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Ionic liquids as recyclable solvents for diethylaminosulfur trifluoride (DAST) mediated fluorination of alcohols and carbonyl compounds

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Abstract—The first simple and efficient method for the synthesis of mono and *gem*-difluorinated molecules using [C_8mim][PF_6] ionic liquid as a recyclable solvent medium with diethylaminosulfur trifluoride (DAST) as the fluorinating reagent, is reported.

The room temperature ionic liquids (RTILs) belong to an important class of solvents, which have attracted growing interest recently because of their unique physical, chemical and fine tuneable properties.[1] RTILs can dissolve a large number of organic compounds as well as transition metal derivatives. Since they possess no effective vapour pressure and can be often recycled, RTILs offer an attractive alternative to conventional organic solvents.[1,2]

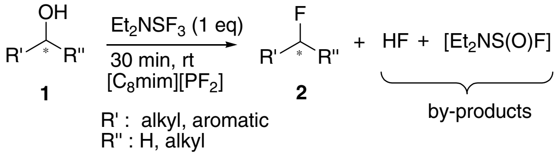
Introduction of fluorine atom(s) in molecules strongly modifies their physical, chemical and physiological properties.[3] Such fluorinated compounds have found many applications in pharmaceutical and agrochemical fields.[4] Numerous fluorinating reagents and methodologies have been developed and both electrophilic[5] and nucleophilic[6] fluorinations have been reported in ionic liquids. Dehydroxy-fluorination is another very useful method to introduce fluorine selectively to a substrate and diethylaminosulfur trifluoride (DAST) is a reagent of choice for this goal.[7] However, to the best of our knowledge, there is no report describing the use of ionic liquids as solvents for DAST-mediated fluorination.

We report here that ionic liquids can be used as solvents to perform fluorination reactions using DAST, with significant advantages regarding the reaction conditions and the purification procedure, as well as the recycling of the ionic liquid.

We selected 1-octyl-3-methylimidazolium hexafluorophosphate, [C_8mim][PF_6] as solvent medium, based on its physical properties:[1] due to the C_8 chain, it has a low viscosity, a low density and a low melting point and this should allow the use of low temperatures which are sometimes necessary for high selectivities.[8] Furthermore, this combination of a C_8 chain with the hexafluoro-phosphate anion affords a highly hydrophobic character, which should minimize the loss of RTIL during aqueous work-up.

Firstly, the primary and secondary saturated aliphatic alcohols **1a** and **1b** (Scheme 1 and Table 1) were used as models for these reactions.

They were subjected to fluorination at room temperature in [C_8mim][PF_6], using DAST (1 equiv) and the fluorinated products **2a** and **2b** were obtained in 82% and 80% yields, respectively, in pure form simply by



Scheme 1. Dehydroxy-fluorination in [C_8mim][PF_6] as solvent.

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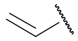
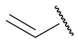
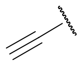
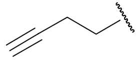
Table 1. Dehydroxy-fluorination of alcohols with aliphatic and/or unsaturated side-chains

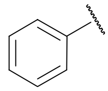
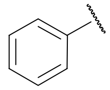
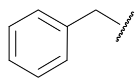
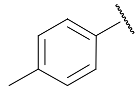
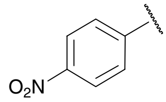
Entry	R′	R″	Yield (%)
a	C_7H_{15}—	—H	82[a,b]
b	C_6H_{13}—	—Me	80[a,b]
c		—C_5H_{11}	75[a,c]
d		—Me	71[a,b,c]
e		—C_5H_{11}	50[a,b]
f		—H	67[b]

[a] Distilled.

[b] Extracted.

[c] Mixture with regioisomeric primary fluoride.

Table 2. Dehydroxy-fluorination of alcohols with aromatic moieties

Entry	R′	R″	Yield (%)
g		—Me	77[a]
h		—H	96[a]
i		—H	84[b]
j		—Me	78[a]
k		—Me	90[b]

[a] Distilled.

