*:4,5-*b'*]dithiophene **235** and -diselenophene **236**, which are known p-channel semiconducting materials, were modified via palladium-catalyzed Suzuki-Miyaura coupling reaction. The reaction proceeded in moderate yields and gave compounds **237**, **238** which can act as n-semiconductors [120].



Another method for the synthesis of 2,6-diphenylbenzo[1,2-*b*:4,5-*b'*]dithiophene **241** and diselenophene fluorinated derivatives **242** was based on the reaction of their bismetalates with perfluoroarenes. The same transformation was also performed with trimethylsilyl derivatives using a catalytic amount of cesium fluoride in the presence of 18-crown-6 [121].

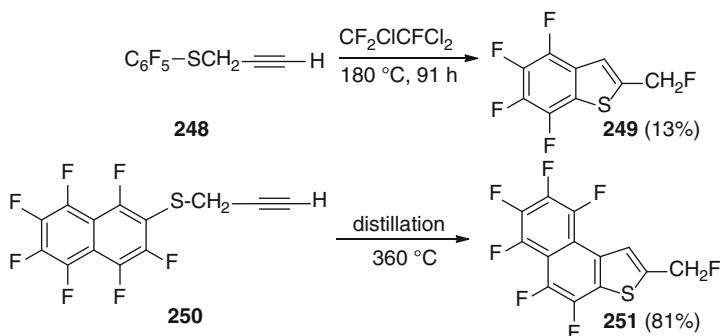


The synthesis of functionalized anthradithiophenes was achieved through condensation of thiophenes derivatives with cyclohexane-1,4-dione. The starting 5-perfluorophenyl-2,3-thiophenedicarboxaldehyde was prepared in 45 % yield by Stille coupling of 5-(tributylstannyl)-2,3-bis(1,3-dioxolan-2-yl)thiophene with bromopentafluorobenzene. The reaction of thiophenedicarboxaldehyde with cyclohexane-1,4-dione gave intermediate quinone **244** that produced dipentafluorophenylanthradithiophene **245** on reduction. The latter is a semiconductor for organic thin-film transistors (OTFTs) [109]. A similar reaction with a 5,6,7,8-tetrafluoroanthracene derivative leads to 7,8,9,10-tetrafluoro-2-pentafluorophenyltetraceno[2,3-*b*]thiophene **247**.



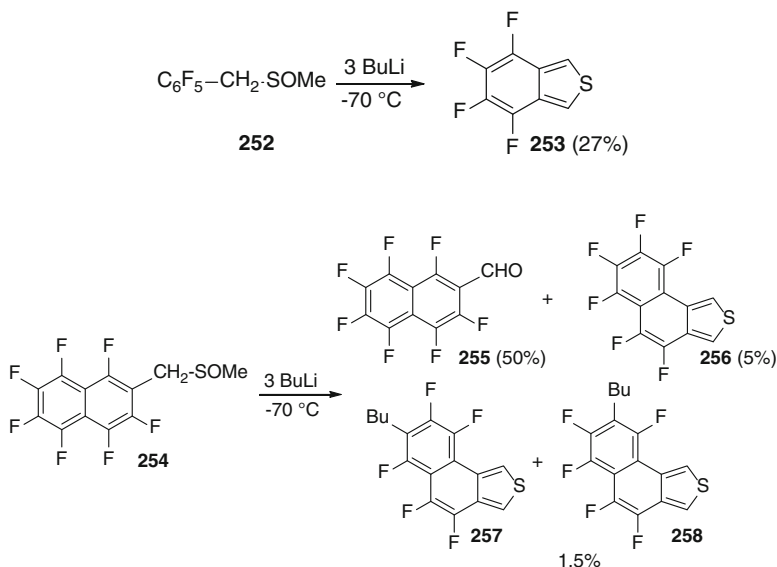
8 Benzothiophenes with Perfluorinated Carbocycle

Benzothiophenes with a fully fluorinated carbocycle are usually prepared by way of cyclization reactions. For example, when pentafluorophenyl prop-2-ynyl sulfide **248** in Freon 113 was heated at 180 °C 4,5,6,7-tetrafluoro-2-fluoromethylbenzo[*b*]thiophene **249** was obtained in low yield. A similar isomerisation of the naphthalene compound **250** was more efficient and gave the 2-fluoromethyl derivative **251** in 41 % yield. Distillation of the starting compound under vacuum through silica-filled tube led to the target compound **251** in 81 % yield [122].

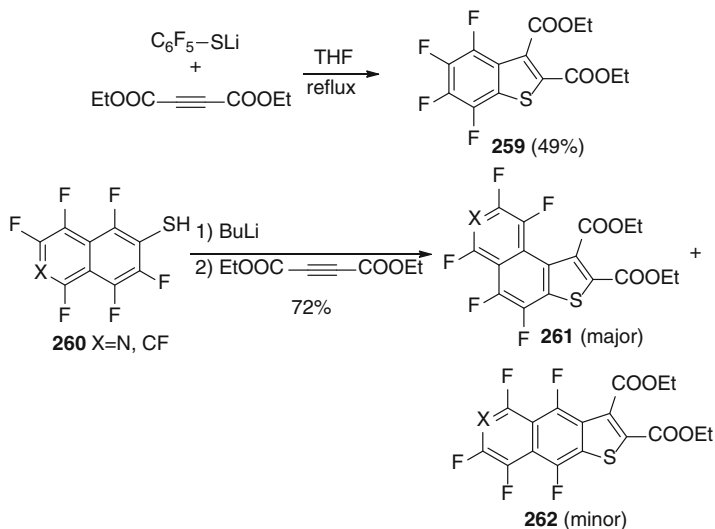


More often, such compounds are synthesized via cyclization induced by organo-metallics. For example, 2,3,4,5,6-pentafluorobenzyl methyl sulfoxide **252** gave 4,5,6,7-tetrafluorobenzo[*c*]thiophene **253** on treatment with BuLi in THF at -70 °C. The mechanism invokes the nucleophilic replacement of *ortho*-fluorine by CH₂Li and

aromatization. Treatment of the naphthalene sulphoxide **254** with BuLi gave 4,5,6,7,8,9-hexafluoronaphtho[1,2-*c*]thiophene **256** in inseparable mixture of the 7- and 8-butyl derivatives **257** and **258**, as well as the aldehyde **255** in 50 % yield [123].



In 1967, the formation of diethyl 4,5,6,7-tetrafluoro-benzo[*b*]thiophen-2,3-dicarboxylate **259** in 49 % yield, by the reaction of lithium pentafluorobenzenethiolate with diethyl acetylenedicarboxylate in THF under reflux, was reported [124]. Later, the cyclization reaction was shown to occur under very mild conditions (-70 to -58 °C) in 74 % yield [125]. A similar reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiolate and its isoquinoline derivative with dimethyl acetylenedicarboxylate was reported to give polyfluorinated condensed products **261** and **262** [126].



9 Conclusion

Fluorinated thiophene derivatives have found a broad application as biologically intriguing molecules and especially as modern organic materials. However, methods for their synthesis are still limited. The direct fluorination or trifluoromethylation of thiophene is either not selective or proceeds in low yields. The most convenient approach to fluorothiophenes and their benzoanalogues involves lithiation-fluorination reactions. Other common methods are based on heterocyclizations with participation of methyl thioglycolate, or cycloaddition reactions. The scarce methods for fluorinated thiophenes synthesis give a chance for synthetic chemists to elaborate new, better pathways to these intriguing and useful compounds.

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