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Indium(III)-catalysed aryl sulfonylation reactions

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Abstract—A rapid, high yielding and regioselective process has been developed for the synthesis of biaryl sulfones via sulfonylation reactions catalysed by indium(III) chloride.

1. Introduction

Biaryl sulfones are a common feature in pharmaceutical products.[1a] We were interested in structures of general formula **1** as versatile intermediates in the preparation of a range of pharmaceutically active agents.[1b]

It was envisaged that the 4-fluoro group in **1** could be replaced by a variety of nucleophiles[2] using array style chemistry to provide a diverse range of target structures for screening (Scheme 1). Thus, a robust high yielding route to intermediates **1** was sought.

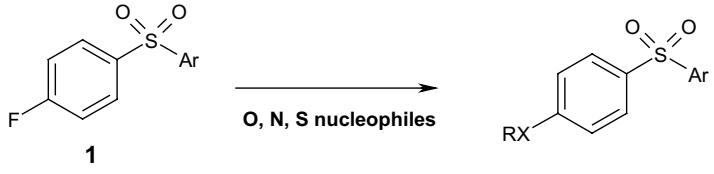
Our attention focussed on aryl sulfonylation methodologies (Scheme 2). Although the aryl sulfonylation of aromatic systems is known in the literature,[3–5] it is less well documented than the corresponding Friedel–Crafts acylation reaction.[6]

4-Fluorobenzenesulfonyl chloride has already been used in this type of reaction but the yields obtained were modest when $Bi(OTf)_3$[4] (52%) or $AlCl_3$[7] (43%) was used as the catalyst and bromobenzene and anisole as substrates, respectively. For other sulfonyl chlorides, indium(III) chloride and indium(III) triflate have been used[3] and from the data reported for the latter reagent we were encouraged that high yields of product could be achieved from this type of reaction using 4-fluorobenzenesulfonyl chloride.

2. Results

After piloting a number of Lewis acid and solvent combinations, we identified indium(III) chloride/triflic acid in TFA as the preferred reagent. Using this system, we investigated the 4-fluorophenylsulfonylation of a range of activated and deactivated substrates (Table 1).

Typically[8] the reagents were combined and heated to the temperature indicated until the reaction was complete as indicated by HPLC.



Scheme 1. Nucleophilic displacement of fluoride by RX^- (X = O, N, S).

Keywords: Sulfonylation; Friedel–Crafts; Indium(III) chloride.
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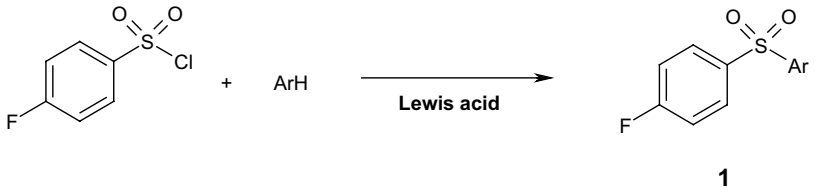
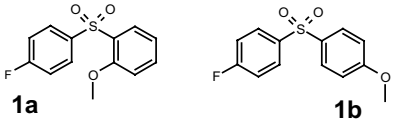
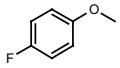
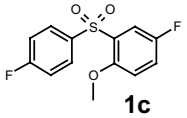
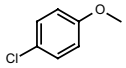
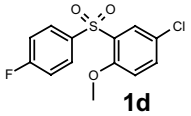
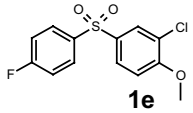
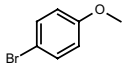
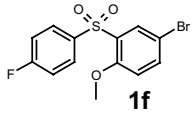
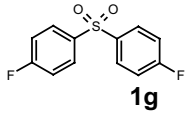
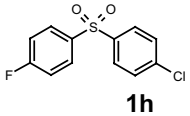
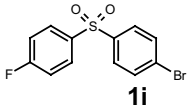
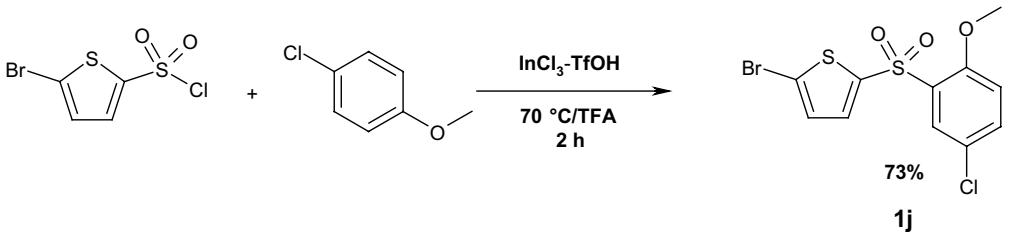


