



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, sulfilmines 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 (Umemoto) [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, Umemoto 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

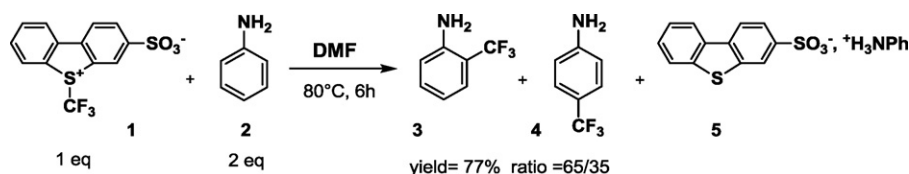
The trifluoromethylation of aniline in the presence of *S*-(trifluoromethyl)dibenzothiophenium-3-sulfonate **1** was chosen as model reaction (Scheme 1). The choice of this trifluoromethylation reagent was motivated by the simplified purification protocol claimed by Umemoto et al. [14]. Under classical 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.

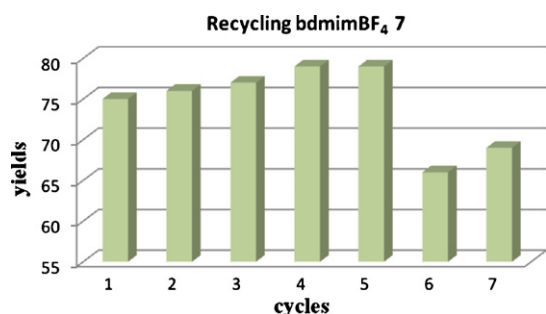


Fig. 1. Recycling experiments of the liquid ionic 7.

2.2. Recycling

After cooling, a simple extraction of the crude mixture with diethyl ether afforded products **3** and **4** accompanied by traces of unreacted aniline **2** (easily removed by washing with a slightly acidic aqueous solution) [9b]. More importantly, at the end of the reaction, the unwanted sulfur aromatic part dibenzothiophene-3-sulfonate, precipitated as an ammonium sulfonate salt **5** in the IL. This compound can be removed by simple filtration, but this operation can be omitted. Indeed, the ionic liquid, still containing byproduct **5**, can be reused five times without loss of efficiency (Fig. 1). The very small increase of the yield is simply explained by the presence of unreacted sulfonium salts **1**, still present in the bdmimBF₄. The slight decrease of the yield depicted in run 6 is due to the accumulation of the side product **5** entailing stirring problems. At this stage, simple filtration did not permit to retrieve the yields obtained during the first five runs. Further purification of the ionic liquid by column chromatography on silica gel could be necessary.

Table 2

Evaluation of the trifluoromethylating activity of the sulfonium salts in bmimBF₄ for 6 h at 80 °C.

Entry	Sulfonium salts	Yields% (o/p) ^a
1	 1	71 (61/39)
2	 12	70 (59/41)
3	 13	53 (61/39)
4	 14	61 (57/43)
5	 15	85 (60/40)

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

2.3. Scope of the sulfonium salt

Umemoto's reagent **12** and sulfonium salts **13–15** prepared in our group [9b] have been tested on the model reaction with the readily available bmimBF₄ **6** as solvent. All the salts proved perfectly soluble in the ionic liquid. The results are reported in Table 2.

Once again, during this study, no influence of the nature of the sulfonium salt on the isomeric ratio has been noticed. As expected, Umemoto's reagent (Table 2, entry 2) revealed a trifluoromethylating power equivalent to the sulfonium **1** (entry 1). The presence of bulky electron-donating methyl groups affects the yield of trifluoromethylated compound (entries 3 and 4) [17]. However, as expected, an additional nitro group is beneficial and gave the best yield (85%; entry 5). This is in accordance with the proposed enhanced reactivity of electron-poor sulfonium salts. Furthermore, we were very pleased to notice that with sulfonium salt **15**, the byproduct (2,4-dimethyl-10-nitro-dibenzothiophene) released during the transformation precipitated in the IL. While allowing the selective extraction of trifluoroanilines **3** and **4**, as in the case of Umemoto's sulfonated sulfonium salt **1**, the salt **15** gave a better yield.

3. Conclusion

We have shown that the trifluoromethylation reaction with sulfonium salts could effectively be performed with various sulfoniums in ILs in place of the toxic DMF solvent. ILs gave yields that are, at least, as good as the yields obtained under classical condition while providing an easier isolation of the trifluoromethylated target. Hydrophobic ILs with short alkyl chain should be privileged for this reaction. Furthermore, for at least one example, ILs could be recycled and reused without any purification for five runs, allowing a greener chemistry. Lastly, easily prepared reagent **15** providing the highest yield without any cumbersome work-up may prove the choice reagent for electrophilic trifluoromethylations.

Further developments of these new reaction conditions are under study in our laboratory.

4. Experimental

4.1. General

Each reaction was carried out under an argon atmosphere in freshly distilled solvent, unless otherwise noted. DMF was distilled from calcium hydride. NMR spectra were recorded on a Bruker AC 200 spectrometer. For ¹⁹F (282 MHz) NMR spectra, the reference was internal CFCl₃ (0 ppm).

4.2. General procedure for trifluoromethylation of aniline in DMF

Under an argon atmosphere, trifluoromethylsulfonium salt (0.44 mmol) was added to a stirred solution of aniline (0.88 mmol, 80 µL) in dry DMF (0.5 mL). The mixture was stirred for 6 h at 80 °C. At the end of the reaction, the solution was cooled and 2 mL of CDCl₃ were added. Then 35 mg of trifluoromethoxybenzene were introduced as internal reference for ¹⁹F NMR yield determination. The yield and the ratio of ortho and para isomers were determined by integration of the signals of the CF₃ [15].

4.3. General procedure for trifluoromethylation of aniline in ILs

Under an argon atmosphere, trifluoromethylsulfonium salt (0.44 mmol) was added to ILs (0.4 mL) then aniline (0.88 mmol, 80 µL) was added to the mixture and stirred for 6 h at 80 °C. The

reaction solution was then extracted with ether (3×10 mL). The organic layer was concentrated and 2 mL of CDCl_3 was added. Then 35 mg of trifluoromethoxybenzene were introduced as internal reference for ^{19}F NMR yield determination. The yield and the ratio of ortho and para isomers were determined by integration of the signals of the CF_3 .

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