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Selective elemental fluorination in ionic liquids

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Dedicated to Prof. Dr. mult. Alois Haas on the occasion of his 80th birthday.

ABSTRACT

Selective elemental fluorination in ionic liquids (ILs) will be presented as a new methodology. The tested reagents are organic disulphides and organic iodides. In addition, the stabilities of the ionic liquids [EMIM][$(C_2F_5)_3PF_3$], [BMPL][$(C_2F_5)_3PF_3$], [BMPL][OTf] and [BMPL][$B(CN)_4$] against diluted fluorine (5 vol% in nitrogen) are investigated.

1. Introduction

Elemental (selective) fluorinations of organic compounds can be carried out in water (for example synthesis of 5-fluorouracil) [1,2], in organic solvents like CH_3CN (syntheses of 2-substituted carbonyl compounds) [3], in CCl_3F (synthesis of $C_6F_5IF_2$) [4] or in a mixture of $CHCl_3/CCl_3F$ (fluorination of double bonds) [5]. Protonic acids, for instance formic or sulphuric acids, can be used as reaction media for direct fluorination of aromatic compounds [6]. Further possibilities for the syntheses of organofluorine compounds have been reviewed [7]. However, to the best of our knowledge such reactions have not been reported in ionic liquids. So the question arises if it is possible to fluorinate especially organic compounds in ionic liquids.

In this contribution, we report selective elemental fluorination of organic disulphides and organic iodides in ionic liquids. Usually, these products are unstable against water (4-*tert*-butyl-2,6-dimethylphenylsulphur trifluoride is an exception).

2. Results and discussion

First, the stability of selected ionic liquids against 1 equiv. of diluted elemental fluorine at 0 °C was investigated in absence of further substances. As a requirement, the cation and the anion of the ionic liquid had to be stable against oxidation and degradation.

The selected ionic liquids [EMIM][$(C_2F_5)_3PF_3$], [BMPL][$(C_2F_5)_3PF_3$], [BMPL][OTf] and [BMPL][$B(CN)_4$] were treated for 0.5 h with a mixture of fluorine in nitrogen (5 vol%), then degassed with nitrogen and finally NMR spectroscopically investigated (see Table 1).

These experiments reveal that the $[EMIM]^+$ cation is more sensitive against fluorine than the $[BMPL]^+$ cation. In case of [BMPL][OTf], formation of HF was detected, in which selective fluorination of organic substrates can be complicated. In general, the weakly coordinating anions $[CF_3S(O)_2O]^-$ and $[(C_2F_5)_3PF_3]^-$ are completely inert against elemental fluorine (5 vol% in nitrogen) at 0 °C. For fluorinations of organic substances the ionic liquids [BMPL][$(C_2F_5)_3PF_3$] and [BMPL][$B(CN)_4$] seem to be favoured.

The butyl group in the $[BMPL]^+$ cation becomes mono fluorinated at all positions, whereas the terminal position of the alkyl chain is preferably attacked (Scheme 1).

Since [BMPL][$(C_2F_5)_3PF_3$] is commercially available (Merck KGaA, Germany) in multi-kg quantities, most of the following reactions were advantageously carried out in this ionic liquid. By fluorination with diluted fluorine (5 vol% in nitrogen) the cation in [BMPL][$(C_2F_5)_3PF_3$] was not affected and over 90% of the ionic liquids used could be recovered.

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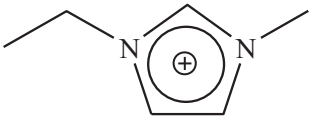
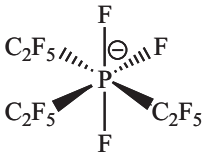
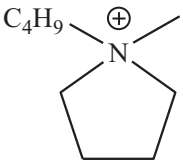
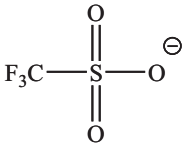
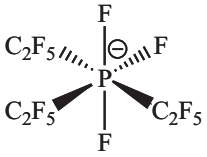
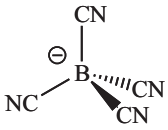
Table 1
Selected ionic liquids tested against a mixture of 1 equiv. of fluorine diluted with nitrogen (5 vol%) at 0 °C.

