Synthesis of self-organizing mesogenic materials containing a sulfur-based five-membered heterocyclic core

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The majority of low molar mass calamitic mesogenic systems in the literature contain linear cores based on the 1,4-disubstituted phenyl ring. Heterocyclic cores such as thiophene impart unique physical properties as their slightly bent structure leads to features including a reduced packing ability (generally giving rise to lower melting points than their phenyl counterparts), a medium to strong lateral dipole, high anisotropy of the polarizability, low viscosity *etc.* This *critical review* describes the most recent synthetic methodology that has been used to prepare thiophene, 1,3-thiazole, and 1,3,4-thiadiazole-based mesogenic materials. (154 references)

Introduction

Heterocycles are of great importance as core units in thermotropic liquid crystals due to their ability to impart lateral and/or longitudinal dipoles combined with changes in the molecular shape. These materials hold great potential for use in spatial light modulation,[1] all-optical signal processing, optical information storage,[2] organic thin-film transistors,[3,4] fast switching ferroelectric materials,[5] fluorescent probes for the detection and analysis of biomolecules[6] *etc.* Thiophene in particular has emerged as a core unit that is receiving increasing attention. Materials containing thiophene, 1,3-thiazole, or 1,3,4-thiadiazole core units have significant lateral dipole moments (Fig. 1) that help to contribute to physical parameters such as increased dielectric anisotropy and dielectric biaxiality. The latter property allows for AC field stabilization, a feature that is currently essential for ferroelectric device operation.[7,8]

Ferroelectric liquid crystal devices use materials in the chiral smectic C phase (SmC*) which is a tilted smectic with a spontaneous polarization that may be reoriented upon application of an external electric field.[9] The constituent chiral molecules are tilted within diffuse layers where the tilt angle θ is temperature dependent, generally having an inverse relationship with temperature. Upon passing from layer to layer the director (direction of orientation of the long molecular axes) is seen to rotate in either a clockwise or counter-clockwise fashion [determined by the absolute configuration of the constituent molecules and the proximity of the stereocenter to the rigid molecular core (ignoring axial chirality)] to generate a macroscopic helical structure where the helical axis is normal to the layer plane. The local layer symmetry is C_2 and there is a time-dependent alignment of the molecular dipoles along the C_2 axis, leading to a spontaneous polarization along this axis, which is parallel to the layer planes and perpendicular to the tilt direction.[9] This structure is therefore helielectric and can be made truly ferroelectric by the application of an external electric field which unwinds the helix. Reversal of the field will

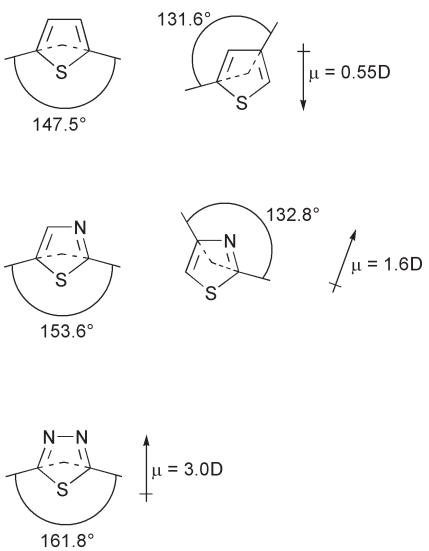

Fig. 1 Bond angles and dipole moments of thiophene, 1,3-thiazole, and 1,3,4-thiadiazole

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see the molecules rotate through an angle equal to 2θ, and it is this reorientational effect that is the basis of the ferroelectric display. When a ferroelectric device is fabricated, the liquid crystal is introduced into a thin cell (the cell thickness is smaller than the helical pitch of the material being introduced so as to suppress helix formation) using a vacuum. The liquid crystal itself is usually heated into the smectic A phase (SmA, an orthogonal smectic phase that is the most fluid of all the smectic variants) to allow for good alignment. The cell is then cooled and the material enters the SmC* phase where the molecules tilt and the tilt is accompanied by a volume contraction. In response, the layers are seen to buckle in order to fill the space created which results in the formation of chevron domains.[10] The molecules have a small pre-tilt at the surface of the cell (due to boundary conditions) and the layers may tilt in the same sense as the pre-tilt (C1 chevron domain) or with the opposite sense (C2 chevron domain).[8] At the interface where the two domains meet within the cell, a defect forms that is observed as a zigzag. This results in a serious loss of contrast and effectively renders the display as useless.

Technological advances in display engineering have allowed the construction of displays solely consisting of C2 chevron domains. However, the one drawback with this type of display is found upon removal of the external electric field. Instead of the molecules remaining in the desired position, there is a slight molecular relaxation that results in a reduction of contrast. To counteract this, an AC field is applied to maintain the desired orientation of the molecules that requires a high dielectric biaxiality (related to the magnitude of the transverse dipole moment). Clearly, heterocyclic materials can be synthesized that have high dielectric biaxiality built into the compact core unit. In phenyl-based materials lateral substituents are required to impart high dielectric biaxiality but the addition of any increased molecular breadth results in a lowering of the mesophase (intermediate phase) thermal stability and an increase in the viscosity.

Sulfur-based heterocycles are also being used to elucidate the structures of complex mesophases such as the smectic C variants [ferrielectric (SmC^*_{FI1} and SmC^*_{FI2}), and α-phases (SmC^*_{α}) in particular]. Resonant X-ray scattering has been used to probe the molecular ordering through scattering near the sulfur K edge and this has provided detailed and unambiguous proof of the repeat structure of the ferrielectric variants.[11,12]

Thiophenes have also played a major role in the synthesis of systems displaying supramolecular chirality when dissolved in solvents where dissolution is not strongly favored.[13] Polyalkoxythiophenes have constituted such a class of materials and are found to strongly interact through the stereoregular orientation of the side chains (containing a stereocenter).[14] The resulting highly ordered structure gives rise to significant optical activity and the observation of circularly polarized luminescence.

Five-membered heterocycles have potential promise for flexoelectric applications such as found in bistable nematic displays. A number of thiophenes[15] have already been evaluated for such applications, and other bent heterocycles may have equal promise. Vertical alignment (VA) displays operating with very short switching times and viewing angles of up to 170° require molecules with negative dielectric anisotropy. Once again the in-built lateral dipole of the five-membered heterocycles holds potential for such applications. The multi-domain vertical alignment method (MVA) is of particular importance having being commercialized in late 1997.

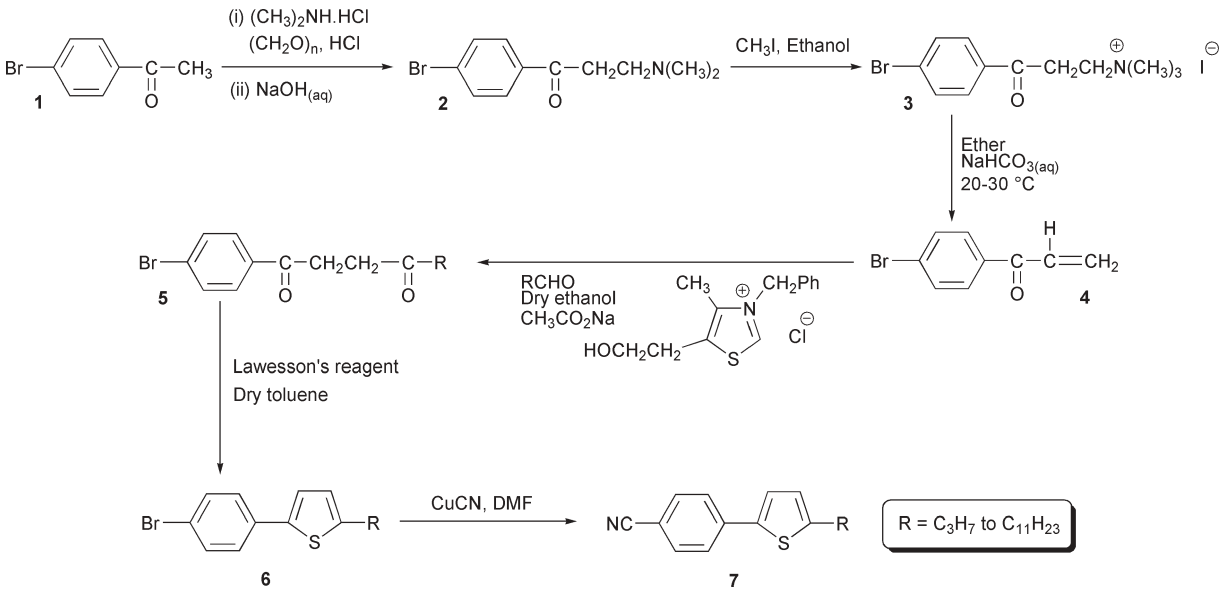
The organic thin-film field-effect transistor (OFET) has emerged as a technology that has the potential to replace amorphous silicon-based technology. Although OFETs currently have mobilities lower than their inorganic counterparts, the potential for low-cost easily processed flexible circuitry, has resulted in an explosion of synthesis in this area. Thiophene, and in particular oligothiophene-based materials, have emerged as excellent semiconductors[16,17] that show mobilities up to 1 $cm^2\ V^{-1}\ s^{-1}$ and on/off ratios greater than 10^3. Addition of alkyl chains often leads to increased solubility that can aid in solution-based processing such as spin coating.[18] Recently, a number of mesogenic materials have been synthesized where the self-assembly of these materials has led to the observation of increased mobility through greater film ordering.[19]

1. Thiophene

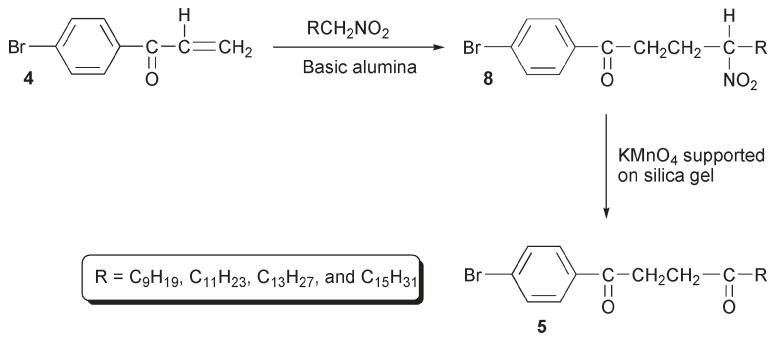
Synthesis of thiophene derivatives may be accomplished by one of two approaches; (i) ring closure of suitable 1,4-dicarbonyl precursors or (ii) modification of an intact heterocycle by electrophilic and/or nucleophilic aromatic substitution, the choice of methodology often being dictated by the identity of the target molecule and its ease of preparation. Synthesis of thiophene derivatives is most commonly performed using modification of an intact ring with ring-closure reactions being necessary in only a limited number of cases.

1.1 Ring closure in the formation of thiophenes

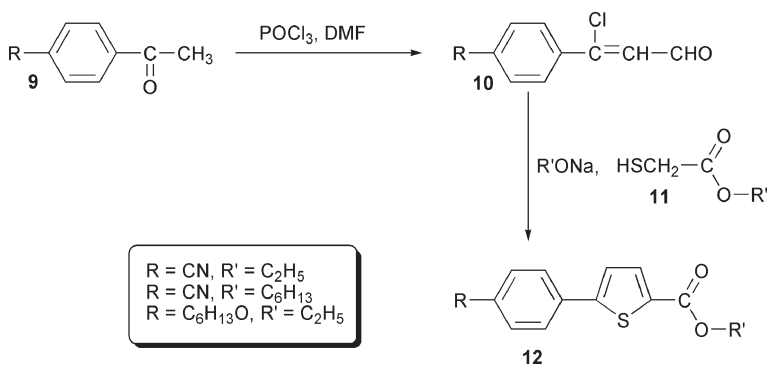
In 1992 Marson *et al.* reported the synthesis of 2-alkyl-5-(4-cyanophenyl)thiophenes **7** using ring-closure methodology (Scheme 1).[20] Benzophenone (**1**) was converted into **2** using the Mannich reaction[21,22] followed by quaternization and Hofmann elimination[23] of **2** to give α,β-unsaturated carbonyl derivative **4**. The Stetter reaction[24,25] was used to obtain the key β-diketone **5**. Cyclization of such β-dicarbonyl compounds to give thiophene rings has been accomplished with the use of sulfurization agents including phosphorus pentasulfide and Lawesson's reagent.[26–28] The use of phosphorus pentasulfide is somewhat capricious,[29] and such reactions are not always reproducible, while Lawesson's reagent has emerged as the most widespread choice due to its reliability, generally high yielding results, and ease of use.[26] The synthesis described by Marson *et al.* could have been more effectively accomplished using modification of an intact thiophene ring constituting a divergent approach that is ideally suited to the synthesis of a homologous series. Approaches to similar systems that utilize manipulation of an intact thiophene ring have previously been reported by others and are discussed in the proceeding section. These divergent approaches can be performed on large scales and give good-excellent yields of the final products.



Scheme 1 Synthesis of 2-alkyl-5-(4-cyanophenyl)thiophenes **7** by Marson *et al.*



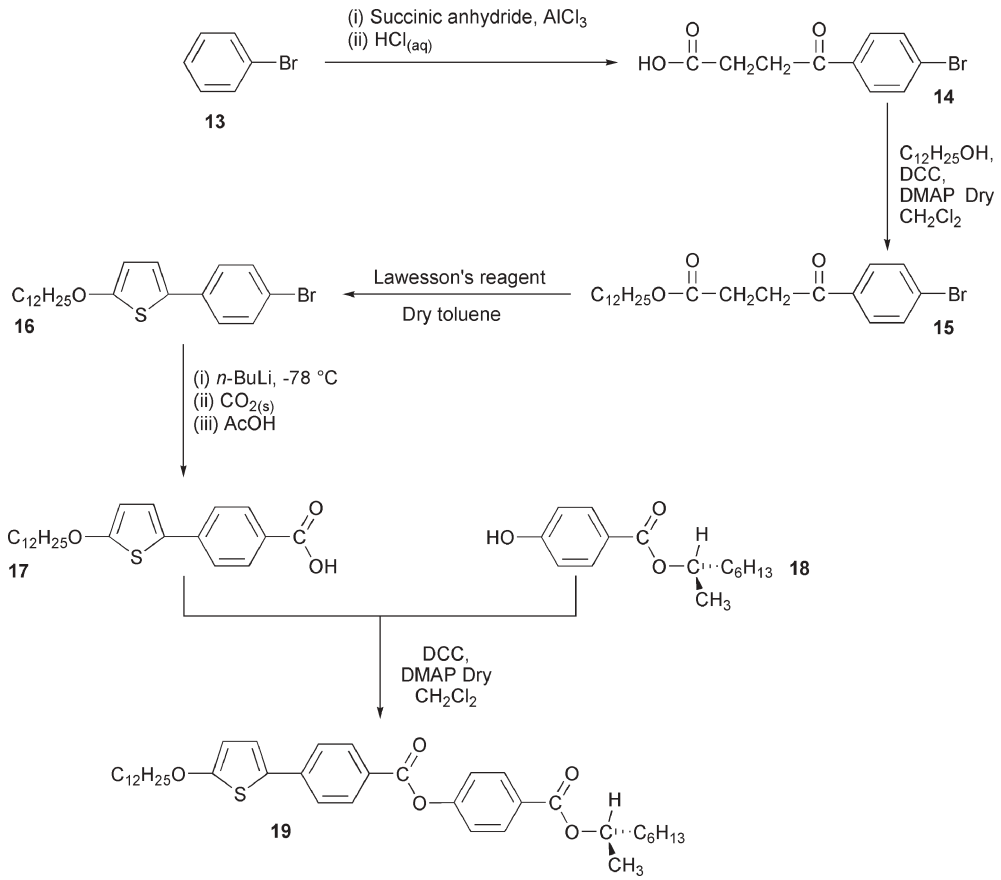
Scheme 2 Alternative synthesis of key β-diketones **5** using conjugate addition and Nef reaction.



