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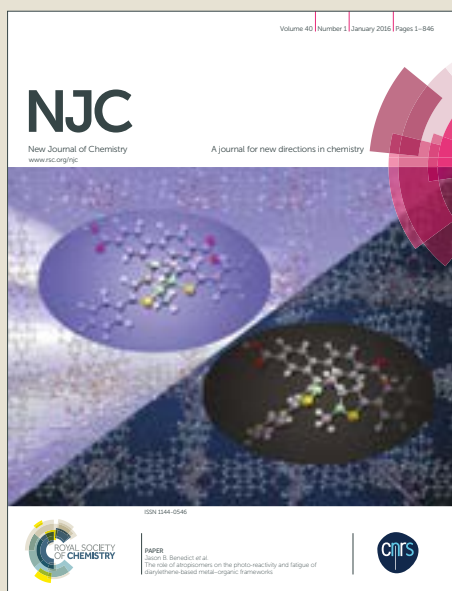
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LETTER

Chiral Ionic Liquid Crystals based on Thiourea

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Chiral ionic liquid crystals based on the *S*-methyl-*N,N'*- α -methylarylthiuronium cation have been prepared and studied. Most salts, interestingly including an example with the bistriflimide anion, display a SmA* phase with anion-dependent transition temperatures. The salts, which are able to distinguish enantiomers of chiral anions *via* formation of diastereomeric adducts, may find application as chiral reaction media.

Substituted thioureas function as non-covalent acid catalysts *via* formation of hydrogen bonds¹ and have been employed successfully as organocatalysts and co-catalysts in reactions such as asymmetric Michael additions,² Baylis-Hillman reactions³ and others.⁴ Starting from the catalyst developed by Schreiner,¹ which featured electron-withdrawing 3,5-trifluoromethylphenyl rings either side of the thiourea moiety, many variations have been developed including unsymmetric and asymmetric derivatives, thereby forming chiral and bifunctional acid-base catalysts. On the other hand, the ability to discriminate between enantiomeric anions is important in the fields of abiotic anion receptors⁵ and asymmetric ion-pairing catalysis.⁶ *N*- α -Methyl-aryl thioureas have been investigated for selective anion binding,⁷ and related chiral ionic liquids (ILs) were synthesised recently⁸ and shown to discriminate different enantiomers of chiral carboxylic acids.^{8a} Furthermore, various chiral ILs have shown chiral induction in reactions,⁹ although with one exception¹⁰ the ee was only moderate in most cases.

Liquid crystal (LC) mesophases are characterised by anisotropic, long-range order and effects on the regio- and stereo-selectivity of reactions have been investigated.¹¹ Anti-Arrhenius behaviour was reported as well as detailed studies of Diels-Alder reactions and, while LC solvents had a clear

effect,¹² a major drawback of neutral LCs is their poor solvation ability. Given the exceptional solvation ability of ILs, ionic liquid crystals (ILCs),¹³ become attractive targets for study.

Reactivity in ILC solvents has been investigated with two clear demonstrations of affecting product distribution in Diels-Alder reactions – one using the well-known methyl acrylate/cyclopentadiene system in SmA and columnar solvents,¹⁵ the other concerning inter- versus intra-molecular reactivity with hexadienyl acrylate in highly ordered rectangular phases.¹⁶ However, even greater reward would come from the ability of a LC solvent to effect chiral induction because of the interplay between chiral centres and the steric constraints of the LC order. This may well be independent of the existence of a specifically chiral mesophase where the length scales associated with the chirality are likely too long to affect the reaction outcome. Therefore, we were keen to identify candidate chiral ILs that could be elaborated into a liquid-crystalline molecule. The chiral thiuronium-based ionic liquids developed by Foreiter and Seddon^{8a} were identified as a target structures.

