# Fluorodediazoniation in ionic liquid solvents: new life for the Balz–Schiemann reaction

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## Abstract

Drawbacks associated with the classic Balz–Schiemann reaction are eliminated in a series of examples by conducting fluorodediazoniation in ionic liquid solvents, thus opening up a new horizon for a much in demand process. © 2001 Elsevier Science B.V. All rights reserved.

## 1. Introduction

The Balz-Schiemann reaction (first reported in 1927) [1] is a classical method for replacing the diazonium group ($-N_2^+$) by fluorine (fluorodediazoniation). The original procedure involved heating $PhN_2^+BF_4^-$ without solvent. Despite the fact that this reaction has many drawbacks (see further), interest in the "Schiemann reaction" and its variants has not diminished over time because regiospecific fluorine introduction into aromatics, polyaromatics and heterocycles continues to be a challenge [2,3] and aryl fluorides are increasingly in demand as valuable building blocks. The original procedure had reproducibility problems and the yields were quite varied depending on the arene substrates. Alternative approaches were introduced over the years [4] such as utilization of other fluorinated counter ions (e.g. $PF_6^-$, $AsF_6^-$, $SbF_6^-$) [5]; in situ diazotization (e.g. isoamyl nitrite/$BF_4$ etherate) [6] and more recently diazotization with $NOBF_4$ in $CH_2Cl_2$ solvent followed by in situ fluorodediazoniation which provided improved yields and broader substrate tolerance [7]. Other variations involved fluorodediazoniation in HF/pyridine and in $BF_3.Et_2O$ complex [8,9]. Further departures from the classical method involved the use of triazenes in HF/pyridine as precursors to $ArN_2^+$ [10].

A large body of experimental evidence argues in favor of a heterolytic mechanism (aryl cation) for thermal dediazoniation and there is much evidence that photochemical dediazoniation is also heterolytic [4]. Detailed studies suggest a tight ion pair mechanism where $BF_4^-$ reacts directly with $Ph^+$ [11]. Isomer distribution in arylation of aromatics with $PhN_2^+$ in low nucleophilicity solvents is typical of *electrophilic* arylation [4]. Although existing procedures offer reasonable improvements over the classic Balz–Schiemann reaction, the yields are in some cases still modest. An even more important drawback is environmental concerns and disposal problems if these modified procedures were to be carried out in the large scale production of aryl fluorides. Advantages associated with the use of room temperature ionic liquids as designer solvents (and catalysts) for certain organic reactions have become apparent through a number of recent studies [12–16]. Their utility in alkylation [17], Friedel–Crafts acylation [18], hydrogenation [19], Diels–Alder [20,21] and Heck [22] reactions has been demonstrated. A major concern is the relatively high cost of these compounds which makes recycling/re-use an important issue for further study.

## 2. Results and discussion

We report here on the utility of 1-ethyl-3-methylimidazolium [emim] and 1-butyl-3-methyl-imidazolium [bmim] salts with $BF_4^-$ and $PF_6^-$ counterions as solvents for fluorodediazoniation (Scheme 1) and for in situ diazotization (with $NOBF_4$ and $NOPF_6$)/fluorodediazoniation (Scheme 2) to produce fluoroaromatics in quantitative yields without the need for conventional aqueous work-up procedures. We also report simple steps for recycling/re-use of the

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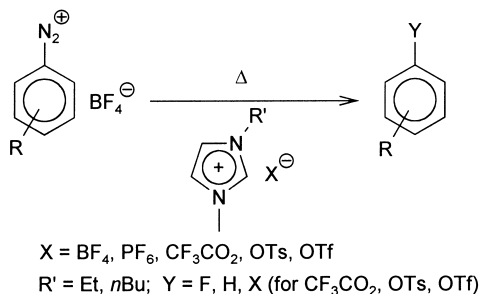
Scheme 1. Fluorodediazoniation of aromatic diazonium salts in ionic liquid solvents.

ionic liquid solvent. The use of [emim][CF₃CO₂], [emim][OTf] and [emim][OTs] ionic liquids with ArN₂BF₄ salts allows fluorodediazoniation and counter-ion exchange (metathesis)-nucleophile trapping pathways to be examined. The data are summarized in Tables 1 and 2.

In most cases diazonium salts are soluble in the ionic liquids and fluorodediazoniation is conveniently accomplished by heating the mixture until the reactions are complete. Product isolation is accomplished by addition of Et₂O. With the alkyl-substituted diazonium salts, the BF₃ or PF₅ Lewis-acid byproducts and the HF impurity initiated alkyl disproportionation leading to a mixture of products (¹H NMR and GC). These side reactions are prevented by addition of the Hünig base NEt*i*Pr₂ before Et₂O is added (or by adding aqueous NaHCO₃ instead of the Hünig base following ether extraction).