Scheme 3 Use of the Fiesselmann synthesis in the synthesis of thiophene carboxylates.

Intermediates **5** were also accessed using an alternative strategy[30] (Scheme 2) that employed the conjugate addition of anions derived from nitroalkanes[21,31] to α,β-unsaturated ketone **4** to afford γ-nitroketones **8** which were then subjected to Nef reaction[32] using potassium permanganate supported on silica gel. Titanium(III) chloride, aqueous hydrogen peroxide (30%) in methanol, and other reagents typically utilized in the Nef reaction proved to be less successful.

In the same paper alkyl 5-arylthiophene-2-carboxylates **12** were prepared using the Fiesselmann thiophene synthesis (Scheme 3) to effect conjugate addition and subsequent ring closure between appropriate alkyl thioglycolates **11** and β-chlorocinnamaldehydes **10**.[33] Phosphorus oxychloride in DMF (Vilsmeier–Haack formylation) was added to ketones **9**[34] to give a mixture of the (*E*) and (*Z*)-isomers of β-chlorocinnamaldehydes **10**.[35,36] Compounds **10** were then



Scheme 4 Synthesis of alkoxythiophenes by novel ring-closure methodology.

reacted with alkyl thioglycolates **11** in base to give esters **12**.[33] Both of these steps proceed in poor to modest yields and the esters could again be more effectively synthesized from intact thiophene rings.

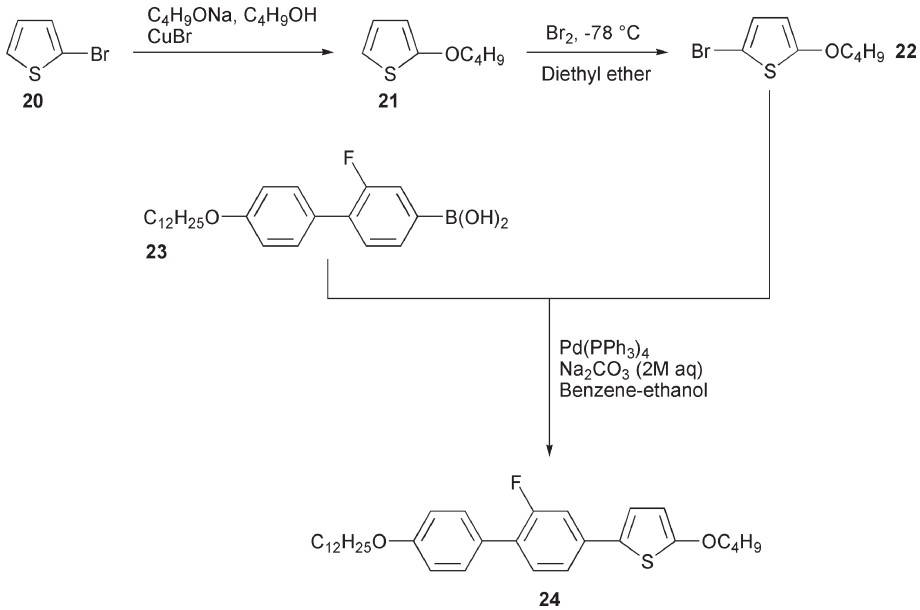
Formation of the thiophene ring in the condensation reaction requires a proximal (*Z*) relationship of the aldehyde and the thioether moieties. Since the reaction between the alkyl thioglycolates and β-chlorovinyl aldehydes is non-stereospecific,[37] the authors should have separated the diastereomeric (*E*) and (*Z*)-β-thioacetic ester aldehydes before cyclization.

In 2001 Seed *et al.* reported the first viable synthesis of alkoxythiophenes from γ-keto esters using ring-closure methodology.[38,39] Scheme 4 illustrates the synthesis of a typical material that was targeted for ferroelectric applications. The key γ-keto acid **14** was synthesized from the Friedel–Crafts reaction of bromobenzene with succinic anhydride in the presence of aluminium chloride.[40] Complete regiocontrol and avoidance of debromination was accomplished by careful control of the reaction temperature.

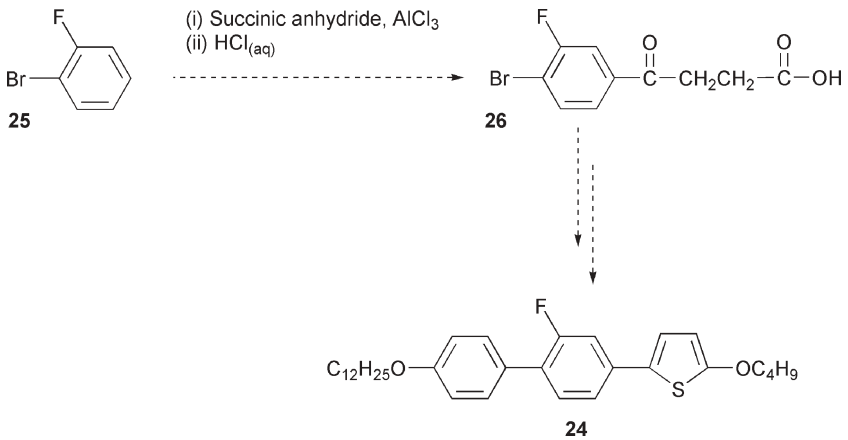
Esterification of **14** was accomplished using 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and *N*,*N*′-dicyclohexylcarbodiimide (DCC).[41] Cyclization of **15** was effected using Lawesson's reagent with careful monitoring of the reaction time being essential to the success of the reaction. Extended reaction times resulted in alkoxy chain cleavage and ring decomposition to give unidentified by-products. In the same year a useful modification of the reaction conditions was reported whereby microwave irradiation was used in a rapid (3–7 min.) solvent-free protocol.[42] Again, careful monitoring of the reaction time is critical for success. Sedavkina *et al.*[43] have demonstrated that phosphorus pentasulfide is unacceptable as a sulfurization source in the cyclization of β-keto esters as 5-alkyl-4-thiolen-2-ones and 5-alkyl-3-thiolen-2-ones are observed to be the major products instead of the desired alkoxythiophenes.

Although alkoxythiophenes look to be simple targets and at first glance closely resemble their alkoxybenzene analogs, they cannot be synthesized in the same way as alkoxybenzenes. Alkoxybenzenes are most commonly synthesized by reaction of a phenol and an alkyl halide in the presence of a base such as potassium carbonate. A similar analogy cannot be found in thiophene chemistry as 2-hydroxythiophenes exist almost entirely as equilibrium mixtures of the 3-thiolen-2-one and 4-thiolen-2-one tautomers (some hydroxythiophenes do exist when the hydroxyl group is stabilized by intramolecular hydrogen bonding to an *ortho* substituent).[44–46] Alkylation of these unsaturated thiolactones has been attempted under numerous conditions with a complex mixture of products often resulting.[47,48]

Nucleophilic substitution of 2-bromo,[49,50] 2-chloro,[51,52] 2-fluoro,[53] and 2-iodothiophenes with metal alkoxides has been somewhat successful with modest yields of alkoxythiophenes being obtained when sodium alkoxides containing four or fewer carbon atoms were used. Longer alkyl chains (as often required for mesogenic materials) give very low yields that are unfeasible for large-scale reactions. Kiryanov *et al.* used such



Scheme 5 Synthesis of alkoxythiophenes using inefficient nucleophilic substitution.



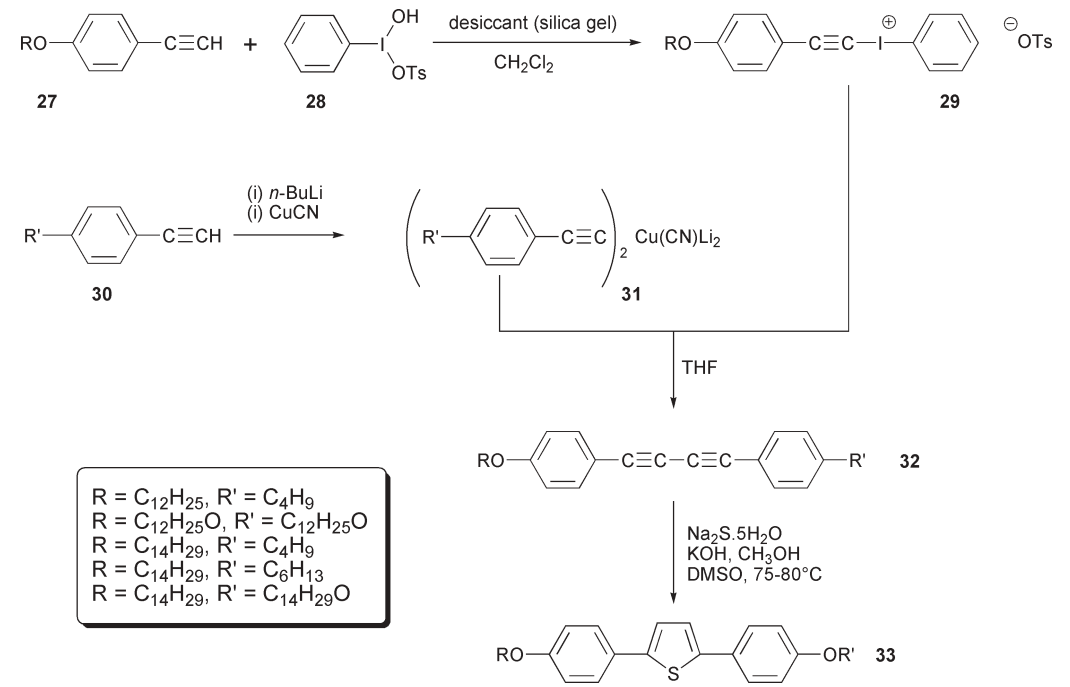
Scheme 6 Theoretical pathway to target **24** using ring-closure.

substitution in the synthesis of 2-butoxythiophene **21** (Scheme 5).[54] A poor yield (14%) was obtained after purification, again highlighting the problems with this chemistry. In this case a ring-closure approach was unlikely to lead to a clean product. A typical pathway to the desired target **24** might involve synthesis of an appropriate dicarbonyl precursor such as **26** (Scheme 6). Due to the opposing directing effects of bromine and fluorine, acylation of **25** would be expected to lead to regioisomeric mixtures as noted in an analogous electrophilic substitution reaction described by Smith *et al.*[55]

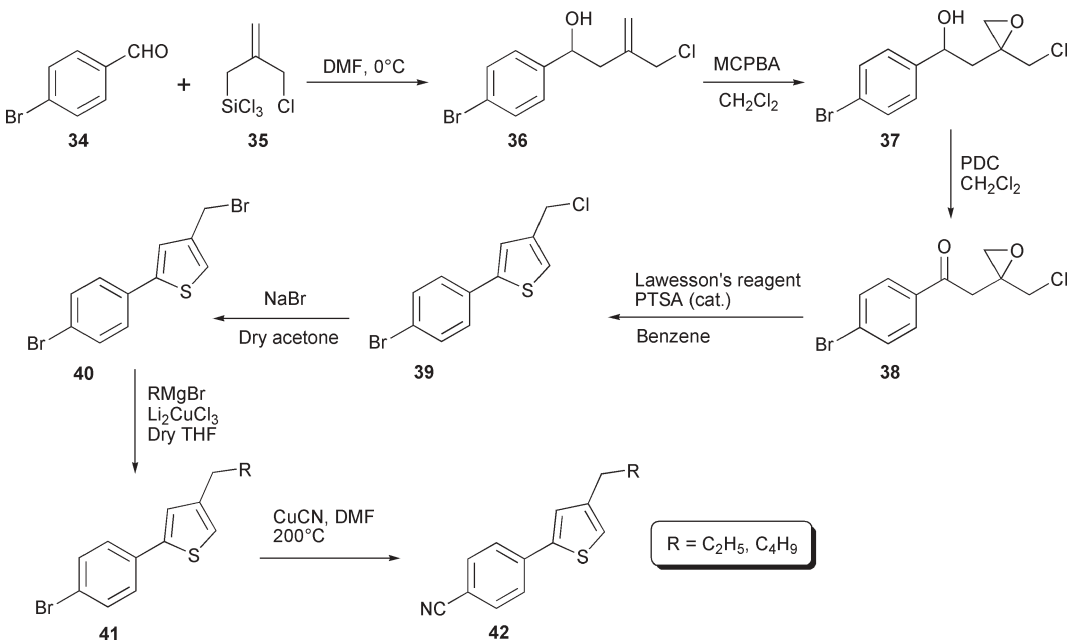
The reactivity of **21** is quite striking and is highlighted in its unusually rapid reaction (2 min.) with bromine at −78 °C. Higher temperatures gave rise to significant quantities of 3,5-dibrominated product in addition to the desired monobrominated adduct. Bromination using NBS was not attempted.

Diarylthiophenes have also been prepared through conversion of diacetylenes with sodium sulfide (Scheme 7).[56] The requisite diacetylenes **32** were obtained through selective coupling of alkynyl(phenyl)iodonium tosylates **29** with higher order cyanocuprates **31** (lower order cuprates were noted to give rise to substantial levels of homocoupling). Modest yields of 52–58% were obtained upon cyclization using the protocol developed by Voronkov *et al.*[57]

2,4-Disubstituted thiophenes are rarely seen in the liquid crystal literature as their more bent shape tends to suppress mesophase formation. In 2001 Kim *et al.* reported the first ring-closing approach to 2,4-disubstituted thiophene-containing mesogens.[58] In the key reaction, Lawesson's reagent was used to effect cyclization of β,γ-epoxy ketones *via* thionation of the carbonyl and regioselective opening of the epoxide by sulfur at the less crowded carbon (Scheme 8). Allylation of aldehyde **34** with allyltrichlorosilane **35** in DMF gave homoallylic alcohol **36**.[59] In the same paper intermediates analogous to **36** were obtained using titanium tetrachloride-mediated reaction of allylsilanes with acid chlorides.[60] Oxidation of **36** with MCPBA gave epoxide **37** which was subsequently oxidized with pyridinium dichromate (PDC) to give β,γ-epoxyketone **38**. In the subsequent thionation reaction, the order of addition of reagents was found to be



Scheme 7 Use of diacetylenes as precursors for 2,5-disubstituted thiophene synthesis.



Scheme 8 Synthesis of 2,4-disubstituted thiophenes *via* thionation and cyclization of β,γ-epoxy ketones.

important in order to maximize the yield of thiophene produced. As might be expected, addition of *p*-toluenesulfonic acid prior to the addition of Lawesson's reagent gave rise to significant quantities of furans being produced.[61] The reaction was therefore carried out by first adding Lawesson's reagent to **38** in benzene and heating under reflux for 30 min. before adding *p*-toluenesulfonic acid. It is interesting to note that the experimental procedure does not mention the use of a dry atmosphere. Given that Lawesson's reagent is significantly hygroscopic, one would expect to see the use of anhydrous conditions. Finally, the alkyl group was then introduced through a Finkelstein reaction using sodium bromide followed by alkyl coupling with Kochi's catalyst.[62] Aryl bromide **41** was finally converted into nitrile **42** using copper cyanide in DMF.[63]

1.2 Modification of an intact thiophene ring

Both 2,5- and 2,4-disubstituted thiophenes are synthesized primarily by modification of an intact thiophene ring.