Cation	Anion	Products of fluorination		HF (rel. mol%)
		Cation (rel. mol%)	Anion (rel. mol%)	
 [EMIM]		31	–	–
 [BMPL]		8	–	15
		11	–	–
		–	4[a]	–

[a] ^{11}B NMR spectroscopy shows a reaction mixture in the range of −30 to −35 ppm.

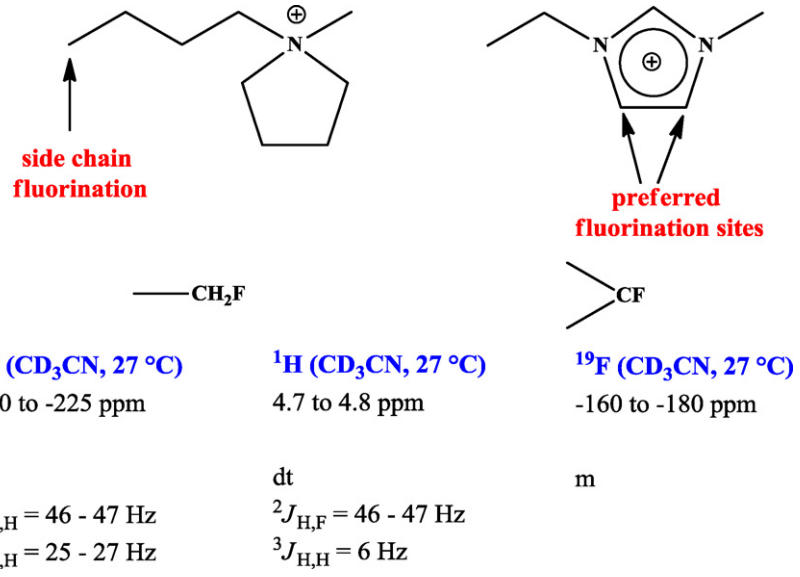
Diphenyldisulphide could be quantitatively and selectively (according to NMR) converted to phenylsulphur trifluoride with a stoichiometric amount of fluorine in selected ILs at 0 °C.

4-*tert*-Butyl-2,6-dimethylphenyl disulphide showed no reaction. Under these conditions (Schemes 2 and 3), the lack of reactivity is a result of the sterically hindered disulphide bridge due to the two methyl groups in *ortho* position of the aryl group.

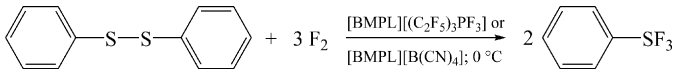
However, Umemoto et al. were successful in the synthesis of 4-*tert*-butyl-2,6-dimethylphenylsulphur trifluoride through the reaction of the corresponding disulphide in presence of AgF_2 in 1,1,2-trichlorotrifluoroethane as well as in the presence of elemental chlorine and metal fluorides in CH_3CN [8]. The yields were amounted to 64 up to 68%.

The compound $PhSF_3$ could be stored in $[BMPL][(C_2F_5)_3PF_3]$ under nitrogen at 20 °C without any decomposition.

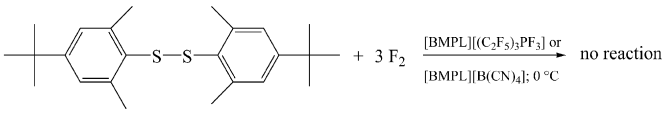
In case of the compound 2,4-dinitrophenylsulphur trifluoride, the direct fluorination of bis(2,4-dinitrophenyl)disulphide in liquid hydrogen fluoride at 0–5 °C was described in literature [9]. But this



Scheme 1.



Scheme 2.



Scheme 3.

reaction requires special equipment and due to the low solubility of the starting compound, a large amount of toxic and volatile aHF is used.

