Catalytic Arylation of Sulfamoyl Chlorides: A Practical Synthesis of Sulfonamides

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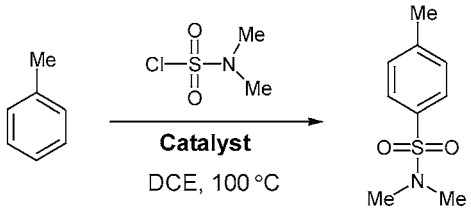
Abstract: Commercially available indium(III) triflate is shown to be an efficient catalyst for the sulfamoylation of aromatics.

Key words: catalysis, Lewis acids, indium, arylations, sulfonamides

Aromatic sulfonamides are of significant interest to the synthetic chemist due to their bioactive nature, most notably as pharmaceuticals. Over 30 drugs containing this functionality are in clinical use, including, antibacterials, diuretics, anticonvulsants, hypoglycemics and HIV protease inhibitors.[1] The most popular route to aromatic sulfonamides involves the chlorosulfonation of an arene, to give the sulfonyl chloride, and subsequent reaction with an amine.[2] However this approach is marred either by the need to employ a large excess of chlorosulfonic acid which leads to acidic waste or the undesirable formation of the diaryl sulfone.[3] The reaction of trialkylarylstannanes and sulfonyl isocyanates has also been employed.[4] Electrophilic substitution reactions introducing the SO_2NR_2 moiety directly have less precedent. Exceptions include the aluminium chloride promoted thia-Fries rearrangement[5] and sulfamoylation.[6] The use of stoichiometric Lewis acids or tin reagents is undesirable, particularly on an industrial scale, due to the serious waste problems. Thus, the development of a catalytic process would offer a cleaner alternative to existing methodologies for reactive aromatics. In this communication a successful strategy for the synthesis of aryl sulfonamides using an indium catalysed sulfamoylation process is presented.

At the outset of the study we examined the sulfamoylation of toluene with *N*,*N*-dimethylsulfamoyl chloride in the presence of 20 mol% of selected catalysts (Scheme 1).



Scheme 1

As can be seen from Table 1, for the different catalysts tested it was interesting to note that only the two indium complexes were able to turnover to afford product. It was clear that the reaction was not being promoted to any great extent by triflic acid (entry 10) and the cation present plays a crucial role in determining catalytic activity (entries 3–7). The use of AgOTf (entries 8 and 9) results in a TfO^-/Cl^- exchange to prepare the activated sulfamoyl triflate in situ which reacts with the aromatic compound releasing triflic acid.[7] To obtain a modest yield the reaction is stoichiometric with respect to AgOTf. Previous work by Dubac[8] [for $Bi(OTf)_3$] and ourselves [for $In(OTf)_3$] have established that TfO^-/Cl^- exchange occurs readily at bismuth and indium centres enabling recycling of triflic

Table 1 Catalyst Evaluation in Sulfamoylation Process[a]

Entry	Catalyst	Yield (%)
1	$AlCl_3$	20
2	$InCl_3$	43
3	$In(OTf)_3$	86
4	$La(OTf)_3$	0
5	$Sc(OTf)_3$	19
6	$Yb(OTf)_3$	0
7	$Bi(OTf)_3$	19
8	AgOTf	15
9	AgOTf (100 mol%)	56
10	TfOH	9

[a] **Procedure**: A stirring mixture of toluene (5 mmol) dimethylsulfamoyl chloride (1 mmol) and catalyst (20 mol%) in DCE (5 mL) was heated to 100 °C for 24 h. The reaction mixture was then partitioned between DCM and 1 M HCl. The aq layer was washed with DCM three times and the combined organics were washed with brine, dried over anhyd $MgSO_4$ and concentrated to afford crude sulfonamide product which was purified by flash chromatography using petroleum ether:ethyl acetate (4:1) as eluent to afford dimethyl-*p*-toluenesulfonamide as a white crystalline solid, mp 79–81 °C (lit.: mp 83–83.5 °C).[18] ^{1}H NMR ($CDCl_3$): 2.45 (s, 3 H, Ar-Me), 2.68 (s, 6 H, N-Me), 7.23–7.26 (m, 2 H), 7.64–7.69 (m, 2 H). Expected: C, 54.3; H, 6.60; N, 7.0%. Found: C, 54.3; H, 6.55; N, 7.0 %.