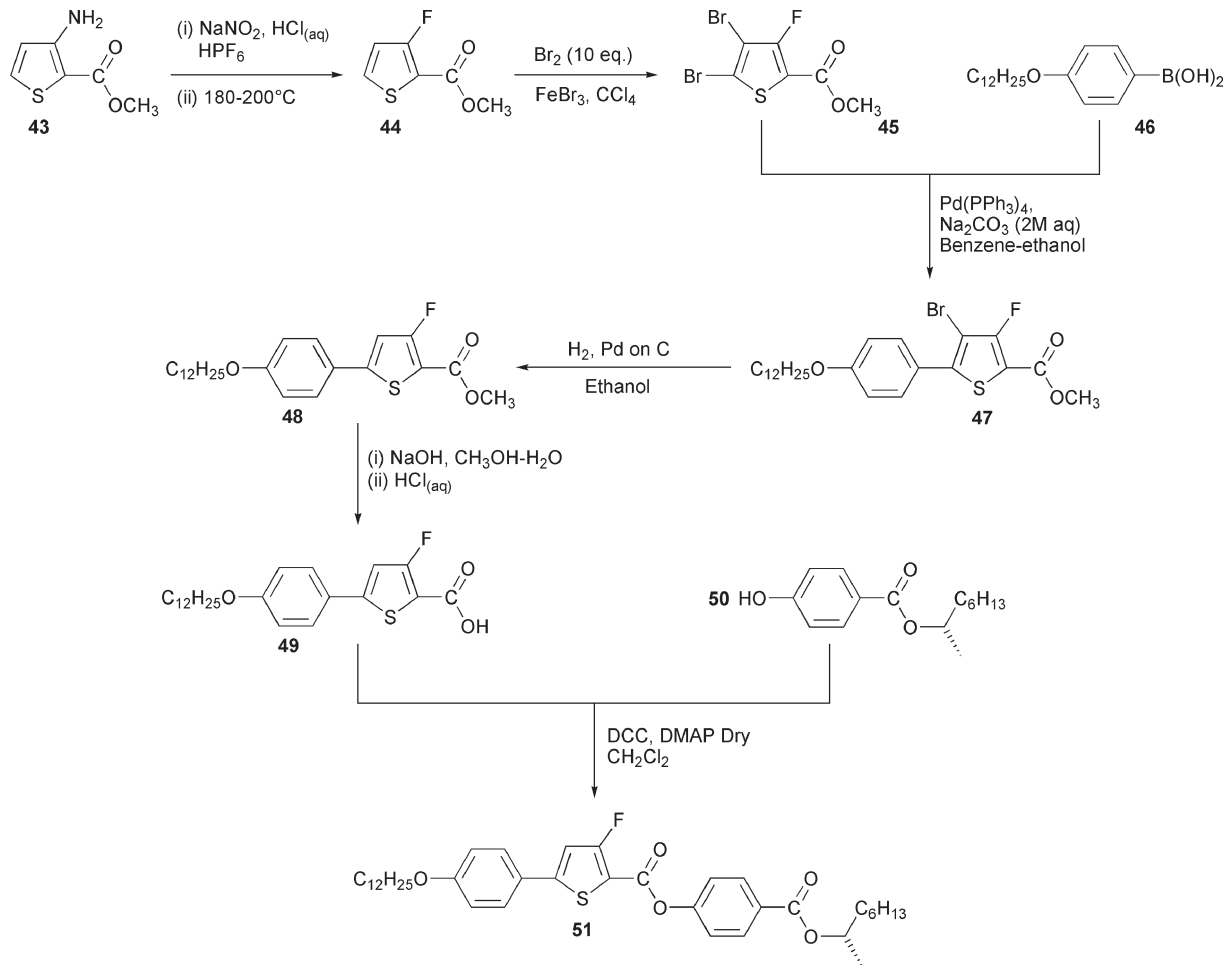
Organometallic chemistry (especially use of alkyllithiums) has flourished in liquid crystal synthesis over the last 20 years, and the ease of preparation of thienyllithiums through halogen–metal exchange and deprotonation at the acidic α-position, has simplified the preparation of useful synthetic precursors on relatively large scales.[64]

Again, 2,5-disubstituted thiophenes dominate the literature (increased molecular linearity leading to higher mesophase stability)[65] and have found uses mostly in nematic and ferroelectric applications.

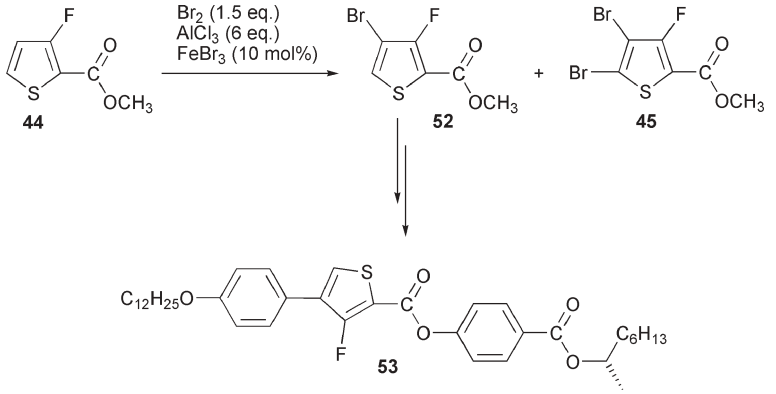
Bromothiophenes, iodothiophenes, stannylthiophenes, and thienylboronic acids are the most common precursors that are subjected to palladium-catalyzed cross-coupling to make the rigid heteroaryl core. Thienylboronic acids are less commonly observed in syntheses as there is a slight risk of proto-deboronation[66] when the boronic acid moiety is in close proximity to the electron-withdrawing sulfur atom (or another electronegative unit).

Fluorinated thiophenes have recently emerged as promising ferroelectric host/dopant materials. Kiryanov *et al.* reported the first synthesis of such materials using a modification of Kobafard's[67] Balz-Schiemann methodology (Scheme 9) to introduce fluorine into the heterocyclic ring.[68] Reaction conditions for the Balz-Schiemann chemistry (conversion of **43–44**) were critical to the success of the reaction and included plunging a large surface area reaction vessel straight into an oil bath at 200 °C (gradual heating led to extremely poor yields). Regioselective cross coupling of **45** at C(5) was expected due to the electron deficient nature of this position promoting faster oxidative addition of Pd(0). An 83 : 2 regioisomeric mixture of C(5) : C(4) coupling was observed with the two isomers being separable by column chromatography. Hydrogenolysis of **47** gave debrominated material **48** that was subsequently saponified and esterified under DCC/DMAP conditions.[41] In the same paper, 2,4-disubstituted-3-fluorothiophene **53** was prepared *via* key building block **52** (Scheme 10). Preparation of **52** was possible using the "swamping catalyst effect" to direct the regioselective bromination.[69] Aluminium chloride was used to coordinate to the ester carbonyl in **44**, resulting in deactivation of the thiophene ring and strongly directing any electrophilic substitution *ortho* to fluorine.

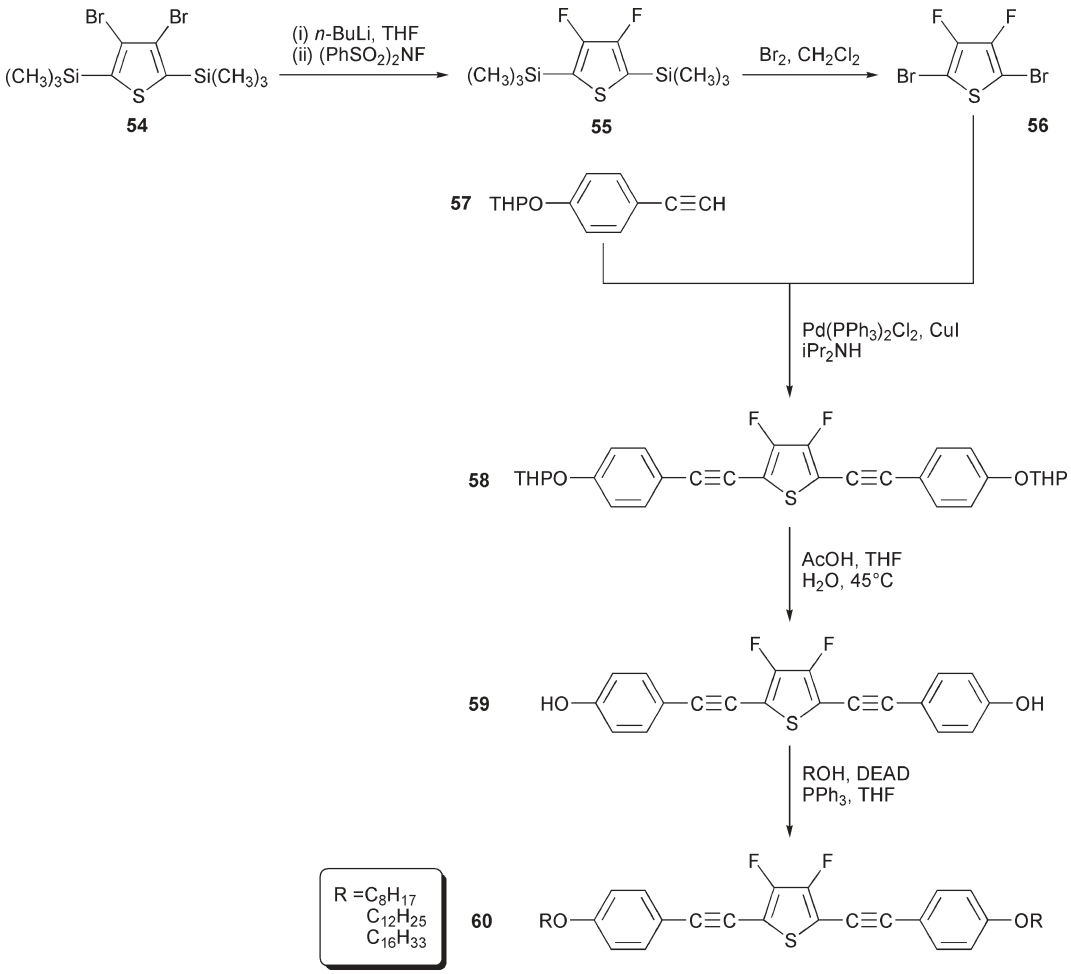
However, the ring was so deactivated that reaction did not take place without a unique modification to the standard protocol. Addition of the softer Lewis acid iron(III) bromide provided sufficient activation and gave a 79 : 8 mixture of **52** : **45** (separable by crystallization/chromatography). The additional use of iron(III) bromide in "swamping catalyst" chemistry is unprecedented and holds significant potential for use in other deactivated heterocyclic systems.



Scheme 9 Synthesis of fluorothiophenes by Kiryanov *et al.*



Scheme 10 Use of regioselective "swamping catalyst" chemistry in the synthesis of 2,4-disubstituted thiophenes.



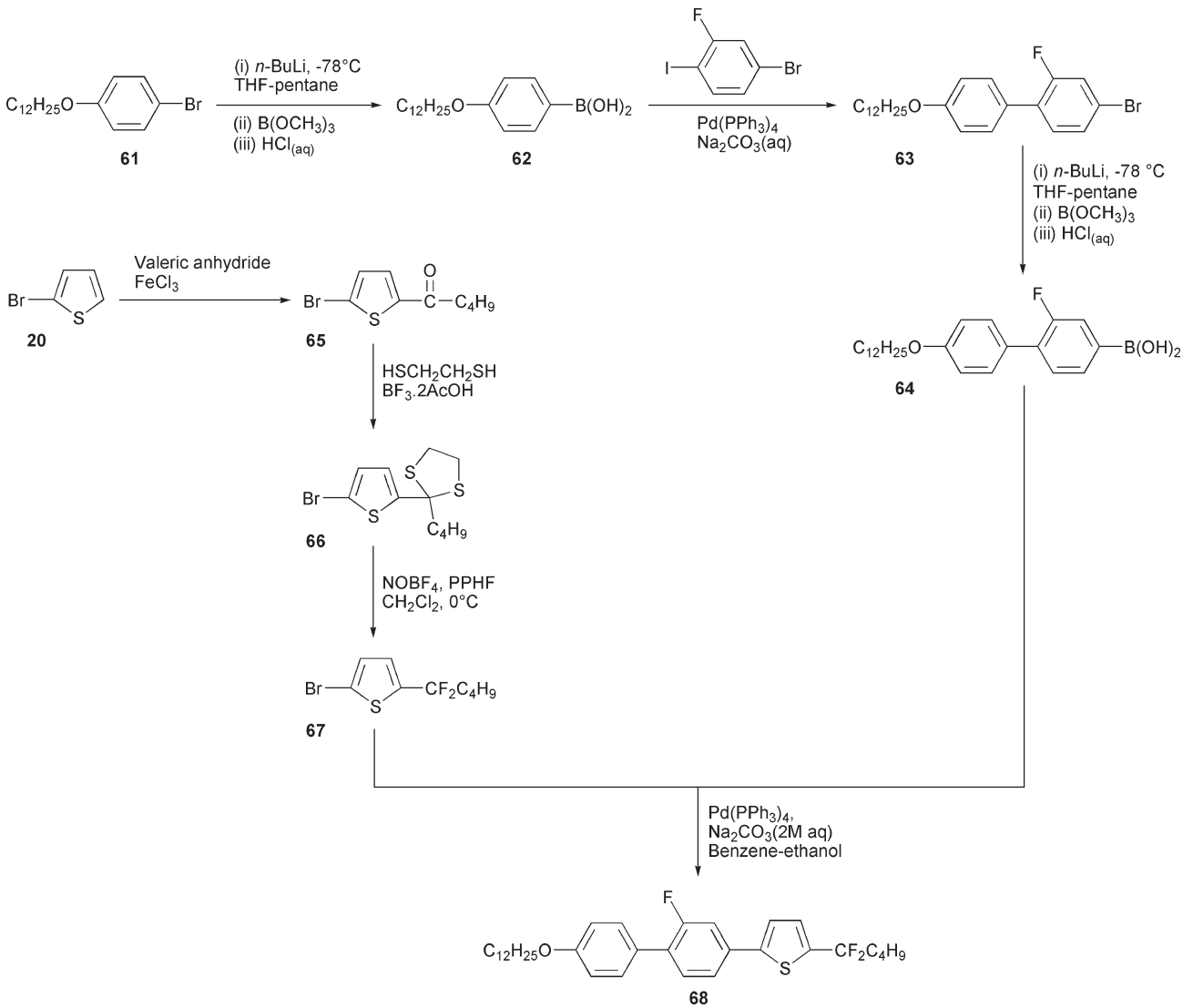
Scheme 11 Preparation of fluorothiophenes using electrophilic fluorination

Swager *et al.* have recently been focused on an investigation of bent-shaped asymmetric molecules to create mesophases with polar ordering.[70] As part of this programme of research they constructed a number of 2,5-disubstituted-3,4-difluorothiophenes using electrophilic fluorination (Scheme 11) of an organolithium to introduce fluorine onto the heterocycle. Trimethylsilyl derivative **54** underwent halogen–metal exchange with one equivalent of *n*-butyllithium and was reacted with the electrophilic fluorinating reagent *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSI).[71] Further halogen–metal exchange with another equivalent of *n*-butyllithium and reaction with NFSI gave the target **55** (addition and fluorination with the final equivalent of organolithium was carried out in four portions, with fluorination being carried out after the addition of each aliquot of *n*-butyllithium). Bromination of disilane **55** proceeded with *ipso*-silyl