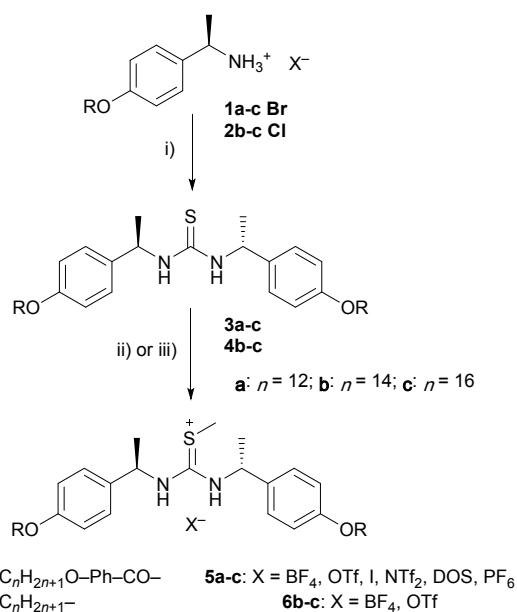
Schemes 1 & 2 show the thiuronium ILCs identified for study. Compounds **5** and **6** (Scheme 1), were chosen because of the ready commercial availability of both enantiomers of 4-methoxy- α -methylbenzylamine. The (*R*)-enantiomer was chosen for study and *S*-methylation minimised disruption to the overall anisotropy of the cation by retaining a rod-like shape. LC properties were induced *via* the R group as an alkyl chain (**6**) or 4-alkoxybenzoyl group for the more anisotropic **5**.

Key to preparation of **5** and **6** (Scheme 1) is reaction of the α -methylbenzylamine with thiocarbonyldiimidazole as a source of a C=S unit. For **5**, BF₄⁻ and OTf⁻ salts were made by direct methylation using [Me₃O][BF₄] or MeOTf, respectively, while dodecyl sulfate (DOS), PF₆⁻ and bistriflimide (Tf₂N⁻) salts were prepared by metathesis from the iodide, in turn obtained from a methylation using MeI. Compounds **6** were prepared by MeI methylation followed by treatment with basic Amberlyst resin and neutralisation with the corresponding acid.

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Biphenyl salts **13** were prepared to vary the cation structure. Chirality is introduced *via* a chiral ^tbutylsulfonamide

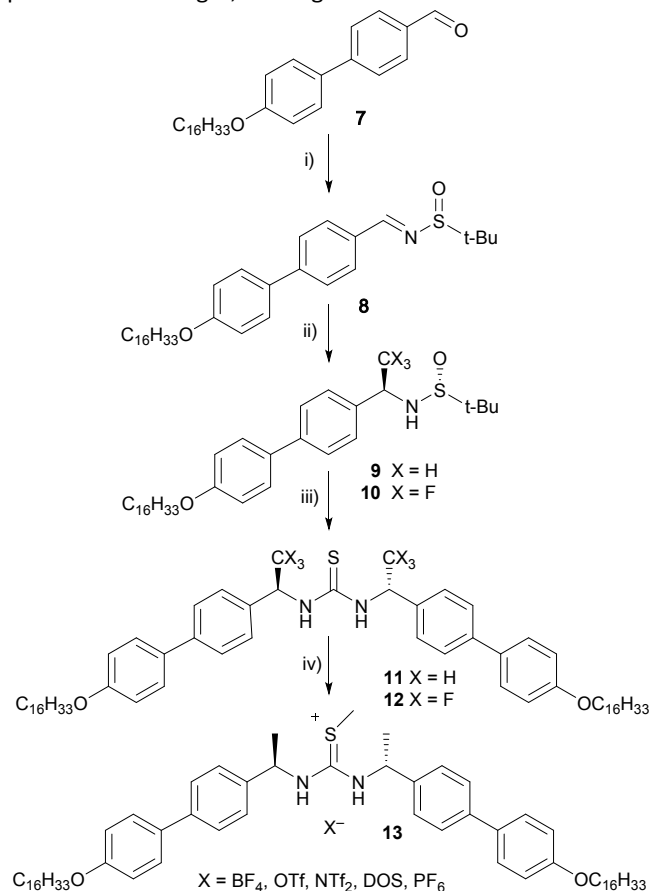


Scheme 1. Synthesis of chiral thiuronium ILCs. Reaction conditions: i) NEt₃, thio-CDI, DMF, rt, overnight, ii) [Me₃O][BF₄], MeOTf or Mel, DMF, rt overnight, for NTf₂, PF₆, DOS: (a) LiNTf₂, NH₄PF₆ or SDS, MeOH, 60 °C, 2 h, (b) H₂O., iii) 1. Mel, DMF, rt overnight, 2. Amberlyst A26, HBF₄ or HOTf.