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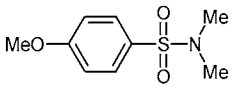
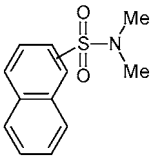
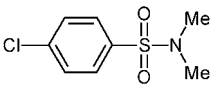
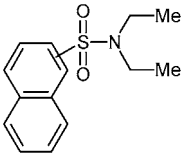
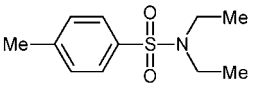
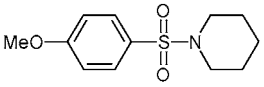
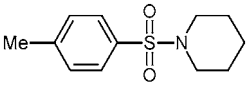
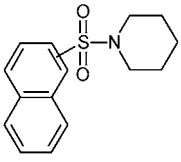
acid and leading to very efficient Friedel–Crafts acylation and sulfonylation reactions.[9] This does not happen with some of the other metal triflates [$Sc(OTf)_3$, $Yb(OTf)_3$, and $La(OTf)_3$].[10]

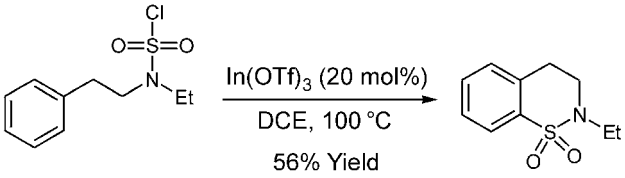
The difference in catalytic activity for indium and bismuth may well be due to the relative stability constants of their complexes with the sulfamoylating agent (chloride or triflate) and the product sulfonamide. Interestingly, lowering the catalytic loading of $In(OTf)_3$ to 10 mol% affords 60% yield and 5 mol% of catalyst affords 30% yield of product. This suggests that it takes six molecules of product to poison each indium atom. Indeed, if six equivalents of the product (relative to the catalyst) are added at the start of the reaction, no new product is formed. This is the first time we have noted product inhibition in indium catalysed aromatic functionalisation reactions. If equimolar amounts of aromatic and sulfamoyl chloride are used $In(OTf)_3$ is still an effective catalyst albeit the reaction is slower affording a 47% yield of product after 24 hours.

Using the optimised conditions the scope of the reaction was established by variation of the aromatic and sulfamoyl chloride (Table 2). The quoted yield is for isolated, purified products.[11] The reaction gave consistently good results with activated aromatics across a range of sulfamoyl chlorides but isolated yields were low with deactivated substrates such as chlorobenzene.

Table 2 Scope of Indium Catalysed Sulfamoylation[a]

Aromatic	Sulfamoyl chloride	Product	Yield (%)	Ref.
Anisole	Dimethyl	 (*o*:*m*:*p*; 45:0:55)	99	18
Naphthalene	Dimethyl	 (α:β; 34:66)	99	13
Chloro-benzene	Dimethyl	 (*o*:*m*:*p*; 0:0:100)	24	13
Naphthalene	Diethyl	 (α:β; 37:63)	44	15
Toluene	Diethyl	 (*o*:*m*:*p*; 0:0:100)	64	6
Anisole	Piperidyl	 (α:β; 36:0:64)	80	16
Toluene	Piperidyl	 (*o*:*m*:*p*; 0:0:100)	51	6
Naphthalene	Piperidyl	 (α:β; 24:76)	56	16

[a] **Typical Procedure**: A stirring mixture of aromatic (5 mmol) sulfamoyl chloride (1 mmol) and $In(OTf)_3$ (20 mol%) in DCE (5 mL) was heated to 100 °C for 24 h. The reaction mixture was then partitioned between DCM and 1 M HCl. The aq layer was washed with DCM three times and the combined organics were washed with brine, dried over anhyd $MgSO_4$ and concentrated to afford crude sulfonamide product which was purified by flash chromatography using petroleum ether:ethyl acetate (4:1) as eluent.



Scheme 2

Finally, it has been established that an indium catalysed intramolecular sulfamoylation reaction is possible. Under the predetermined conditions *N*-ethyl phenethylsulfamoyl chloride reacts to afford the cyclic aryl sulfonamide product in a modest (unoptimised) yield (Scheme 2).[12] The full scope of the intramolecular process is yet to be explored.

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