NMR analysis of the [emim][BF₄] phase following removal of organics and excess Hünig base by ether, shows intact ionic liquid and [HNEt*i*Pr₂][BF₄]. The latter is removed by addition of propyl acetate. In reactions using [bmim][PF₆], the ionic liquid itself is slightly soluble in propyl acetate. Thus, several fluorodediazoniation reactions were performed without regeneration of ionic liquid with no drop in yields before removing the accumulated [HNEt*i*Pr₂][PF₆]. Table 2 summarizes representative examples of one-pot diazotization/fluorodediazoniation reactions using [bmim][PF₆] and [emim][BF₄] ionic liquids.

It is generally agreed [4,11] that in conventional solvents fluorodediazoniation occurs via a tight ion pair. Dediazonia-
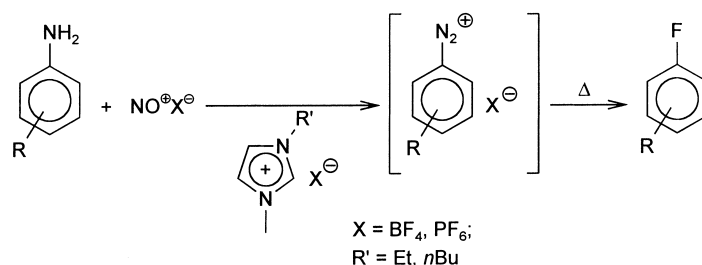


Scheme 2. One-pot diazotization-fluorodediazoniation in ionic liquid solvents.

Table 1
Dediazoniation of diazonium salts

| Ionic liquid | RArN₂BF₄ (R) | RArX (X) | Base | Temperature (°C) | Yield (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Isolated | NMR | GC |
| [emim][BF₄] | *p*-MeO | F | – | 120 | 86 | 100 | |
| | 2,4,6-(Me)₃ | F | NEt*i*Pr₂ | 70 | | 100 | |
| | *p*-tBu | F | NaHCO₃ | 70 | >71 | 100 | |
| | *p*-Br | F | – | 90 | | 100 | |
| | *p*-Cl | F | NEt*i*Pr₂ | 110 | | 100 | |
| | *o*-Me | F | NEt*i*Pr₂ | 30 | | 100 | |
| | H | F | – | 70 | | 100 | |
| | *p*-NO₂ | F | NaHCO₃ | 80 | 90 | 100 | |
| | *m*-NO₂ | F | – | 50 | 95 | 100 | |
| | *p*-CN | F | NEt*i*Pr₂ | 70 | | 100 | |
| | 2,4,6-(Br)₃[a] | H | – | 120 | | 100 | |
| [bmim][PF₆] | 2,4,6-(Me)₃ | F | NEt*i*Pr₂ | 80 | | 100 | |
| | H | F | NEt*i*Pr₂ | 100 | | 100 | |
| | *p*-NO₂ | F | NEt*i*Pr₂ | 110 | | 100 | |
| [emim][CF₃CO₂] | *p*-MeO | –OCOCF₃ | – | 120 | | 100 | |
| | *m*-NO₂ | H and –OCOCF₃ | – | 30 | | | ~28 and, ~72 |
| [emim][OTs] | *p*-tBu | –OTs | – | 95 | 75 | 100 | |
| [emim][OTf] | *o*-Me | –OTf | – | 70 | 94 | 100 | |

[a] Homolytic dediazoniation (see [27]).

Table 2
One-pot diazotization/fluorodediazoniation

| Ionic liquid | NOX (X) | RarNH$_2$ (R) | RArN$_2$X yield (%)[a] | Temperature (°C) | RArF yield (%)[a] |
|---|---|---|---|---|---|
| [bmim][PF$_6$] | PF$_6$ | H | 100 | 96 | 100 |
| | BF$_4$[b] | H | 100 | 100 | 100 |
| [emim][BF$_4$] | BF$_4$ | 2,4,6-(Me)$_3$ | 100 | 70 | 100 |

[a] Determined by ^{1}H NMR.
[b] Counterion exchange with ionic liquid.

tion of ArN$_2$$^+$BF$_4$$^-$ salts in [emim][CF$_3$CO$_2$], [emim][OTs] and [emim][OTf] ionic liquids offered the opportunity to see if these novel, highly ionizing, polar media could encourage the formation of a solvent separated ion-pair, whereby the Schiemann reaction would compete with nucleophile quenching by the ionic liquid counter-ion. NMR monitoring (proton chemical shifts of the imidazolium core are counterion dependent) showed, however, that on mixing metathesis occurs; subsequent dediazoniation produces the esters (nucleophile quenching products) (see Table 1).