auxiliary (Scheme 2) allowing both methyl and trifluoromethyl groups to be installed. Use of CF₃ groups allows investigation of the effect a highly electron-withdrawing group on the N-H acidity of the thiuronium group, which may affect the catalytic activity of the compounds. The biphenyl aldehyde **7** was reacted with (*R*)-tert-butanesulfinamide to form a sulfinylimide (**8**).¹⁷ A methyl group was then introduced using MeMgBr,¹⁸ while a trifluoromethyl group used trifluoromethyl trimethylsilane;¹⁷ both reactions give the desired diastereomer in large diastereomeric excess (>90% by ¹H NMR spectroscopy). The modified sulfinylimides were then hydrolysed to the amine and reacted with thiocarbonyldiimidazole. The final compounds were prepared *via* methylation and anion exchange as above, although it was more convenient to obtain the BF₄ salt by metathesis of dodecylsulfate. Methylation of **12** however proved difficult, as the electron-withdrawing CF₃ groups made the central sulfur atom too electron poor. Forcing conditions (microwave under pressure) were investigated, but while some product formed, degradation increased and it was not possible to isolate these derivatives in useful yields.

While neither of the triflates was mesomorphic, BF₄ salts of **6b** and **6c** showed a SmA* phase over a short range, likely reflecting the small size of the mesogenic alkoxyphenyl unit in relation to the bulk of the *S*-methylthiuronium core, and so attention turned to the more anisotropic ester derivatives **5**. All of the esters **5** were liquid crystalline and showed SmA* phases; the typical focal conic texture is shown in Figure 1. The thermal data are collected in Table 1.

A typical DSC trace and SAXS diffraction pattern, displaying the sharp (001) reflection peak are shown in Figure S1. The data for **5a** BF₄ to **5c** BF₄ show little dependence of the melting point on chain length, although there is a stabilisation of the



Scheme 2. Synthetic route for biphenyl-based thiuronium ILCs. Reaction conditions: i) Ti(OEt)₄, H₂NS(=O)^tBu, THF, N₂, rt, overnight, ii) MeMgBr (X = H) or TMS-CF₃, TBAT, THF, N₂, -15 °C, warming to rt overnight, iii) (a) HCl, MeOH/dioxane, rt, 2 h, then NaOH, DCM, (b) thio-CDI, DCM, rt overnight, (iv) [Me₃O][BF₄], MeOTf or Mel, DMF/DCM, rt overnight, for Tf₂N, PF₆, DOS: (a) LiNTf₂, NH₄PF₆ or SDS, MeOH, 60 °C, 2 h, (b) H₂O.

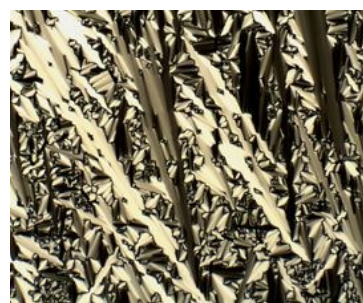


Figure 1 SmA* texture of **5c** BF₄ on cooling at 148 °C (100x magnification in a planar cell)

SmA* phase of ca 28 °C from C12 to C16, so that **5a** BF₄ has a SmA* range of 15.9 °C, while **5c** BF₄ has a range of 48.6 °C (Figure S1).

Considering the anions, the greatest phase stabilities are seen for BF₄ and PF₆ salts, consistent with their small size, although the much greater crystal phase stability for the PF₆

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salt is noteworthy. Consistent with many other observations in the literature by ourselves¹⁹ and others,²⁰ use of DOS destabilises both the crystal and the SmA* phase on account of its size (Figure S1).