In order to check the reactivity of phenylsulphur trifluoride in $[BMPL][(C_2F_5)_3PF_3]$, this compound was successfully reacted with benzyl alcohol and 2-phenyl-1,3-dithiane to benzyl fluoride and difluoromethyl benzene (Scheme 4), as described in the literature [8,10].

It is also possible to fluorinate nonafluorobutyliodide as well as 4-fluoroiodobenzene to the corresponding organoiodine(III) difluorides (Schemes 5 and 6) in $[BMPL][(C_2F_5)_3PF_3]$, which is a good alternative to solvents like CCl_3F, perfluorohexane or perfluorocyclobutane [11].

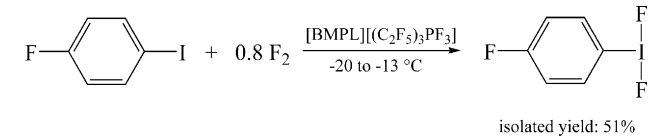
For the first time, it was possible to synthesise 4-$FC_6H_4IF_2$ by direct fluorination at such high temperatures (−20 °C). Naumann and Rüther prepared this target compound by direct fluorination (5 vol%) in CCl_3F at −100 °C [12].

In case of $C_4F_9IF_2$, the addition of trifluoroacetic anhydride leads to nonafluorobutyliodine(III) bis(trifluoroacetate), which can be purified by low temperature crystallisation. During the synthesis of nonafluorobutyliodine(III) difluoride, an excess of fluorine results in a mixture of $C_4F_9IF_2$ and $C_4F_9IF_4$.

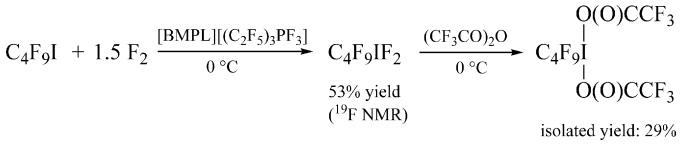
3. Experimental

All moisture sensitive compounds were handled under an atmosphere of dry argon. Reactions were carried out in glass vessels or in traps made from FEP tubes (o.d. = 4.1 mm, i.d. = 3.5 mm or o.d. = 9.0 mm, i.d = 8.0 mm). Fluorine gas (Solvay) was passed through a layer of KF to absorb traces of HF and its flow was adjusted to 2 mL/min by means of a mass flow controller (MKS type 1479A). At the same time a flow of nitrogen was adjusted to 38 mL/min by a second mass flow controller (MKS type 1179A) and both gases were mixed in stainless steel bellow tube (i.d. = 4 mm). The gas mixture was forced through a FEP tube (i.d. = 0.7 mm) and finally bubbled through the ionic liquid while stirring with a small magnetic stirring bar. CH_3CN (supplier: KMF) was purified by reflux and distillation in sequence over $KMnO_4$ and P_4O_{10}, respectively.

NMR spectra were recorded on a Bruker NMR spectrometer AVANCE 400 (^{19}F at 376.50 MHz and ^{1}H at 400.13 MHz). The



Scheme 5.



Scheme 6.

chemical shifts were referenced to TMS (^{1}H), CCl_3F (^{19}F) (C_6F_6 as a secondary reference, $\delta = -162.9$ ppm). The ratio of ^{19}F and ^{1}H nuclei in the products was determined by NMR spectroscopy after addition of 1,3,5-trifluorbenzene or benzotrifluoride.

3.1. Syntheses, use and recovery of ionic liquids

The ionic liquids used in this study were prepared according to the methods described in the literature: $[EMIM][(C_2F_5)_3PF_3]$ (yield 93%, H_2O: 19.2 ppm, Cl^-: <5 ppm) [13]; $[BMPL][(C_2F_5)_3PF_3]$ (yield 88%, H_2O: 36.3 ppm, Cl^-: 27.5 ppm) [13]; [BMPL][OTf] (yield 70%, H_2O: 29.3 ppm, Cl^-: <5 ppm) [14]; $[BMPL][B(CN)_4]$ (yield 85%, H_2O: 33.6 ppm, Cl^-: <5 ppm) [15].

