



Ionic liquids as new media for electrophilic trifluoromethylation reactions

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ABSTRACT

The electrophilic trifluoromethylation of aniline with a range of trifluoromethyl sulfonium salts has been studied in ionic liquids as solvent. The best ionic liquid for this reaction was identified after extensive scrutiny of the influence of the cation's nature (imidazolium or pyridinium salts), the effect of the alkyl side chain length of the cation, as well as that of the counter anion. Recycling experiments have demonstrated that the purification protocol was greatly simplified over conventional reactions performed in DMF and that the solvent could be reused five times without significant loss of activity.

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Research thematic of our group

The ILV Fluorine group at Versailles is mainly involved in the following research topics:

- Synergy between fluorine and sulfur with emphasis to straightforward one pot synthesis of perfluoroalkyl sulfonium salts, sulfilimines and sulfoximines. Preparation of electrophilic perfluoroalkylating reagents (or precursors thereof) as well as synthesis and physico-chemical properties studies of electron withdrawing groups.
- New and emergent fluorinated substituent: trifluoromethoxy aliphatic compounds.
- Use of new media for green chemistry: fluorous solvents for catalysis, ionic liquids for the improvement of fluorination reactions.
- Fluorinated analogues of compounds of therapeutic interest: estradiol, fulvestrantTM, and tamoxifenTM involved in breast cancers regulation.
- Preparation of fluorinated ligands for porous solids: fluorinated MOFs (coll. Porous solids group in Versailles, MIL materials).

More details as well as references at: <http://www.ilv.uvsq.fr/research/Echo/Fluor/fluor.html>.

1. Introduction

Since the pioneering work of Yagulpolskii early published in 1984 [1], various sulfur based electrophilic trifluoromethylating reagents have been described. Their structures rely upon biaryl

trifluoromethyl sulfonium salts (Shreeve) [2], dibenzothiophenium salts (Umamoto) [3], benzothiophenium salts (Shibata) [4] and a sulfoximine derivative (Shibata) [5]. Recently, the group of Togni succeeded in the preparation of very efficient hypervalent iodine(III)-CF₃ reagents [6]. Lastly, Umamoto described trifluoromethyl oxonium salts as powerful electrophilic reagents [7].

Our contribution in this field concerns the great improvement of the preparation of two types of reagents. We indeed unlocked the access to a trifluoromethyl sulfoximine precursor of Shibata's reagent, thanks to a new and high yielding procedure, which avoids the use of hazardous compounds and conditions [8]. We also proposed a one pot and benchmark procedure, which allowed the easy homemade preparation of biaryl and dibenzothiophenium sulfonium salts [9]. Our group also studied the scope of the sulfonium salts based reagents with a mechanistic study showing that the radical pathway appears to be the predominant route for the trifluoromethylation with such reagents [10]. All these studies shed some light on the advantages and drawbacks of sulfonium salts. In particular, their use suffers from two drawbacks: poor solubility in non-polar solvent and the release of a sulfur aromatic core able to compete with the nucleophilic species to be trifluoromethylated. This core and resulting trifluoromethylated derivatives are sometimes not easily removed during the final purification step.

Over the past decade, ionic liquids (ILs) have been the subject of intense research as effective reaction media for a wide range of organic reactions and other applications in chemistry [11]. ILs are defined by the combination of organic cations and appropriate anions with melting points close to room temperature [12]. They exhibit negligible vapor pressure and are usually poorly miscible with non-polar organic solvents. As a consequence reaction products are more easily extracted and the ionic liquid can be recycled [13].

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For all these reasons, we expected ILs as a green answer to the two drawbacks, previously mentioned concerning the electrophilic trifluoromethylation with sulfonium salts. On one hand, they should be able to solvate the polar ionic sulfonium salts insuring better solubility, on the other hand they may improve the purification step. To verify these hypotheses, we describe in this article a study devoted to the choice of the best ionic liquid for the purpose of trifluoromethylation, recycling experiences and the scope of this new reaction media.