Table 1. Thermal data for all thiuronium compounds

Compound	Transition	T / °C	ΔH / kJ mol ⁻¹
5a BF₄	Cr – SmA*	115.0	10.1
	SmA* – Iso	130.9	1.1
5b BF₄	Cr – SmA*	116.0	22.8
	SmA* – Iso	150.6	1.2
5c BF₄	Cr – SmA*	110.0	18.3
	SmA* – Iso	158.5	1.2
5c OTf	Cr – Iso	117.6	11.3
	(SmA* – Iso)	(98.0)	(0.67)
5c PF₆	Cr – Iso	146.8	39.3
	(SmA* – Iso)	(146.8) [†]	(40.5)
5c DOS	Cr – SmA*	50.9	27.9
	SmA* – Iso	93.2	3.4
5c Tf₂N	Cr – SmA*	39.4	20.8
	SmA* – Iso	103.4	2.4
6b BF₄	Cr – SmA*	85.6	52.5
	SmA* – Iso	98.8	1.8
6c BF₄	Cr-Iso	100.8	68.5
	(SmA* – Iso)	87.1	1.0
13 BF₄	Cr – SmA*	128.3	19.0
	SmA* – Iso	159.3	0.6
13 OTf	Cr – SmA*	117.4	19.4
	SmA* – Iso	124.7	1.3
13 PF₆	Cr – SmA*	96.5	21.6
	SmA* – Iso	176.4	1.0
13 DOS	Cr – Iso	124.5	47.4
13 Tf₂N	Cr – Iso	133.6	70.3

[†]Temperatures are taken from DSC and represent onset temperatures for a large melting peak and a much smaller clearing peak, hence the apparent equivalence in temperature.

There is a similar observation for the bistriflimide anion and the slightly smaller triflate. Bistriflimide has often been held to suppress liquid crystal phase formation in ionic liquids, but it is likely that this applies mainly to simple imidazolium salts. Thus, with a melting point of *ca* 40 °C and a SmA* range of some 60 °C, **5c Tf₂N** has a useful range as a possible solvent.

Of the biphenyl compounds **13**, the BF₄, OTf and PF₆ salts were mesomorphic showing enantiotropic SmA* phases, with

the most stable found for the BF₄ and PF₆ salts. DOS and Tf₂N salts melted directly to the isotropic liquid with no monotropic mesophase observed.

Table 2. Data from small-angle X-ray scattering

Compound	d(001) / Å	T / °C	T/(T _{SmA*–Iso})/ °C
5c BF₄	47.7	134.3	0.85
5c PF₆	57.3	107.8	0.73
5c OTf	57.7	80.5	0.82
5c DOS	42.8	72.1	0.77
5c Tf₂N	58.1	71.4	0.69
13 BF₄	43.0	143.8	0.9
13 OTf	46.2	121.1	0.97
13 PF₆	47.4	136.5	0.77

X-Ray diffraction data showed a sharp (001) reflection at low angle (Figure S1) corresponding to the lamellar periodicity of the SmA* phase and a broader reflection at *ca* 20° 2θ corresponding to the lateral periodicity of the flexible chains; the data are collected in Table 2.

From the single crystal structure of 1,3-bis(1-phenylethyl)-thiourea,²¹ the calculated fully extended length of a **5c** cation is *ca* 59 Å, and that of **13** is 61 Å. **5c PF₆**, **5c OTf** and **5c Tf₂N** show layer spacings equating to the length of the cation, whereas **5c DOS** and **5c BF₄** show a reduced spacing, indicating a combination of chain folding and/or interdigitation. There is rather little temperature dependence in the spacing, so that in, for example, **5c BF₄** for which variable-temperature data were recorded, decreasing the reduced temperature from 0.99 to 0.85 to 0.71 increased the layer spacing by 6% and 14% from 45.0 to 47.7 to 51.3 Å, respectively. That the reduced spacing is found with the largest (DOS) and smallest (BF₄) anions used is unexpected and does not suggest a straightforward explanation. For the biphenyl compounds **13**, the observed layer spacing is fairly consistent and independent of the anion with some degree of chain folding/interdigitation.