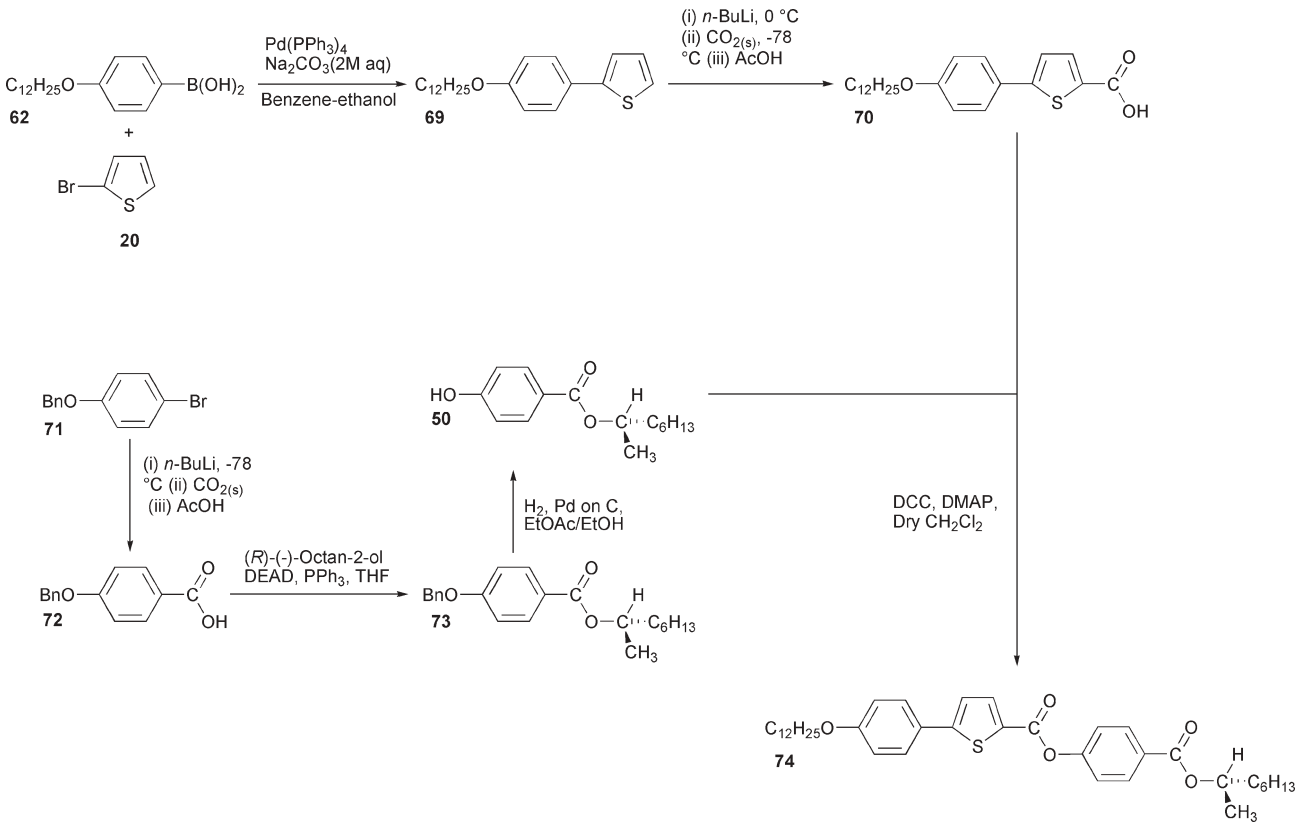
cleavage to give dihalide **56**. Sonogashira coupling[72] of **56** with THP protected phenol **57** followed by acidic hydrolysis of the protecting group gave **59**. Etherification of **59** under Mitsunobu conditions[73] gave targets **60**.

Hsu *et al.* recently reported the first examples of mesogenic multiynyl materials with a thiophene-based central core.[74] These Y-shaped 2,3,5-tris(4-alkoxyphenylethynyl)thiophenes were constructed *via* a low-yielding (a maximum yield of ~34% was reported) Sonogashira coupling of 4-alkoxyphenylethynes with tetraiodothiophene. The analogous tetraynyl systems were, surprisingly, non mesogenic.

The first α,α-difluorothiophenes were reported by Kiryanov *et al.*[54,75] with the fluoro-based unit being designed to impart high dielectric biaxiality for ferroelectric applications. The original report utilized DAST (diethylaminosulfur trifluoride) to effect transformation of the carbonyl group of a thienylketone to the α,α-difluoromethylene unit (28% yield). Other methods of fluorodeoxygenation were attempted (use of DeoxoFluor® and MorphDAST) although yields were also unsatisfactory for multigram scale synthesis and required extended reaction times (18 h–6 d). In an alternative approach, thienylketones were converted into 1,3-dithiolane derivatives followed by fluorodesulfurization (use of pyridinium poly(hydrogen fluoride)/1,3-dibromo-5,5-dimethylhydantoin, pyridinium poly(hydrogen fluoride)/*N*-bromosuccinimide, and pyridinium poly(hydrogen fluoride)/*N*-iodosuccinimide). Use of nitrosonium tetrafluoroborate/pyridinium poly(hydrogen fluoride) in a modification of the procedure described by York, Prakash, and Olah,[76] provided the difluoro derivatives in excellent yields with a reaction time of 6 min. Extended reaction times resulted in product decomposition and after 3 h none of the desired product could be isolated. A typical synthetic scheme to a typical difluorothienyl-based liquid crystalline target is given in Scheme 12. Boronic acid **62** was synthesized using a THF–pentane (4 : 1) solvent mixture due to the insolubility of precursor **61** in neat THF at −78 °C (synthesis of **64** also utilized similar conditions due to the insolubility of bromobiphenyl **63**). **62** underwent selective Suzuki coupling with 4-bromo-2-fluoro-1-iodobenzene to give **63**. **20** was acylated with valeric anhydride using iron(III)



Scheme 12 Synthesis of a typical α,α-difluorothienyl based liquid crystal



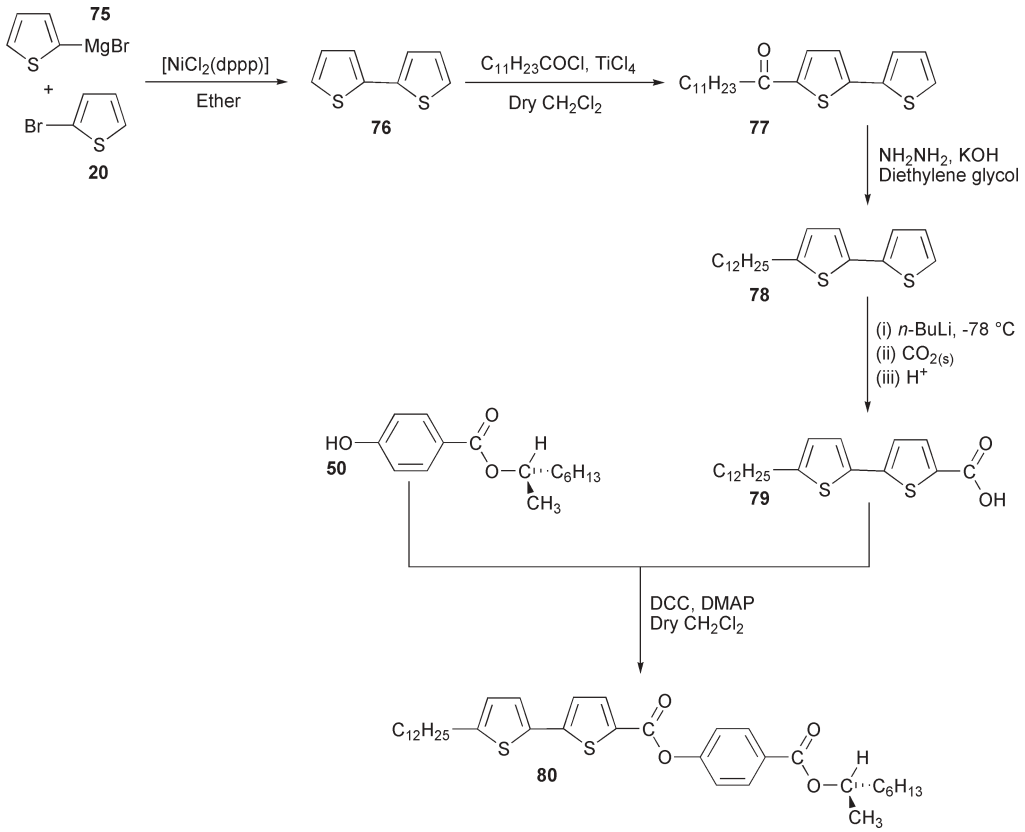
Scheme 13 Synthesis of a thiophene-2-carboxylate mesogen by Seed *et al.*

chloride as catalyst followed by dithiolane formation using $BF_3 \cdot 2HOAc$. Dithiolane **66** was treated with $NOBF_4$/PPHF in dichloromethane at 0 °C for 6 min. to give **67**. Unfortunately all of the α,α-difluorothiophenes synthesized (including the liquid crystal products) undergo decomposition to the thienylketone upon prolonged exposure to silica gel during flash chromatography or TLC analysis (a similar hydrolytic instability has been observed in *N*,*N*-dimethyl-2-perfluoroalkylanilines).[77] Fortunately, rapid filtration through a silica plug was found to give pure products with minimal decomposition.

The first ferroelectric thiophene esters were reported independently by Seed and Matharu in 1996.[78] A large variety of thiophene-based ester and thioester compounds have been prepared since these reports. A common way of introducing the ester unit involves lithiation of an appropriate thiophene unit followed by carboxylation, acidification, and esterification with an appropriate phenol/alcohol. Scheme 13 illustrates a typical pathway to ferroelectric target **74**.[39] Deprotonation of **69** was carried out below 0 °C (typically 0 to −10 °C) and the resulting thienyllithium was carboxylated with dry ice.[79] The obtained carboxylate salt was acidified by dissolution in hot acetic acid and precipitating the free acid by the addition of ice. This procedure was found to be preferable over acidification with HCl as carboxylate salts were not always successfully acidified by aqueous acid (presumably due to issues of solubility). Phenol **50** was prepared by carboxylation of protected phenol **71**, esterification with (*R*)-octan-2-ol under Mitsunobu conditions (with inversion of configuration at the stereocenter), and deprotection of the benzyl group using catalytic hydrogenation. The benzyl protecting group was chosen as this group is relatively robust, synthesized in high yields, and removed easily and in near-quantitative yields.[80] Chin and Goodby[81] have demonstrated the use of methyl carbonate as a phenolic protecting group in mesogenic synthesis. In the author's experience, isolation of LC precursors protected with this functional group is somewhat awkward as they are often produced as voluminous precipitates (filtration and drying tends to be very time consuming) and are less tolerant toward both high and low pH.[80]

Matharu *et al.*[82] have examined both chiral bi- and terthiophene esters as candidates for ferroelectric applications (Scheme 14). The bithienyl unit was constructed using nickel-catalyzed cross-coupling[83] of 2-thienylmagnesium bromide with 2-bromothiophene (terthienyls were similarly constructed using 2,5-dibromothiophene instead of 2-bromothiophene). Acylation of bithiophene **76** utilized titanium tetrachloride and dodecanoyl chloride. Wolff–Kishner reduction of ketone **77** gave **78** which was deprotonated at unusually low temperature (−78 °C instead of the usual 0 to −10 °C).

It is interesting to note that the collinear substitution of the bithiophene does not lead to high mesophase thermal stability of **80** [Cryst 57.5 (SmC^*_A 50 SmC^*_{FI} 56 SmC* 56 SmA 57) Iso Liq] which may be due to the substantial molecular breadth imparted by the two sulfur atoms. Addition of an extra ring, however, gave rise to a substantial increase in the mesophase thermal stability (approx. 85 °C higher). Similar methodologies have been reported by the same group in the synthesis of



Scheme 14 Matharu's bithiophene synthesis.

(*S*)-4′-(1-methylheptyoxycarbonyl)biphenyl-4-yl 5-(4-4-decyl-oxyphenyl)thiophene-2-carboxylate.[84]

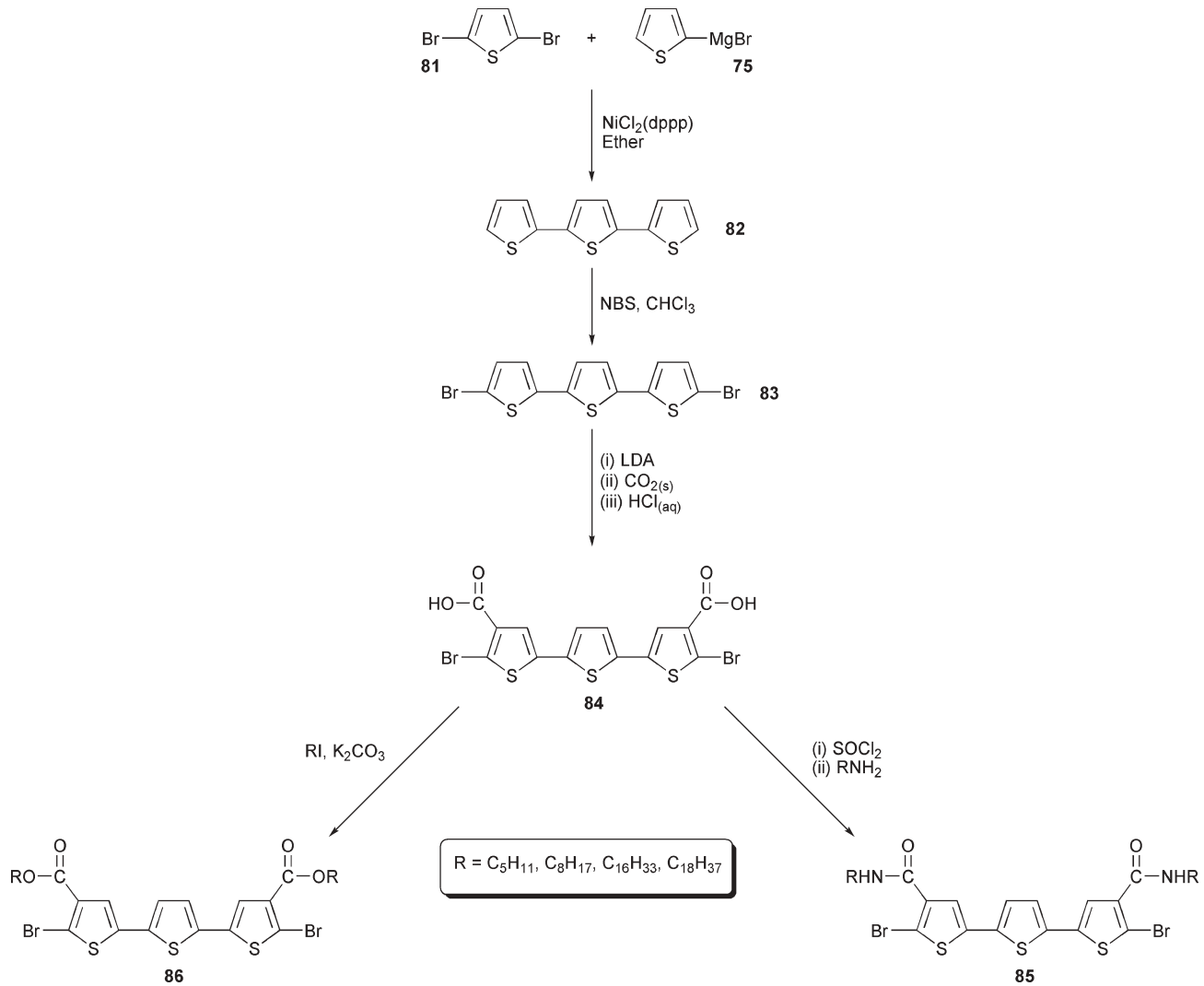
Liu *et al.* have investigated a number of 2,2′:5′,2′-terthienyl derivatives with amide and ester units at the outboard β positions.[85] Interestingly, the amide derivatives **85** (Scheme 15) gave SmA phases (the pentyl derivative was the only non-mesogenic amide) whereas esters **86** were non-mesogenic. The synthesis begins with a nickel-catalyzed cross-coupling of 2,5-dibromothiophene **81** with 2-thienylmagnesium bromide **75**.