[b] Extracted.

direct distillation from the reaction mixture. Alternatively, **2a** and **2b** could be obtained in similar yields by extraction with pentane followed by filtration through a silica gel plug. Removal of the fluorination by-products from the ionic liquid was performed simply by washing with water. After drying under vacuum,[9] [C_8mim][PF_6] could be reused for this fluorination reaction. We have performed three runs obtaining similar yields.

The method was then extended to other primary and secondary alcohols (Table 1).[10,11] Alcohols with different chain lengths **1c** and **1d** furnished fluorinated **2c** and **2d** in 75% and 71% yields, respectively, while the propargylic primary and secondary alcohols **1f** and **1e** gave **2f** and **2e** in 67% and 50% yields, respectively. In the case of entries **1c** and **1d** products **2c** and **2d** were isolated as 1.6:1 mixtures of the secondary and regioisomeric primary fluorides; similar results have been obtained in organic solvents.[7]

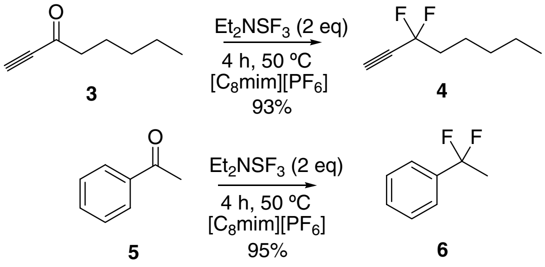
Reactions could also be carried out at low temperature (−40 °C) for entry **1c** in [C_8mim][PF_6], without any change in the progress of the reaction, affording **2c** in the same yield as at room temperature. This is an important result since it has been demonstrated that temperature can play an important role in the stereoselectivity of dehydroxy-fluorination, especially in the case of propargylic alcohols.[8] The volatile fluorinated small molecules were obtained directly through distillation, while the remainder were isolated through the usual extraction–filtration process. The [C_8mim][PF_6] ionic liquid could be recycled for the same, or another DAST-mediated fluorination reaction.

Secondly, we examined alcohols with aromatic moieties and reactions were performed in the same manner as described earlier (Table 2).

The primary and secondary alcohols **1g** and **1i** reacted well with DAST in the IL to produce **2g** and **2i** in 77% and 84% yields, respectively. Benzyl alcohol **1h** furnished **2h** in 91% yield after direct distillation; in this case, a small quantity of the desired fluorinated product was found to remain in the ionic liquid reaction mixture after the distillation, for which further extraction of the reaction mixture with pentane improved the product yield by 5%. Substrates with different inductive substituents on the aromatic moiety were also employed. Secondary alcohols **1j** with a methyl group and **1k**, with a nitro substituent were submitted to dehydroxy-fluorination. The desired products **2j** and **2k** were obtained in 78% and 90% yields, respectively, demonstrating no major role of aromatic substituents on the progress of the reaction.

gem-Difluorination of carbonyl compounds was also examined to extend our process to difluorination (Scheme 2). Propargylic ketone **3** in the presence of 2 equiv of DAST at 50 °C in [C_8mim][PF_6], took 4 h to furnish propargylic *gem*-difluoro product **4** in 93% yield. Acetophenone **5**, under similar reaction conditions, afforded aromatic *gem*-difluoro compound **6** in 95% yield.[12,13]

In conclusion, we have demonstrated that DAST-mediated fluorination can be performed with significant advantages in recyclable [C_8mim][PF_6] as the solvent media. Various alcohols as well as carbonyl compounds were employed for dehydroxy-fluorination and *gem*-difluorination. These reactions could be performed from



Scheme 2. *gem*-Difluorination using [C_8mim][PF_6] as solvent.