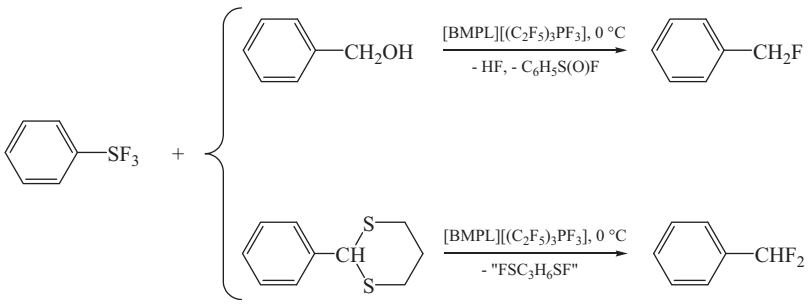
During the fluorination of organic substances, the ionic liquids were not attacked by diluted fluorine (5 vol% in nitrogen). It appears that organic substrates undergo fluorination preferably to ionic liquids. After the reaction, the ionic liquids could be purified by extraction for example with $CHCl_3$ and drying in vacuum. Over 90% of the ionic liquid could be recovered.

3.2. Syntheses of organic disulphides

The used organic disulphides were prepared according to the methods described in literature: $(C_6H_5S)_2$ (yield 66%, m.p. 59 °C) [16]; 4-*tert*-butyl-2,6-dimethylphenyldisulphide (yield 61%, m.p. 126 °C) [8].

3.3. Synthesis of $C_6H_5SF_3$ in $[BMPL][(C_2F_5)_3PF_3]$ and derivatisations

$(PhS)_2$ (1.1 g, 5.0 mmol) was added to cold (0 °C) $[BMPL][(C_2F_5)_3PF_3]$ (15.0 g, 25.5 mmol). Diluted fluorine (5 vol% in nitrogen) was bubbled into the stirred two-phase system. During the reaction, a solution was formed. After the addition of 3.0 equiv. of fluorine, the fluorination was stopped, the mixture degassed with nitrogen and was finally NMR spectroscopically investigated.



Scheme 4.

^{19}F NMR (CD_3CN, 27 °C) δ, ppm: −58.1 (d, $^2J_{F,F}$ = 62 Hz, 2F, axial), −42.4 (t, $^2J_{F,F}$ = 62 Hz, 1F, equatorial). ^{1}H NMR (CD_3CN, 27 °C) δ, ppm: 8.03 (m, 2H), 7.76 (m, 1H), 7.68 (m, 2H).

The addition of benzyl alcohol to the solution of $C_6H_5SF_3$/[BMPL][$(C_2F_5)_3PF_3$] at 0 °C resulted in $C_6H_5CH_2F$.

$C_6H_5CH_2F$: ^{19}F NMR (CD_3CN, 27 °C) δ, ppm: −206.3 (t, $^2J_{F,H}$ = 48 Hz, 1F). ^{1}H NMR (CD_3CN, 27 °C) δ, ppm: 7.43 (m, 5H), 5.39 (d, $^2J_{H,F}$ = 48 Hz, 2H).

After the addition of 2-phenyl-1,3-dithiane to the solution of $C_6H_5SF_3$/[BMPL][$(C_2F_5)_3PF_3$] at 0 °C the product $C_6H_5CHF_2$ was formed.

$C_6H_5CHF_2$: ^{19}F NMR (CD_3CN, 27 °C) δ, ppm: −111.0 (d, $^2J_{F,H}$ = 56 Hz, 2F). ^{1}H NMR (CD_3CN, 27 °C) δ, ppm: 7.50 (m, 5H), 6.62 (t, $^2J_{H,F}$ = 56 Hz, 1H).