Terthienyl **82** was regioselectively dibrominated using *N*-bromosuccinimide in chloroform (the yield was not given in the paper). Once the reactive α-positions were blocked, the authors used LDA deprotonation (a two-fold excess of LDA was used) of the activated 4 and 4″ β positions of **83** to introduce carboxylic acid units which were subsequently converted into amides **85** and esters **86** under standard conditions. The authors rightly note the difficulties involved in the introduction of β substituents when the α positions are unsubstituted, and they elected to retain the bromine substituents in the final products; the authors suggested that the high polarizability of the halogens might lead to enhanced mesogenic nature. It is, however, quite conceivable that the sheer bulk of the halogens will lead to reduced intermolecular attraction and destabilization of the mesophases. It would have been interesting to compare these targets with the debrominated analogs that could have been easily prepared from targets **85** and **86** using catalytic hydrogenation in a single step. Analogous non-mesogenic amide derivatives (with amide groups located at the 5 and 5″ positions) were also reported in the paper.

Thiophene has often been incorporated into the cores of high polarizability materials for use in applications that include third harmonic generation, all-optical switches *etc.* The following section reviews the highlights of this area. Much progress has been made by the Hull group where thiophene has been accompanied by other highly polarizable moieties such as alkylsulfanyl and alkylselanyl chains, isothiocyanate and cyano terminal groups, and naphthyl cores. Introduction of alkylsulfanyl and alkylselanyl chains has been performed using both organolithium and organomagnesium chemistry (Scheme 16).[65,86] Deprotonation of thiophene or bithiophene (**76**) using *n*-butyllithium followed by addition of sulfur at −78 °C and acidic workup gives the thiophene-2-thiol.

These materials have a particularly obnoxious odor and must be rapidly alkylated if dimerization is to be avoided (reversion to the free thiol is straightforward if necessary).[87] Thiophene-2-thiol exists as a tautomeric mixture of the thiol (**99**, major) and thiene-2-thione (**100**, minor) and the latter undergoes Michael-like addition with the thiol to give **101** (Scheme 17).[87]

Disulfide formation also occurs with aerial oxidation of the thiol although this tends to be a minor by-product. Subsequent deprotonation (sodium ethoxide) of the thiol and reaction with an alkyl halide gives the desired alkylsulfanylthiophene **88**. Bithiophene **88** was nitrated with nitric acid–acetic anhydride and reduced to the amine **90** using catalytic hydrogenation.

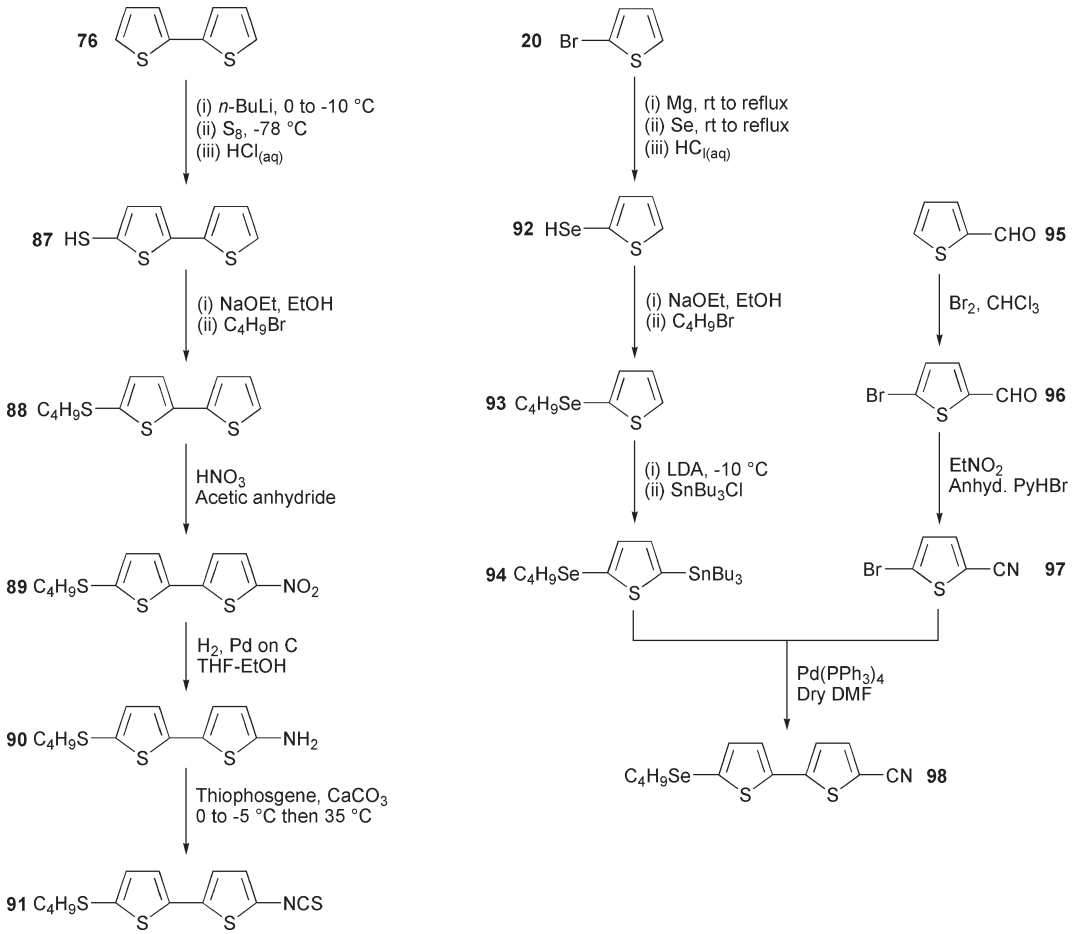


Scheme 15 Synthesis of terthienyl amides and esters using directed lithiation.

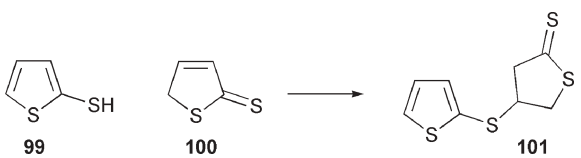
The known instability of thiophene amines prompted us to immediately convert the amine into isothiocyanate **91** using thiophosgene. This reaction is highly temperature sensitive and addition of the amine to thiophosgene should be carried out between 2–5 °C to maximize the yield of isothiocyanate. Due to the electron-withdrawing nature of the thiophene sulfur, it was found that thienylisothiocyanates were much more electrophilic than their phenyl counterparts. Attempted recrystallization of thienylisothiocyanates from ethanol gave reaction of the ethanolic oxygen on the isothiocyanate carbon atom and resulted in the formation of *N*-carbamates. No such reaction occurred when recrystallizing phenylisothiocyanates from ethanol. Jochims procedure has also been successfully used to convert thiophene amines into isothiocyanates although this procedure is more time consuming and uses hazardous reagents.[88]

Alkylselanylthiophene **93** was synthesized by reacting the Grignard derivative of **20** with red selenium (incorrectly reported as gray selenium); red selenium was prepared by the action of concentrated hydrochloric acid on an aqueous solution of potassium selenium cyanide. Acidic workup gave the foul smelling selanol **92** that was alkylated to give **93**. Attempted metallation of **93** (and its alkylsulfanyl analog) with *n*-butyllithium caused attack at the heteroatom and subsequent cleavage of the side chain. Successful deprotonation was achieved by use of the non-nucleophilic base LDA. Reaction of the resulting organolithium with tributylstannyl chloride gave **94**. Bromination of **95** provides a typical example of the directing power of the thiophene sulfur atom. The aldehyde substituent directs to the 4-position of the thiophene ring but the regioselective outcome of the reaction is dominated by sulfur, and bromination occurred exclusively at the 5-position. Conversion of **96** to **97** used the method of Dauzonne;[89] in our hands this method proved to be extremely sensitive to moisture and was not reproducible. Later studies showed the procedure used by Saednya[90] to be higher yielding and much more convenient. Finally, Stille coupling[91] of **94** and **97** gave **98**. Stille coupling was favored over the use of a boronic acid derivative as we expected the boronic acid to be somewhat subject to protodeboronation.

Inoue *et al.* have synthesized hexakis(mono-, di-, and terthiophenylthio)benzenes **106** (Scheme 18) as new discotic liquid crystals with potentially high charge-carrier mobilities.[92]



Scheme 16 Alkylsulfanyl and alkylselanylthiophenes.



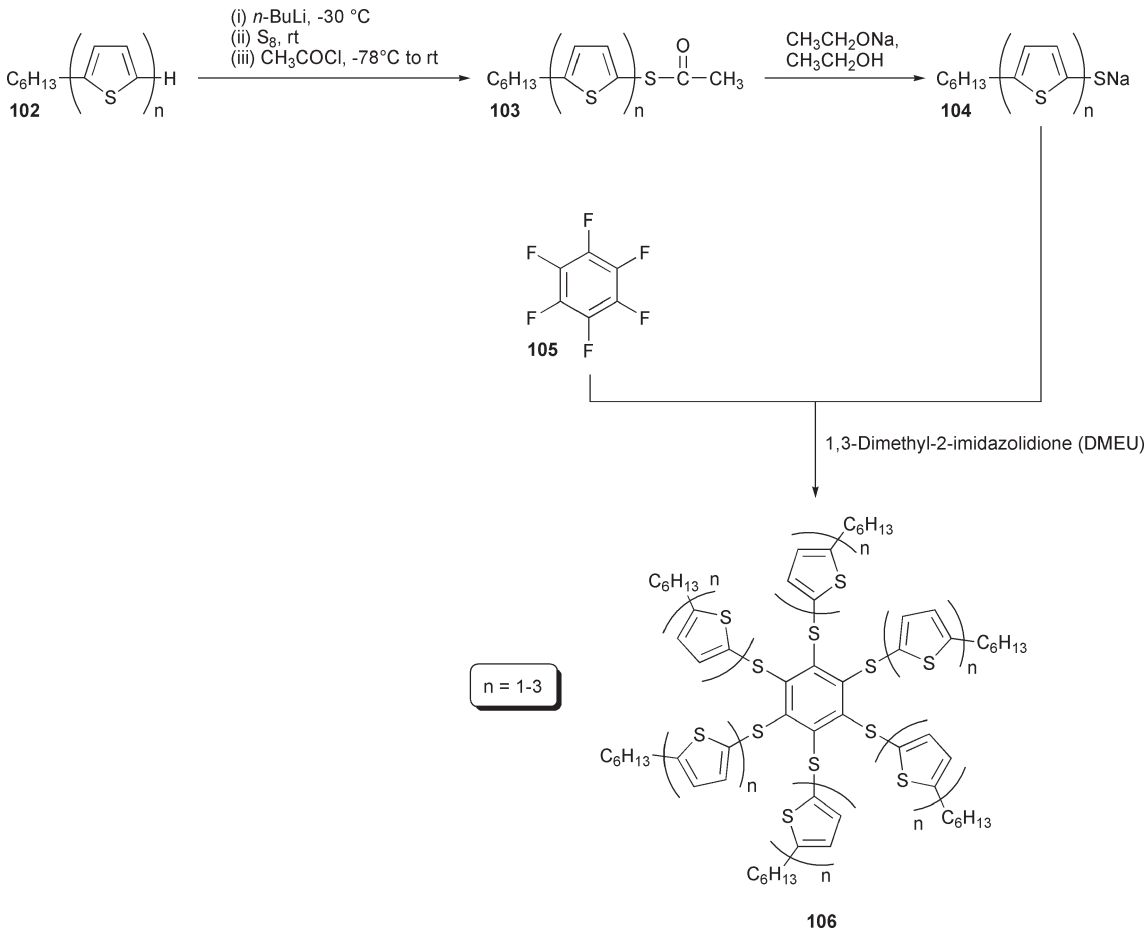
Scheme 17 Dimerization of thiophene-2-thiol.

Hexylthiophenes **102** were deprotonated by *n*-butyllithium followed by addition of sulfur to give the lithium salt of the thiolate. Reaction with ethanoyl chloride at −78 °C gave thioesters **103** that were subsequently transesterified to give the sodium thiolate **104**. Reaction of **104** with hexafluorobenzene under conditions first reported by MacNicol[93] gave targets **106**. Interestingly, instead of adopting the expected discoid structure, the molecules were found to adopt a cylinder-like conformation that gave rise to SmA and SmC phases for the terthienyl compound [$n = 3$; the thienyl ($n = 1$) and dithienyl ($n = 2$) compounds are non-mesogenic].

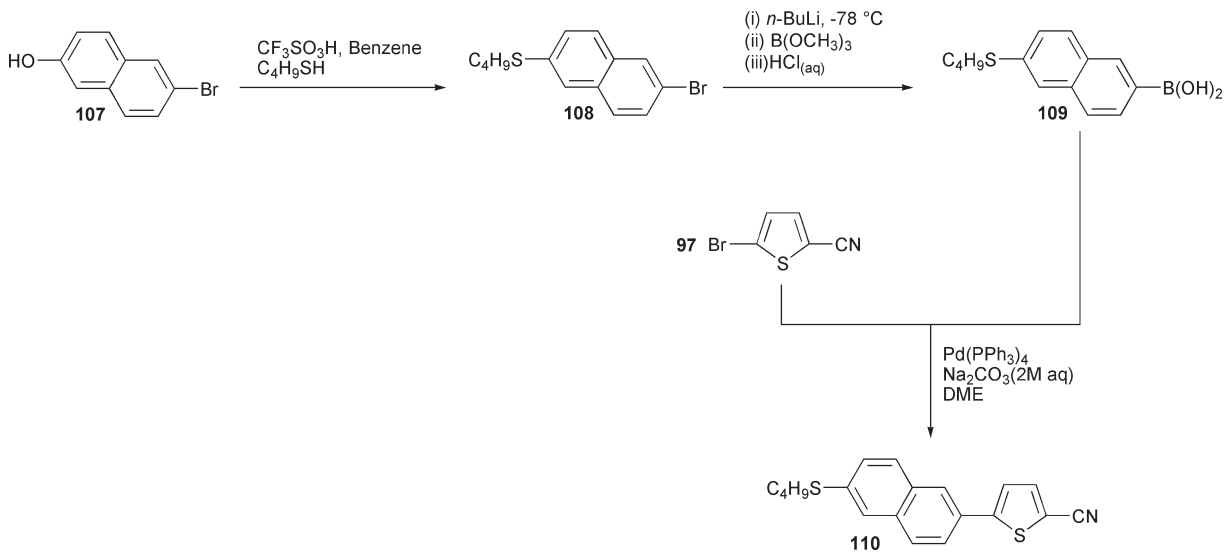
Naphthyl-thienyl systems have also proven to be highly polarizable and have seen several developments in methodology. Scheme 19 shows the synthesis of a typical system where alkylsulfanylnaphthalene **108**[94] was prepared in modest yields by a Bucherer-like reaction.

This method uses an unpleasant mixture of trifluoromethanesulfonic acid, benzene, and butane-1-thiol. The product of the reaction is a black tar that is difficult to work up and purify. Recently, Seed and Mishra-Sharma[95,96] have developed a new protocol for the synthesis of alkylsulfanylnaphthyl units that uses *p*-toluenesulfonic acid, toluene, and an alkane thiol. This method has proven far superior to the former as it gives consistently high yields of clean products that are easy to purify by recrystallization.