Scheme 2. Lewis acid catalysed sulfonylation of aryl substrates.

Table 1

Entry	ArH	*T* (°C)	Time	Yield (%)	Product[8,9]
1		60	30 min	75	 **1a** : **1b** (1 : 1)
2		70	1 h	88	 **1c**
3		70	1.5 h	100	 **1d**
4		70	2 h	76	 **1e**
5		70	12 h	56	 **1f**
6		70	2 h	87	 **1g**
7		70	2 h	80	 **1h**
8		70	2 h	85	 **1i**

Using our conditions, 4-fluorobenzenesulfonyl chloride was reacted with anisole producing a 1:1 mixture of isomers in 75% yield, thus representing an improvement on the literature process.[7] It was thought that the non-selective nature of this reaction was due to the high reactivity of anisole allowing equal amounts of sulf-



Scheme 3. Indium-catalysed sulfonylation with a heterocyclic substrate.

onylation at both the *para* (less hindered) and *ortho* (more hindered) positions. In order to modulate the reactivity of anisole, the effect of halogen substitution on the anisole ring was investigated. It was found that substrates shown in entries 2, 3, 4 and 5 undergo highly regioselective reactions giving a single product and showing a significant improvement in yield compared to the results obtained when $AlCl_3$[10] is the reaction catalyst.

Following these results, we decided to investigate the sulfonylation of less reactive aryl halides (entries 6, 7, 8). Again it was found that a high yielding regioselective process took place giving a more favourable outcome than when $AlCl_3$[11] or $Bi(OTf)_3$[4] are used.

We have extended the scope of this process with the use of heterocyclic sulfonyl chlorides. For example, under our conditions, 5-bromothiophene-2-sulfonyl chloride reacts cleanly and in high yield with 4-chloroanisole to give the desired product **1j** (Scheme 3).

Nucleophilic aromatic substitution reactions of the 4-fluoro group in products **1a**–**1i** could be carried out using standard literature methodology. Furthermore the presence of the bromine atom in products **1f**, **1i** and **1j** allows further elaboration of the structure, for example, by Suzuki couplings or Heck reactions.

3. Conclusions

The use of the indium(III) chloride/triflic acid system for aryl sulfonylation reactions has been studied. Under the conditions we have developed, the reactions were rapid, high yielding and regioselective showing a significant improvement compared to the results obtained in the literature. The use of this methodology in the synthesis of some CNS active drug candidates will be reported in the near future.

Acknowledgements

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References and notes

1. (a) A search of the Derwent World Drug Index gave 147 hits for structures containing a biaryl sulfone moiety; (b) GlaxoSmithKline. Unpublished work.
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8. Typical reaction procedure: the arene substrate (2 mmol), $InCl_3$ (0.2–0.4 mmol), sulfonyl chloride (3 mmol) were all dissolved in TFA (4 mL) and triflic acid (3 mmol) was added at room temperature; the mixture was then heated up to the indicated temperature; when the reaction was complete, it was quenched with water–ice, basified up to pH = 10 and extracted with dichloromethane; chromatography afforded the desired compounds.
9. NMR and mass spectra of all compounds were fully consistent with the structures shown; for all products the substitution pattern was confirmed by NOE experiments.
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