3.4. Synthesis of 4-$FC_6H_4IF_2$ in [BMPL][$(C_2F_5)_3PF_3$]

4-FC_6H_4I (0.96 g, 4.32 mmol) was added to cold (−20 °C) [BMPL][$(C_2F_5)_3PF_3$] (9.54 g, 16.20 mmol). A mixture of fluorine in nitrogen (5 vol%) was bubbled into the stirred two-phase system. During the reaction, a white solid precipitated. After addition of 0.8 equiv. of fluorine, the fluorination was stopped, the reaction mixture degassed with nitrogen and was extracted with $CHCl_3$ (2 × 15 mL). The $CHCl_3$ phase was concentrated in vacuum (1.5 hPa, 20 °C, 1 h) and a mixture of $CHCl_3$/*n*-hexane (3 mL/3 mL) was added. A solution resulted which was cooled to −50 °C. A white solid precipitated which was washed with *n*-hexane (2 × 5 mL) and dried in vacuum (1.5 hPa, 20 °C, 1 h). White solid was obtained in 51% yield (0.46 g, 1.77 mmol).

^{19}F NMR ($CDCl_3$, 27 °C) δ, ppm: −109.1 (m, 1F, 4-*F*C_6H_4), −175.2 (s, I*F*$_2$). ^{1}H NMR ($CDCl_3$, 27 °C) δ, ppm: 7.03 (m, 2H, $H^{2,6}$), 6.37 (m, 2H, $H^{3,5}$).

3.5. Synthesis of $C_4F_9IF_2$ in [BMPL][$(C_2F_5)_3PF_3$]

C_4F_9I (1.3 g, 3.7 mmol) was added to cold (0 °C) [BMPL][$(C_2F_5)_3PF_3$]. Diluted fluorine (5 vol% in nitrogen) was bubbled into the stirred two phase system. During the reaction, a solution was formed. After the addition of 1.5 equiv. of fluorine, the fluorination was stopped, the reaction mixture degassed with nitrogen and was extracted with $CHCl_3$ (35 mL). The $CHCl_3$ phase was concentrated in vacuum (2.0 hPa, 20 °C, 4 h). The yield of $C_4F_9IF_2$ determined from ^{19}F NMR was amounted to 50% (0.46 g, 1.77 mmol). The unreacted educt (43%) and IF_5 (7%) were removed in vacuum before.

$C_4F_9IF_2$ in [BMPL][$(C_2F_5)_3PF_3$]: ^{19}F NMR (CD_3CN, 27 °C) δ, ppm: −82.0 (m, 2F, CF_2), −82.1 (tt, $J_{F,F}$ = 10 Hz, $J_{F,F}$ = 2 Hz, 3F, CF_3), −119.1 (m, 2F, CF_2), −126.7 (m, 2F, CF_2), −174.7 (m, 2F, IF_2).

3.6. Syntheses of $C_4F_9I(OCCF_3)_2$ in [BMPL][$(C_2F_5)_3PF_3$]

C_4F_9I (1.33 g, 3.84 mmol) was added to cold (0 °C) [BMPL][$(C_2F_5)_3PF_3$] (14.4 g, 24.5 mmol). Diluted fluorine (5 vol% in nitrogen) was bubbled into the stirred two-phase system. During the reaction, a solution was formed. After the addition of 1.5 equiv. of fluorine, the fluorination was stopped, the mixture was degassed with nitrogen and $(CF_3CO)_2O$ (1.61 g, 7.66 mmol) was added. The pale yellow solution was stirred for 24 h at 20 °C, and a white solid precipitated. The suspension was extracted with $CHCl_3$ (3 × 5 mL). The $CHCl_3$ phase was concentrated in vacuum (2.0 hPa, 20 °C, 2 h). The residue was crystallised from a mixture of $CHCl_3$/*n*-hexane (5 mL/5 mL) at −60 °C and dried in vacuum (2 hPa, 20 °C, 1 h). The yield was 29% (0.63 g, 1.10 mmol).

^{19}F NMR (CD_3CN, 27 °C) δ, ppm: −61.7 (m, 2F, CF_2), −73.6 (s, $^1J_{C,F}$ = 288 Hz, 6F, CF_3), −80.9 (m, 3F, CF_3), −115.5 (m, 2F, CF_2), −125.7 (m, 2F, CF_2).

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