Occasionally thienylacetylenes have been prepared with the alkyne precursor being a derivative of thiophene. Approaches to these systems have employed the usual Negishi and Sonogashira couplings of various protected acetylenes (trimethylsilylacetylene and 2-methylbut-3-yn-2-ol being typical) with appropriate halothiophenes. This is followed by deprotection and further cross-coupling with a second haloarene to create the desired acetylene. However, in the case of 2-alkylsulfanyl-5-ethynylthiophenes these approaches are not possible due to the instability of the terminal acetylene that decomposes before coupling can take place. A solution to this problem has been presented by Carpita *et al.* who reported one-pot palladium-catalyzed syntheses of diarylalkynes from the reaction of a protected acetylene and a heteroaryl halide under phase transfer conditions.[97,98] This method was employed by Cross in the preparation of targets **115** and **116** (Scheme 20).[99] Deprotection of **113** gave the terminal acetylene (not shown) that was seen to decompose within a few hours to form a tarry mass. Negishi and



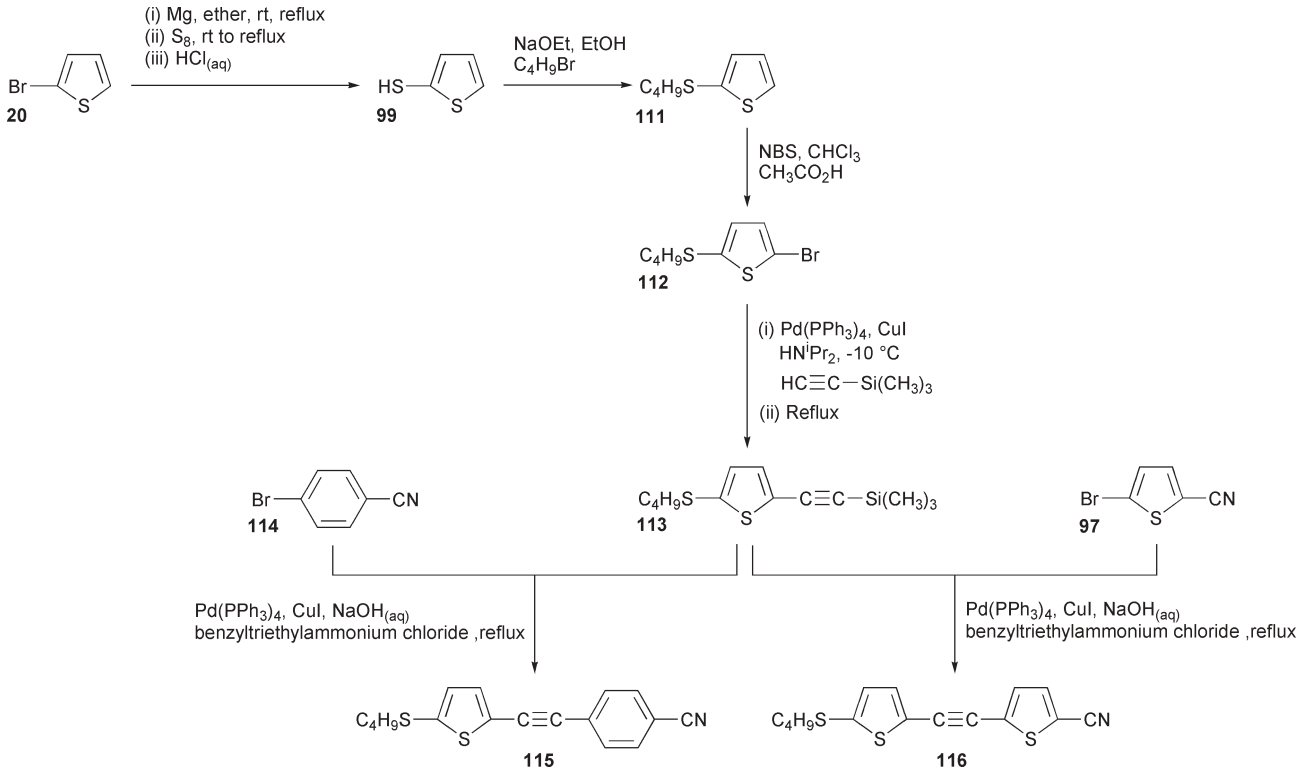
Scheme 18 Inoue's synthesis of hexakis(mono-, di, and terthienyl)thiobenzenes.



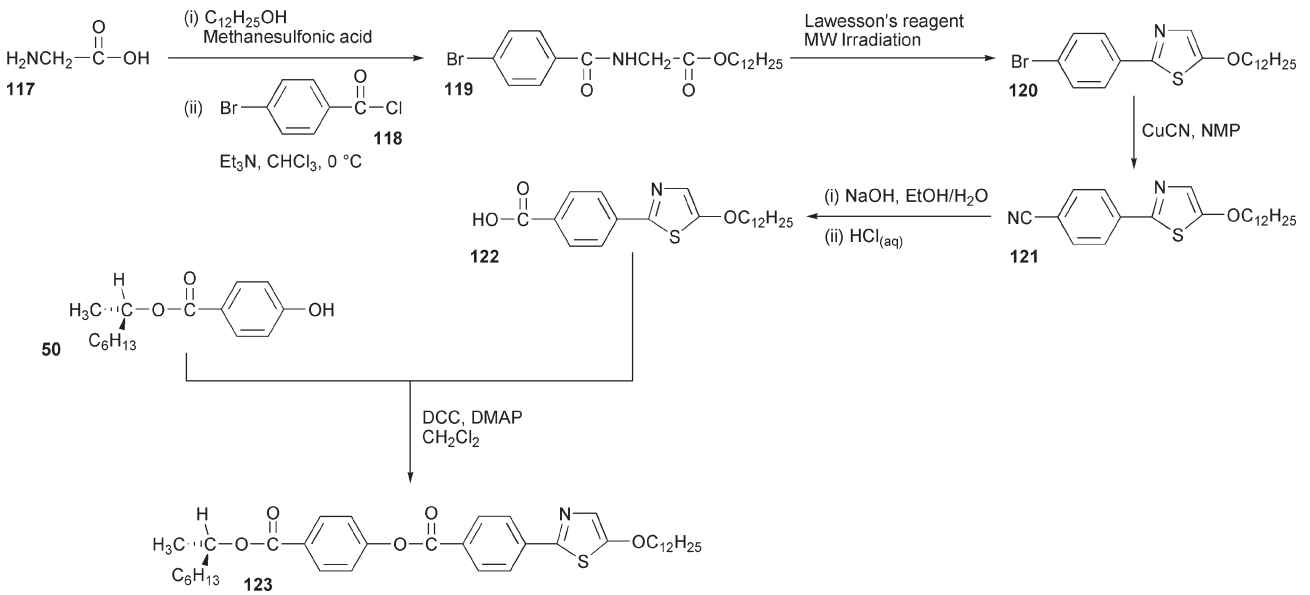
Scheme 19 Synthesis of thienylnaphthalene systems.

Sonogashira couplings were attempted prior to decomposition but met with failure. Coupling of **113** with **97** and **114** under the Carpita conditions gave the desired targets **116** and **115** respectively.

A number of other notable thiophene-containing materials may be found in the recent literature[100–103] although the chemistry is not of significant difference as to be included in this review.



Scheme 20 Use of the Carpita method in the coupling of protected thienylacetylenes.



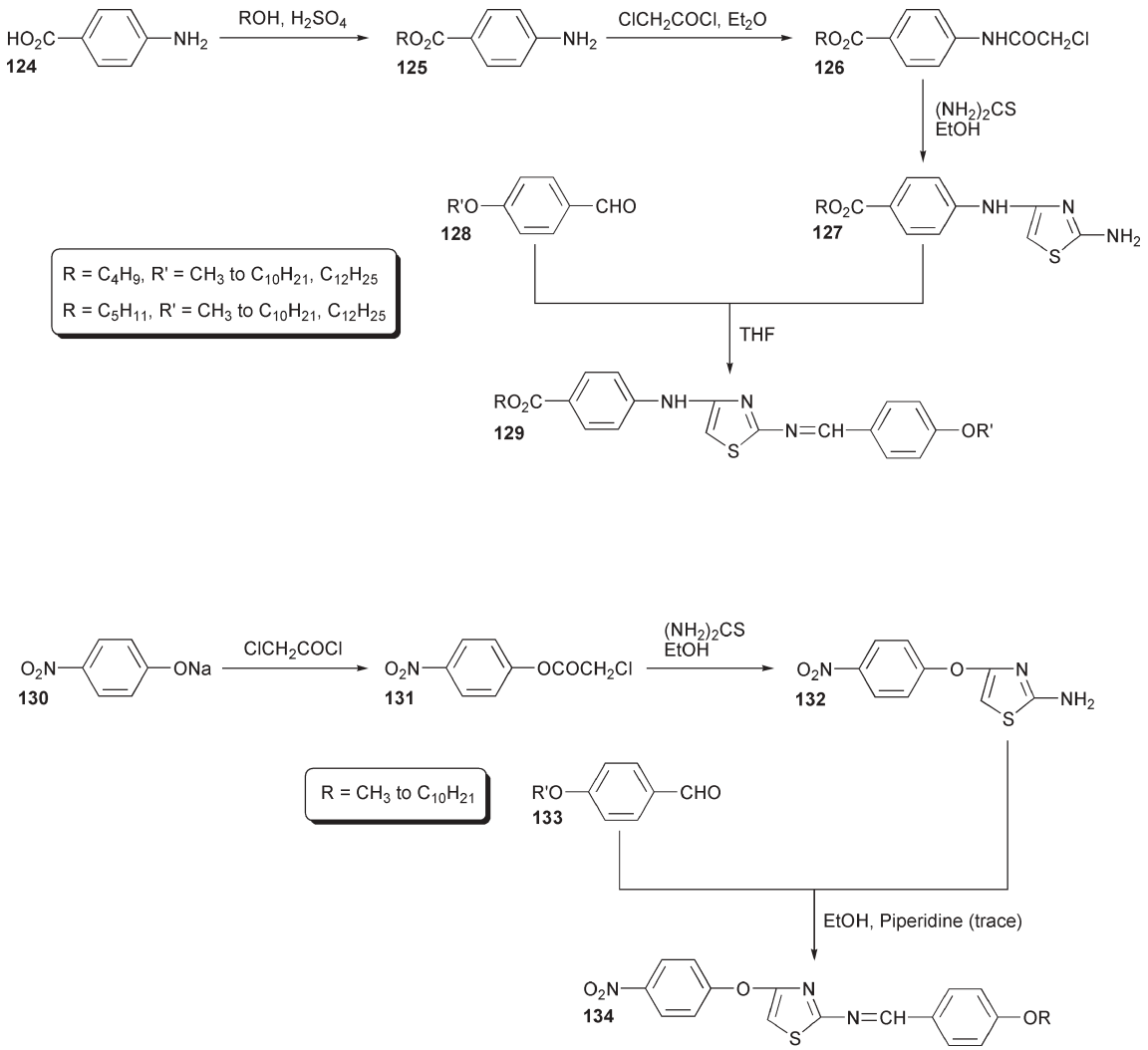
Scheme 21 Synthesis of a ferroelectric 2-alkoxy-1,3-thiazole.

2. 1,3-Thiazoles

2.1 Ring closure in the formation of 1,3-thiazoles

In 2001 Kiryanov *et al.* reported the synthesis of the first 5-alkoxy-2-aryl-1,3-thiazole-containing mesogen **123** (Scheme 21).[42] These materials were targeted as relatively high birefringence ferroelectric materials for use in devices (such as holographic displays and telecommunications interconnects) using advanced complementary metal oxide semiconductor (CMOS)-based pixels.

The key 1,4-dicarbonyl precursor **119** was prepared by esterification of glycine **117** with dodecanol[104] followed by reaction with 4-bromobenzoyl chloride **118**. Ring closure was rapidly effected in a solvent-free protocol using Lawesson's reagent under microwave irradiation. Our initial strategy was to utilize halogen–metal exchange using *n*-butyllithium (on



Scheme 22 2,4-Disubstituted 1,3-thiazole synthesis *via* the Hantzsch synthesis.

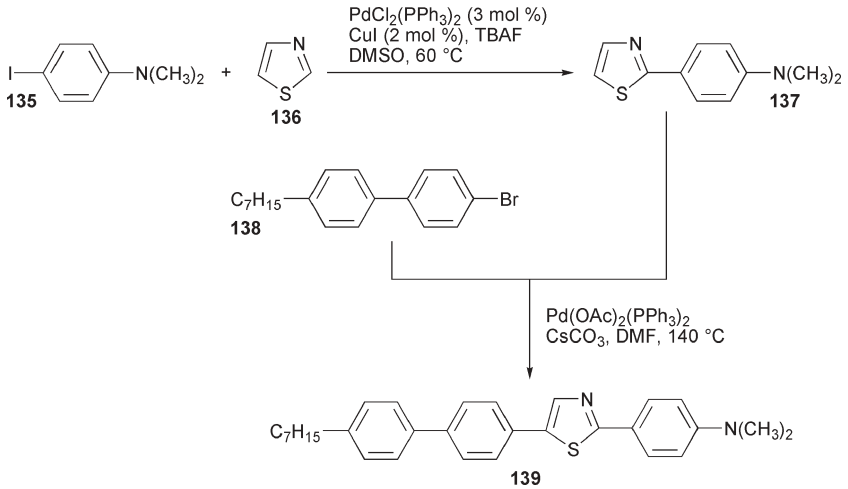
substrate **120**) followed by reaction with dry ice to give the carboxylic acid **122**. It was found, however, that competitive deprotonation at C-4 on the thiazole ring forced us to instead use cyanation[63] and basic hydrolysis of the nitrile to obtain the desired acid. It is interesting to note that a detailed search of the general organic literature reveals that this is the first reported preparation of alkoxythiazoles using Lawesson's reagent (alkoxythiazole preparation has been reported where P_2S_5 was used as the sulfuration agent).[105]

An earlier publication by Dölling *et al.* describes a closely related construction of 2,5-diaryl-1,3-thiazoles using P_2S_5 in a modification of Siegrist's method.[106,107]

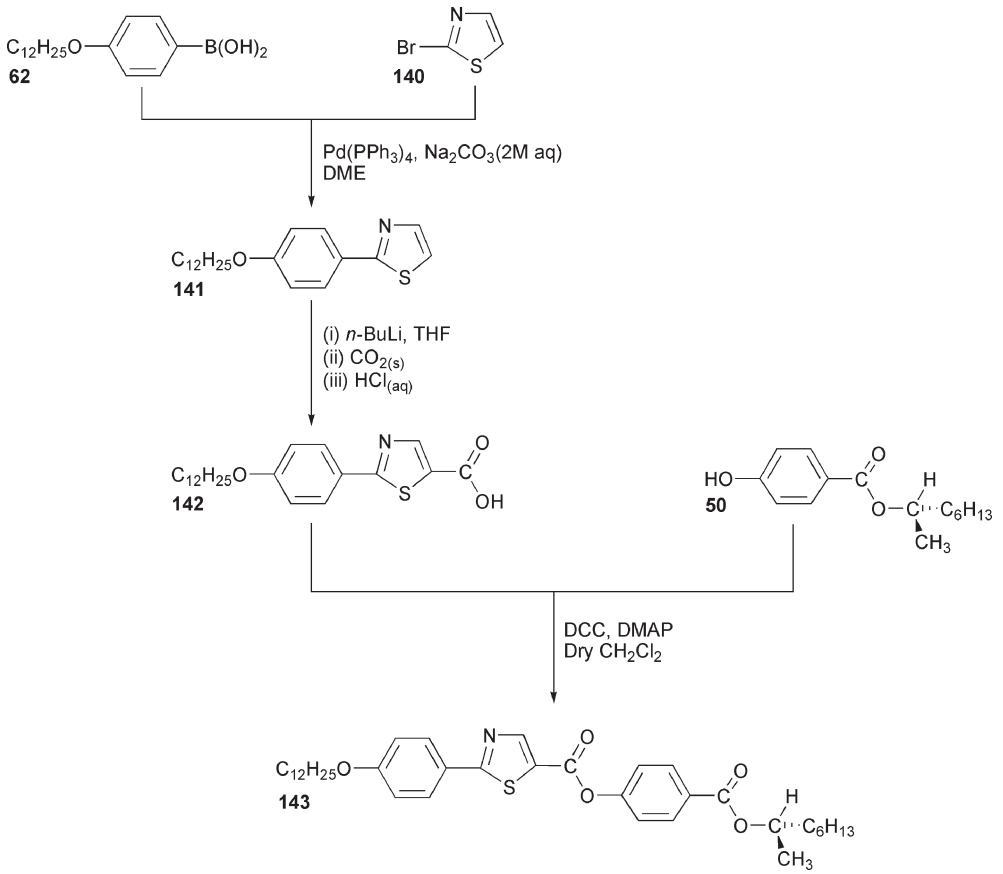
2,4-Disubstituted-1,3-thiazoles have also been examined by Murza *et al.* (Scheme 22).[108–110] Esterification of 4-aminobenzoic acid **124** with butanol or pentanol gave esters **125**. Acetylation of **125** with chloroacetyl chloride gave **126**. Treatment of **126** with thiourea[111] (Hantzsch synthesis) gave 2-amino-1,3-thiazoles **127** which were subsequently converted into the imine targets by reaction with aldehydes **128** in THF at reflux. Aryloxythiazoles **134** (all possessing broad nematic phases) were synthesized in a similar manner, with sodium 4-nitrophenoxide being reacted with chloroacetyl chloride to give the key esters **131** which were again cyclized using thiourea. Closely related materials have been synthesized in an analogous manner by the same group.[112,113]