All thiourea and thiuronium compounds show broad NMR signals for the phenyl rings adjacent to thiourea, as well as for N-H hydrogens. The poor resolution of the phenyl rings arises from restricted bond rotation around the thiuronium moiety due to hydrogen bonding, as well as different degrees of interaction with the solvent (Figure S2.1). However, use of a carboxylate anion forms a strongly hydrogen-bonded complex and the signals become resolved (*e.g.* Figure S2.2), a phenomenon observed previously.^{7,8}

The ability to form strong H-bonds led to thioureas and thiuronium salts being employed for chiral anion recognition, of carboxylates *via* formation of diastereomeric adducts. Using the enantiopure cation the method is accurate enough to determine *ee* by NMR integration,^{8a} which is very useful with respect to batches of drugs containing carboxylic acids, *e.g.*

naproxen or ibuprofen. Chiral anion recognition also suggests application as artificial receptors and as a proof of concept for

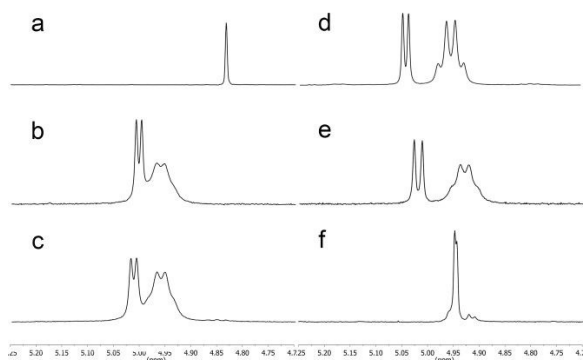


Figure 2. a) Part of the ^1H -NMR spectrum of racemic tetrabutylammonium mandelate showing a) the methine proton, b) the same spectrum after addition of 1 equivalent of 5c BF_4 , c) 5c DOS , d) 5c NTf_2 , e) 13 BF_4 , f) after 1 mol. eq. of 12 .

the usefulness of these compounds as chiral catalysts.

NMR binding studies of the cations **5** and **13** were undertaken to demonstrate that they can distinguish enantiomers. Mandelate (as its NBu_4^+ salt) was used as it gives a simple NMR spectrum with a singlet for its methine hydrogen. Figure 2 shows portions of the NMR spectra after addition of equimolar amounts of racemic tetrabutylammonium mandelate. The mandelate methine peak is split into two signals of equal intensity and shifts downfield (small anion dependence) due to the formation of diastereomeric adducts with **5c** (as BF_4 , Tf_2N and DOS salts) and **13 BF**₄. The splitting in **12** is barely visible, due to overlap of the signals. All ILCs tested demonstrated strong hydrogen bonding to carboxylates, pointing towards their applicability as chiral co-catalysts.

We have, therefore, demonstrated a new, versatile scaffold for chiral ILCs based on the cationic thiouronium hydrogen bond donor, which allows for facile attachment of different mesogens. Most synthesised compounds displayed SmA^* phases. In the case of the benzoate ester compounds (**5**), melting points and mesophase ranges can be tuned by the choice of anion, and to a lesser degree by the length of the alkyl chains. The biphenyl motif was not as versatile, with some non-mesomorphic salts, but others giving enantiotropic ILCs. As a proof of concept for catalytic applications, chiral recognition and sufficient strength of hydrogen bonding interaction with a chiral model substrate was demonstrated *via* the formation of diastereomeric adducts. Due to the low melting point and the weakly-coordinating nature of the anion, which frees up the area around the catalytic thiourea, compound **5c Tf**₂**N** in particular is a promising candidate for use as a co-catalytic, anisotropic reaction medium and investigations into its use are ongoing. Additionally, while the current study focuses on symmetrically substituted thioureas, unsymmetric compounds can be easily synthesised by just adding one more step to the reaction sequence. This increases

the freedom in the design of optimum catalysts, and has the potential to lead to interesting LC phase behaviour.

Conflicts of interest

There are no conflicts to declare.

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