2. Results and discussion

2.1. Trifluoromethylation reaction in ionic liquids

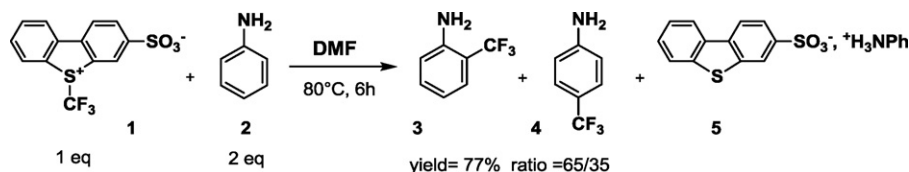
The trifluoromethylation of aniline in the presence of *S*-(trifluoromethyl)dibenzothiophenium-3-sulfonate **1** was chosen as model reaction (Scheme 1). The choice of this trifluoromethylation reagent was motivated by the simplified purification protocol claimed by Umemoto et al. [14]. Under classical conditions the resulting ionic species **5** was easily separated from the trifluoromethylated anilines by washing with water. We first repeated this reaction in order to possess a standard for further yield comparisons. Under carefully anhydrous conditions, and in the presence of distilled DMF as solvent, two isomers **3** and **4** (65/35) were obtained in 77% yield (determined by NMR with internal references [15]).

This yield is slightly better than the one described by Umemoto. We assume that this result can be explained by the only significant difference between the two works: a higher concentration was used in our case, to be in accordance with the reactions developed

in ILs. Two of the most common family of these polar solvents have been used for this study, pyridinium salts and imidazolium salts, both with different side chains and varying anions (Table 1). All these ILs have been prepared according to the literature [16]. The reactions were performed at 80 °C, for 6 h, in a closed vessel to avoid evaporation of aniline. Yields and the ratio of ortho/para trifluoromethylaniline were determined by ¹⁹F NMR and are reported in Table 1.

The influence of four anions was checked with three different imidazolium cations (entries 1–3). Good yields were obtained with NTf₂[−] and BF₄[−] whereas a small drop (10% yield) was observed with TfO[−] or Br[−] as anions. The substitution of the acidic proton in position 2 of the imidazolium ring allowed a slight increase of the yields (entry 2 vs 1 and 3 vs 4). On the other hand, increased length of the alkyl chain on imidazolium ring is deleterious to the yield (entries 1, 4 and 5 and entry 2 vs 3). This phenomenon could be attributed to an enhanced viscosity of the ILs (according to the literature) [12c] leading to a more sluggish and difficult to stir reaction media. Lastly, a pyridinium core as cation is not beneficial to the yield (entry 6). All these results also showed that ILs have no effect on the ortho/para ratio, whatever the nature of the cation or the anion employed.

The use of 1,2-dimethyl-3-butylimidazolium tetrafluoroborate (bdmimBF₄) **7** as solvent gave the same yield than with DMF and appeared as the best ionic liquid for the present purpose. An alternative to DMF as solvent for electrophilic trifluoromethylating reaction has thus been found, reaching our first goal. Next studies were then devoted to the recycling of the ionic liquid and to the improvement of the purification step.



Scheme 1. Trifluoromethylation of aniline in DMF.

Table 1

Evaluation of the trifluoromethylating activity of *S*-(trifluoromethyl)dibenzothiophenium-3-sulfonate **1** in different ILs at 80 °C for 6 h.

Entry	Ionic liquid	Counteranions and yields% (o/p ratio) ^a			
		BF ₄ [−]	NTf ₂ [−]	TfO [−]	Br [−]
1	6	71 (61/39)	67 (62/38)	59 (57/43)	61 (57/43)
2	7	75 (61/39)	69 (60/40)	65 (58/42)	65 (57/43)
3	8	68 (59/41)	68 (64/36)	58 (58/42)	58 (55/45)
4	9	60 (61/39)	–	–	–
5	10	57 (61/39)	–	–	–
6	11	58 (55/45)	–	–	–

^a Yields and ratios were determined by ¹⁹F NMR with internal references.

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