2.2 Modification of an intact 1,3-thiazole ring

A small number of 1,3-thiazoles have been synthesized through a novel tandem transition-metal catalyzed cross-coupling procedure. In 2003 Mori *et al.* reported the preparation of a variety of 2,5-diaryl-1,3-thiazoles *via* a unique metal-catalyzed substitution of a C–H bond.[114] Previous studies by the authors on a TBAF activated Pd/Cu-catalyzed reaction of terminal alkynes with organic electrophiles,[115–117] led them to explore the possibility of further extending this chemistry to sp^2 C–H substitution; the acidity of the hydrogen at the 2 position of a 1,3-thiazole makes this system a logical choice for examination. Coupling of 1,3-thiazole **136** with a variety of iodoarenes such as **135** (Scheme 23) proceeded with high regioselectivity and little of the 2,5-disubstituted by-product [with 4-iodoanisole, no 5-(4-methoxyphenyl)-1,3-thiazole was produced and only 6% of the 2,5-bis(4-methoxyphenyl)-1,3-thiazole was produced]. Subsequent coupling of **137** with an appropriate



Scheme 23 Tandem transition metal-catalyzed preparation of 1,3-thiazoles.

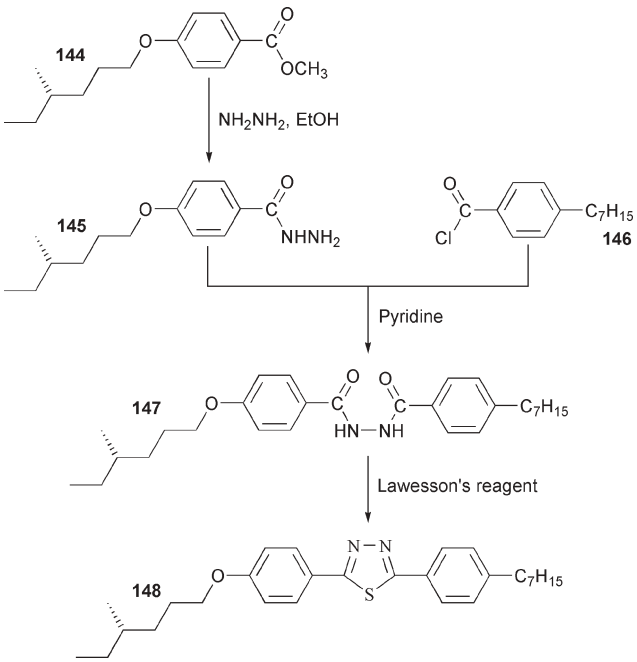


Scheme 24 Synthesis of 2,5-disubstituted 1,3- thiazoles using Suzuki coupling.

iodo- or bromoarene such as **138** using the method of Pivsa-Art *et al.*[118] gave the target **139**.

These materials were designed to test their tunable light emission and liquid crystal properties with different electron-releasing (methoxy and *N*,*N*-dimethyl) and electron-accepting (cyano) terminal substituents giving rise to light-emitting properties whereby the wavelength of light emitted and the intensity of emission were found to be strongly dependent on the identity of the donor–acceptor substituents. In addition, these materials were found to have substantial photoluminescence quantum yields (the example shown has a quantum yield of 0.49).

The Seed group has utilized traditional Suzuki coupling in the preparation of ferroelectric thiazole **143** (Scheme 24).[119] 2-Bromo-1,3-thiazole **140** was cross-coupled with **62** to give **141**. Subsequent regioselective deprotonation α to sulfur followed by carboxylation and acidification gave carboxylic acid **142** which was esterified with **50** to give the target **143**.



Scheme 25 Ring closure in the formation of 1,3,4-thiadiazoles.

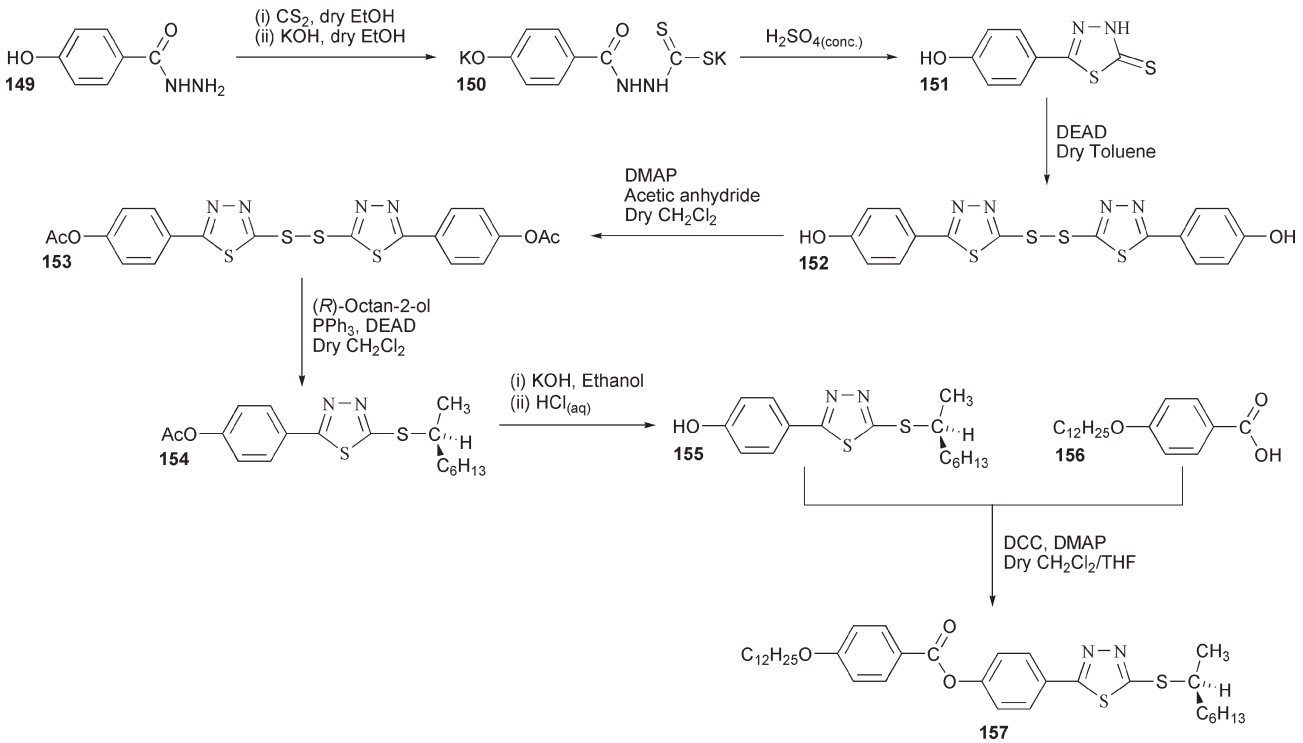
3. 1,3,4-Thiadiazoles

3.1 Ring-closure in the formation of 1,3,4-thiadiazoles

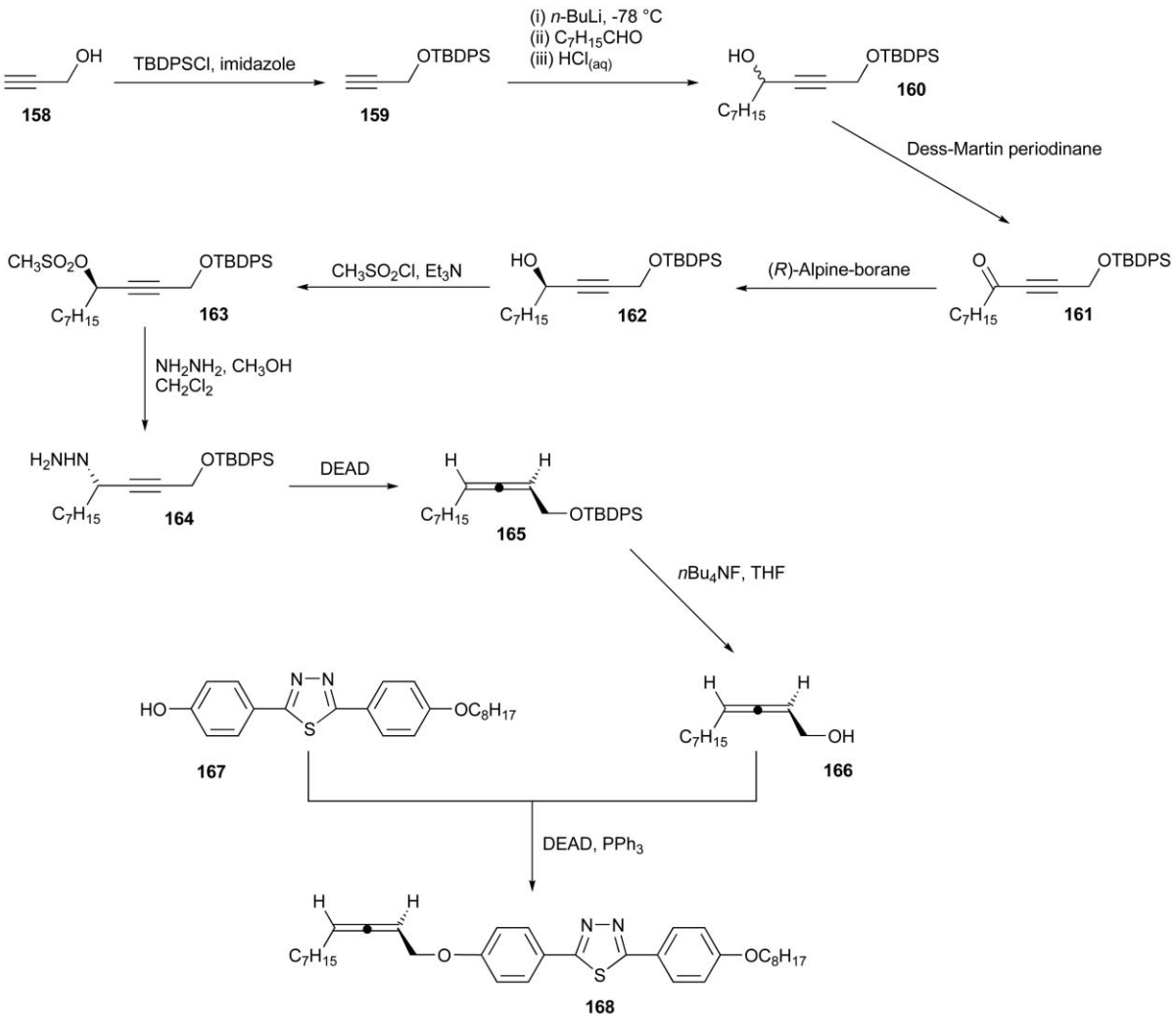
The majority of 1,3,4-thiadiazoles that feature in the LC literature are substituted in the 2 and 5 positions with alkyl and aryl units, and are constructed through sulfurization and cyclization of appropriate diacylhydrazines.[120–124] Early preparative methods used phosphorus pentasulfide[120,125,126] as the sulfurization agent but this was quickly replaced with the more reliable Lawesson's reagent. A typical preparative procedure is outlined in Scheme 25. Methyl ester **144** was treated with hydrazine hydrate in ethanol followed by reaction of the resulting hydrazide **145** with acid chloride **146** to give diacylhydrazine **147**. Cyclization of the diacylhydrazine to give thiadiazoles such as **148** is typically performed using Lawesson's reagent in toluene or THF. A solvent-free protocol has also been recently reported by Kiryanov *et al.*[42]

The 1,3,4-thiadiazole core imparts a large lateral dipole from S to the center of the N–N bond (3.0 D)[127] and the ring is extremely compact. This has stimulated interest in the system in second order nonlinear optical (NLO) applications where bulky donor–acceptor lateral substituents are undesirable.