−40 °C to +50 °C. The more volatile fluorinated products were isolated directly by distillation, in pure form. For the less volatile derivatives, extraction with a non polar solvent, followed by short silica gel filtration, was found to be efficient. The yields for fluorination in RTILs were usually found to be higher than those obtained in classical organic solvents such as CH_2Cl_2.[14]

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10. *Typical experimental procedure for dehydroxy-fluorination*: The ionic liquid $[C_8mim][PF_6]$ (2 ml) in a two-necked round-bottomed flask equipped with a magnetic stirrer, was heated at 50 °C after which it was connected to a high vacuum pump for 6 h to pump off any moisture present. Then after cooling to room temperature (20 °C) under N_2, the alcohol (2 mmol) was added slowly to the stirred solution. After 15 min DAST (2.1 mmol) was added dropwise at room temperature. The reaction mixture was allowed to stir for 30 min under an N_2 atmosphere.
    Purification by distillation: The volatile dehydroxy-fluorinated products were distilled into a trap maintained at about −78 °C under vacuum. *Purification by extraction:* The reaction mixture was extracted using pentane or ether (5 × 3 ml), and then the combined organic phases were washed (3 × 5 ml) with a saturated solution of $NaHCO_3$, filtered through a small pad (1 g) of silica gel and concentrated.
11. *Data for compounds in Table 1*: **2a**–**b** and **2d**–**f** have spectral data in agreement with the literature. Compound (**2c**) pale yellow oil, 75% ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (m, 1H), 5.28 (dm, 2H, $J = 10.6$ Hz), 4.89 (dq, 1H, $J_{H-F} = 48.5$, 6.3 Hz), 1.80–1.25 (m, 8H), 0.90 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8 (d, 1C, $J_{C-F} = 19.4$ Hz), 116.7 (d, 1C, $J_{C-F} = 12.0$ Hz), 93.8 (d, 1C, $J_{C-F} = 166.4$ Hz), 35.2 (d, 1C, $J_{C-F} = 22.0$ Hz), 31.5, 24.3 (d, 1C, $J_{C-F} = 4.7$ Hz), 22.5, 13.9. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ −176.6 (m, 1F). MS data: m/z (EI) 130.1163 ($M^{+\cdot}$ $C_8H_{15}F$ requires 130.1157).
12. *Typical Experimental procedure for gem-difluorination*: The ionic liquid $[C_8mim][PF_6]$ (1 ml) in a two-necked round-bottomed flask was stirred at 50 °C then connected to a high vacuum pump for 6 h to pump off any moisture present. It was cooled to room temperature (20 °C) under N_2 and the ketone (0.8 mmol) added slowly to the stirred solution. After 15 min, DAST (1.6 mmol) was added dropwise at room temperature, then slowly the temperature was raised to 50 °C. The reaction mixture was allowed to stir for 4 h under N_2. The reaction mixture was extracted using pentane (5 × 3 ml), and then the combined organic phase was washed (3 × 5 ml) with a saturated solution of $NaHCO_3$, filtered through a small pad (1 g) of silica gel and concentrated.
13. *Data for gem-difluorinated compounds*: Compound **6** has spectral data in agreement with literature. *3,3-difluorooct-1-yne* (**4**) pale yellow oil 93% ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (t, 1H, $J = 4.9$ Hz), 2.07 (m, 2H), 1.51 (m, 2H), 1.35 (m, 4H), 0.93 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.4 (t, 1C, $J_{C-F} = 232.8$ Hz), 77.0 (t, 1C, $J_{C-F} = 32.0$ Hz), 74.9 (t, 1C, $J_{C-F} = 6.8$ Hz), 38.9 (t, 1C, $J_{C-F} = 25.2$ Hz), 31.0, 22.4, 22.3 (t, 1C, $J_{C-F} = 3.5$ Hz), 13.8. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ −84.04 (tt, 1F, $J = 15.0$, 4.9 Hz). MS data: m/z (EI) 145.0837 ($[M\text{–}H]^{+\cdot}$ $C_8H_{11}F_2$ requires 145.0828).
14. It is clear that extension of this chemistry, involving higher reaction temperatures, first requires a detailed understanding of the thermal and chemical stability of the sensitive DAST and Deoxo-fluor™ reagents in RTILs. Corresponding experiments are under investigation in our group and will be reported in due course.