In 1995, Loos-Wildenauer *et al.* reported the synthesis of a ferroelectric 1,3,4-thiadiazole with enhanced NLO activity and a chiral thioalkyl substituent at the 2-position of the thiadiazole ring.[128] Synthesis of the heterocycle (Scheme 26) began with the reaction of 4-hydroxybenzohydrazide **149** with carbon disulfide and potassium hydroxide to give the dipotassium salt of aroyldithiocarbazate **150**.[129] Acidification of freshly prepared **150** at 0 to −5 °C and concomitant cyclization gave 1,3,4-thiadiazolin-2-thione **151**. Maintenance of temperatures below 10 °C is important if significant disulfide formation (RNHCSSSSCNHR, a thiuram disulfide) is to be avoided.[129] The thione is the most stable tautomeric form and direct alkylation of the thione is not possible. Formation of the thiadiazole disulfide and protection of the phenolic OH group provides a useful etherification precursor. Conversion of protected disulfide **153** into alkylsulfanyl **154** was effected using diethylazodicarboxylate, triphenylphosphine, and (*R*)-octan-2-ol.[130]



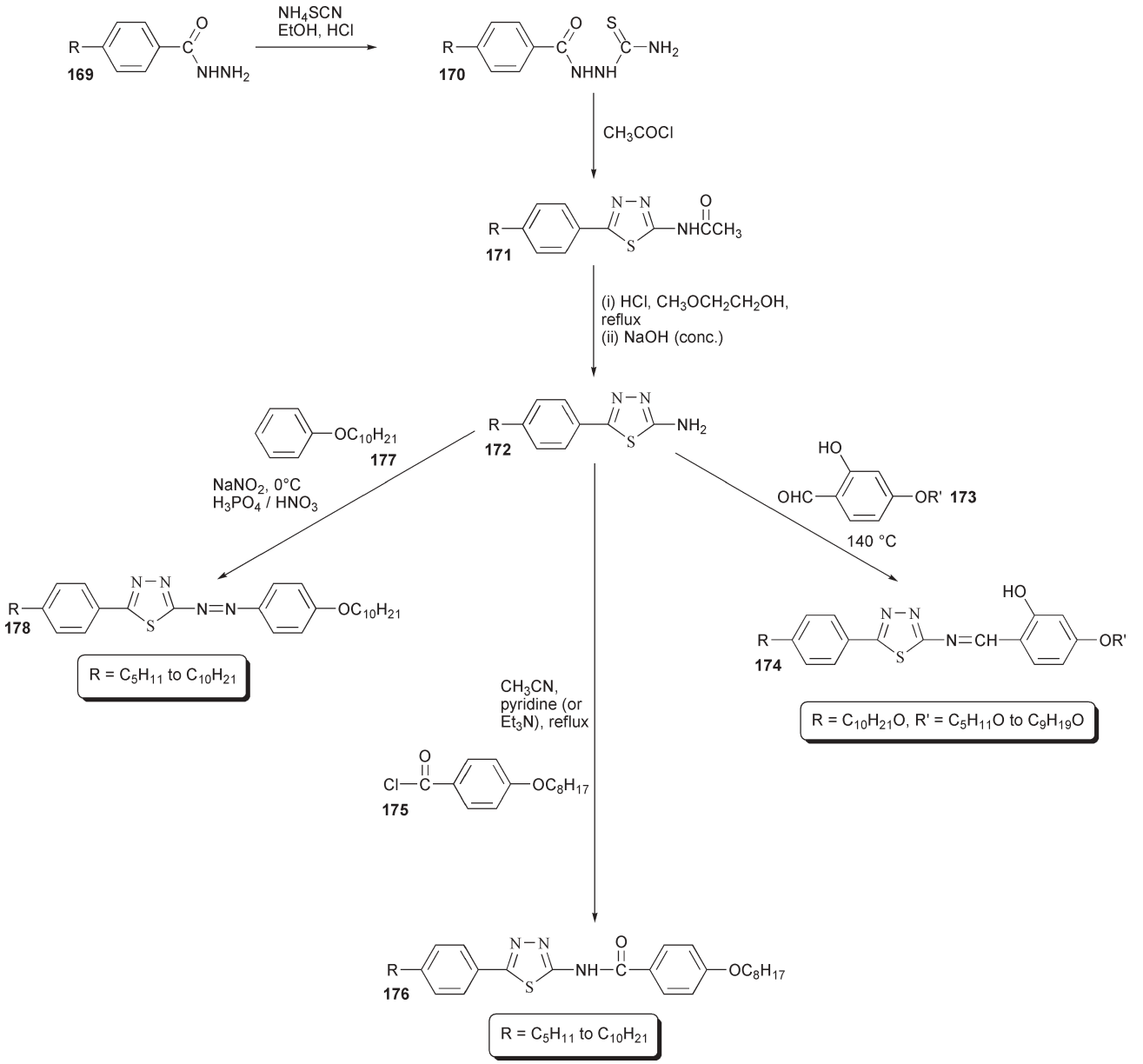
Scheme 26 Synthesis of a 2-alkysulfanyl-1,3,4-thiadiazole for NLO applications.



Scheme 27 Tschierske's synthesis of axially chiral allenes.

The vast majority of ferroelectric LCs are chiral as a result of the incorporation of a stereocenter. Tschierske *et al.* have synthesized a number of 1,3,4-thiadiazole mesogens that are axially chiral by virtue of the incorporation of a chiral allene group.[122,131,132] A representative synthesis of such a material is given in Scheme 27. Propargylic alcohol **158** was protected as its *t*-butyldiphenylsilyl (TBDPS) ether before being deprotonated, and the resulting lithium salt reacted with octanal to give racemic alcohol **160**. Dess–Martin periodinane[133] was used to oxidize the alcohol to afford ketone **161** before the ketone was subjected to asymmetric reduction using (*R*)-Alpine-Borane®.[134] Alcohol **162** was then converted into its mesylate followed by substitution by hydrazine and oxidation with DEAD. The oxidation is followed by a 1,5-sigmatropic shift of hydrogen and loss of nitrogen gas. This reaction is stereospecific and the enantiomeric excess of the product allene is therefore determined by the level of enantioselectivity in the asymmetric reduction of **161** to give **162**. Finally, the TBDPS group was removed using *tert*-butylammonium fluoride (TBAF) before the resulting alcohol was etherified under Mitsunobu conditions to give **168**.

Liquid crystalline thiadiazoles that contain a linking group between the thiadiazole ring and another aryl group constitute a relatively new class of mesogen. A significant portion of literature in this area has come from Parra *et al.*, where Parra's syntheses are centered around 2-amino-1,3,4-thiadiazole building blocks. The amine moiety on the thiadiazole has been transformed into amide,[135,136] imine,[137–143] and azo[144,145] linking groups. A representative synthetic pathway is given in Scheme 28. Hydrazide **169** was reacted with ammonium thiocyanate in a mixture of concentrated hydrochloric acid and ethanol to give thiosemicarbazide **170**. The thiosemicarbazide then underwent cyclization and concomitant dehydration upon reaction with acetyl chloride (in a separate publication,[145] it was observed that pyridine-based thiosemicarbazides did not undergo cyclization with acetyl chloride and were instead cyclized using concentrated sulfuric acid at 0 °C). The resulting thiadiazole **171** was subjected to acidic hydrolysis to give the key aminothiadiazole **172**. Heating **172** with **173** at 140 °C gave imines **174**. The imines shown display the nematic phase with a broad underlying smectic C phase. Similar chiral materials were constructed to afford ferroelectric materials.[143]



Scheme 28 Synthesis of 1,3,4-thiadiazoles with nitrogen-containing linking groups.

Electrooptic switching was attempted to evaluate their potential for device use, but upon application of an external electric field the molecules were observed to decompose (attributed to the instability of the Schiff base functional group).

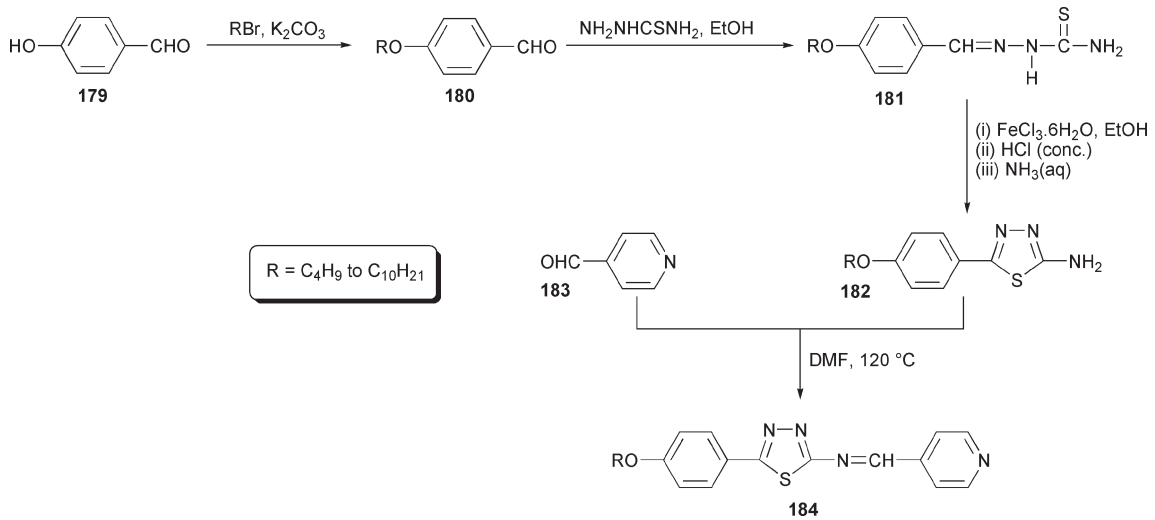
Reaction of **172** with acid chloride **175** gave amides **176**. Introduction of the amide link gave rise to high melting points (all melting points were greater than 195 °C) due to strong intermolecular hydrogen bonding.

Azo compounds **178** were prepared by diazotizing **172** in a mixture of 85% phosphoric acid and nitric acid, followed by addition of decyloxybenzene **177**. The azo compounds again possessed the smectic C phase although this time the linkage is unstable and is subject to photochemical isomerization. Parra's work has demonstrated the power of the thiadiazole ring in supporting tilted phase behavior but all of the linking groups described suffer from drawbacks that make their practical use unlikely.

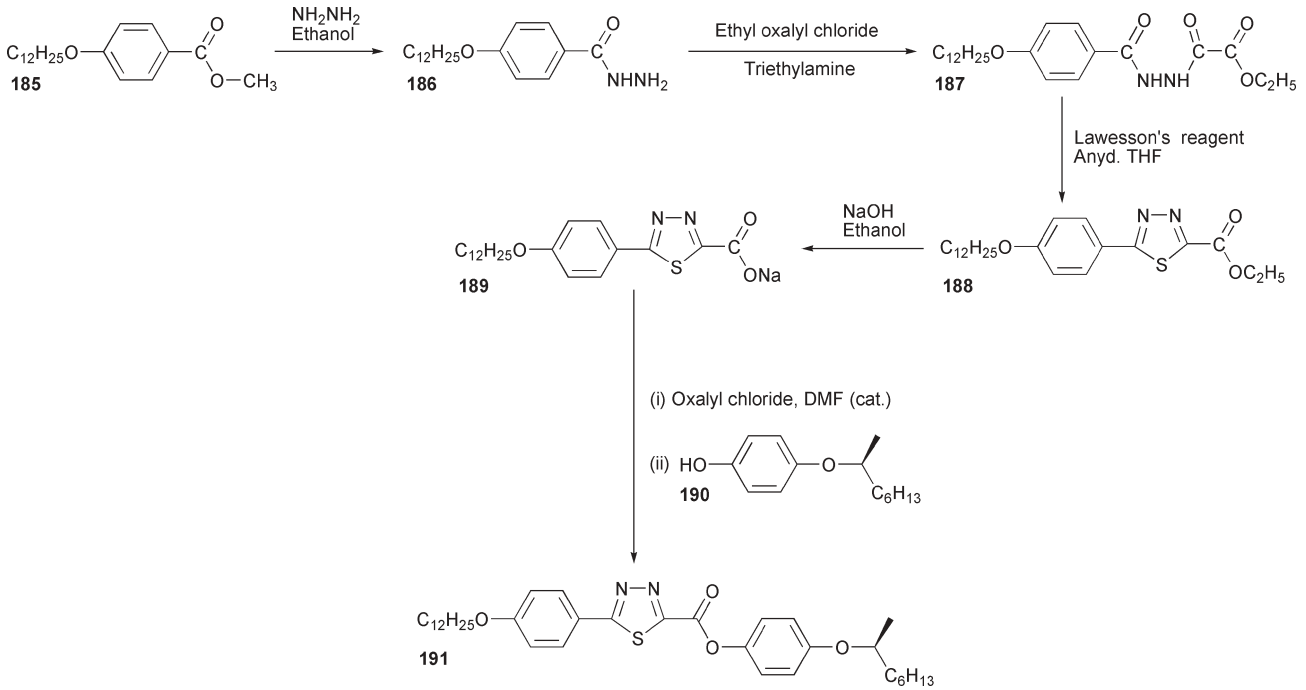
Lai *et al.* have used similar chemistry in the investigation of complexes of similar azo compounds (with a terminal thiadiazole ring) with *m*-alkoxybenzoic acids.[146]

Xu *et al.* have utilized a different ring closure approach[147] whereby an appropriate thiosemicarbazone was chosen as the key precursor (Scheme 29). Aldehyde **180** is treated with thiosemicarbazide in ethanol to give thiosemicarbazone **181**. Cyclization was then effected using iron(III) chloride and hydrochloric acid before neutralizing the obtained hydrochloride salt. The resulting 2-amino-1,3,4,-thiadiazole **182** was reacted with aldehyde **183** to give the Schiff base target **184**.

In 2004 the Seed group initiated a program of study that centered on the synthesis of thiadiazole carboxylate esters. These linking groups have been demonstrated as excellent



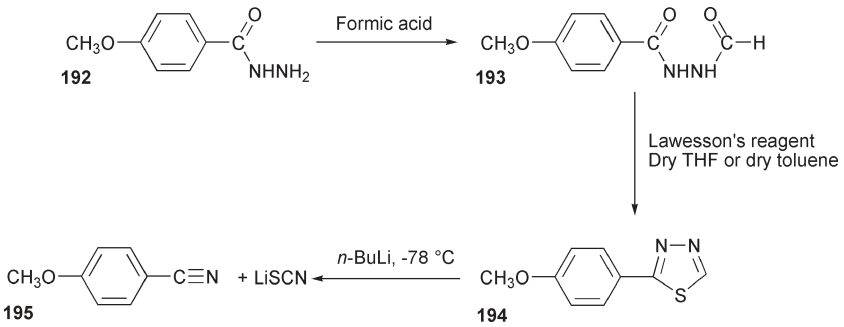
Scheme 29 Synthesis of 1,3,4-thiadiazoles *via* ring-closure of thiosemicarbazones.



Scheme 30 Synthesis of ester linked ferroelectric 1,3,4-thiadiazole **162**.

supporters of tilted phase morphology in phenyl based systems. In addition, there are no problems with photochemical instability or high melting points and this makes them ideal candidates for ferroelectric applications. However, synthesis of these units is far from trivial and there is a notable absence of such synthetic methodology in the general organic literature. Seed's group used a novel ring-closure methodology to achieve the desired targets as shown in Scheme 30.[148] Hydrazide **186** was reacted with ethyl oxalyl chloride to give tricarbonyl **187**. It was postulated that thionation (and subsequent cyclization) of tricarbonyl **187** would occur at the amide-like oxygens based on a prior precedent whereby thionation of an α-carboalkoxy amide occurred exclusively at the amide carbonyl.[149] Ester **188** was then subjected to basic hydrolysis and isolated as the sodium salt **189** since the free carboxylic acid was found to spontaneously decarboxylate (as expected).[150] Esterification of the sodium salt with **190** gave ferroelectric ester **191**. The esterification procedure has since been optimized and it has been found that yields of product are highly dependent upon the temperature at which the esterification is carried out (optimum yields are obtained at a reaction temperature of −4 to −8 °C). The results of these studies will be disseminated shortly.[151]

Attempts were made to synthesize the lithium salts of thiadiazole carboxylic acids from 2-substituted-1,3,4-thiadizoles **194** (Scheme 31). Given the great acidity of the α-hydrogen, we expected to remove this proton with *n*-butyllithium followed by carboxylation. However, once



Scheme 31 Ring-opening of 2-lithio-1,3,4-thiadiazoles.

deprotonated these anions undergo spontaneous ring opening to liberate nitrile by-products **195** in near quantitative yields.

Outlook

Over the past 10 years there has been considerable growth in new synthetic methodology that has allowed for the construction of previously inaccessible structures. Of particular note are the fluorothiophenes, thiazoles in general (since this area is relatively unexploited), and 1,3,4-thiadiazole-2-carboxylates that show significant potential for use in FLC devices. The design of heterocyclic materials for V-shaped electrooptic switching[152] is a particularly exciting prospect.

Numerous achiral mesogens (the so-called "banana" mesogens) have been observed to spontaneously form chiral mesophases.[153] These bent structures are often based on 1,3-disubstituted benzene cores and a logical extension of this would be to evaluate heterocyclic modifications. Given the similar angular nature of 2,4-disubstituted thiophenes and 2,4-disubstituted-1,3-thiazoles, these would be ideal units from which to create a banana-shaped structure containing a heavy atom. Once again, the use of resonance X-ray scattering would be invaluable as a tool to probe the complex structures exhibited by these mesogens.

Preliminary studies[154] on a single fluorothiophene (**51**) have revealed that this material does not exhibit layer contraction upon cooling from the SmA to the SmC* phase (possibly due to conformational changes about the heterocyclic core). If these studies prove to be correct these materials have the potential to open up new areas of ferroelectric research that might ultimately lead to the realization of commercial ferroelectric displays without a need for AC field stabilization.

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