Other aspects of ArN$_2$$^+$ chemistry in ionic liquid solvents are under investigation in our laboratory.

## 3. Experimental section

The [emim][X] ionic liquids (X = BF$_4$, OTf), NOBF$_4$ and NOPF$_6$ were high purity commercial samples (Aldrich) which were used as received. Diazonium salts were prepared by conventional diazotization (NaNO$_2$/HBF$_4$) and precipitation from MeCN/ether [23–25]. The [emim][CF$_3$COO] and [emim][OTs] were prepared from [emim][Cl] by reaction with sodium trifluoroacetate and silver tosylate, respectively, whereas [bmim][CF$_3$COO] was synthesized via [bmim][Cl] and NaCF$_3$CO$_2$ [26]. Ether was dried over sodium whereas other solvents were used without purification. All reactions were carried out in Schlenk tubes.

^{1}H NMR spectra were recorded in [D$_6$]acetone and [D$_3$]chloroform at room temperature using a Bruker AMX 300 instrument.

GC analysis were performed with an HP-5890 capillary GC instrument.

### 3.1. Fluorodediazoniation

#### 3.1.1. Typical run for [emim][BF$_4$]

The [emim][BF$_4$] (990 mg, 5.0 mmol) was charged into a Schlenk tube and diazonium salt (0.5 mmol) was directly added and the mixture stirred. In most cases, the salt is soluble in the ionic liquid. The mixture was heated until gas evolution was observed. Heating was continued for 1–3 h until dediazoniation was complete (assayed by ^{1}H NMR), after which one equivalent of the Hünig base (0.5 mmol NEt*i*Pr$_2$) was added and the solution was extracted with ether. Based on NMR analysis, the ether phase contained the

corresponding fluoroaromatic and some NEt*i*Pr$_2$ whereas the ionic liquid phase contained the [HNEt*i*Pr$_2$][BF$_4$] salt.

#### 3.1.2. Typical run for [bmim][PF$_6$]

The procedure was similar to 3.1.1. In this case, counterion exchange occurs to give [bmim][BF$_4$], but this does not create any limitation. The resulting [emim][PF$_6$/BF$_4$] is slowly transformed into [emim][BF$_4$] after several fluorodediazoniation reactions.

#### 3.1.3. Reaction in [emim][X] other than X = BF$_4$ and PF$_6$

The ionic liquid (3.0 mmol) was charged into a Schlenk tube. The diazonium salt (0.5 mmol) was added and stirred. In most cases the salt dissolves in the ionic liquid in which case counterion exchange could be determined by ^{1}H NMR. The mixture was subsequently heated until gas evolution was observed. It was kept at this temperature for 1–3 h until dediazoniation was complete (^{1}H NMR).

#### 3.1.4. Product characterization and yield determination

Product characterization was based on NMR (and GC). In cases where the Hünig base was not used (see Table), isolated yields were determined after ether extraction and following the removal of solvent. The NMR yields refer to direct analysis of the reaction mixtures without work-up, showing complete disappearance of the diazonium salt and presence of only the resonances belonging to the fluoroarene product and the ionic liquid solvent. In cases where authentic fluoroarenes were available, the identity of the products were further confirmed via GC analysis.

### 3.2. One-pot diazotization/fluorodediazoniation

Nitrosonium salt (NOPF$_6$ or NOBF$_4$; 0.6 mmol) was added to [emim][PF$_6$] or [emim][BF$_4$] (5.0 mmol) and the solution was cooled to 0°C in an ice bath. The aniline (0.6 mmol) was added slowly and the mixture stirred for 30 min at 0°C (viscous ionic liquid) and for 12 h at RT. The progress of diazotization was monitored by ^{1}H NMR. Once complete, the reaction mixture (solution or suspension) was heated until gas evolution was observed. It was kept at this temperature for 1–3 h until the dediazoniation was complete (^{1}H NMR), after which one equivalent of the Hünig base (0.6 mmol NEt*i*Pr$_2$) was added and the solution was extracted with ether. The ether phase contained the

product(s) and some Hünig base. The ionic liquid phase contained the [HNEt*i*Pr$_2$][BF$_4$/PF$_6$] salt (assayed by NMR).

### 3.3. Recycling/reuse of ionic liquid

1. The [emim][BF$_4$]: after removal of the product(s) and excess NEt*i*Pr$_2$ with ether, the ionic liquid was washed with propyl acetate to remove [HNEt*i*Pr$_2$][BF$_4$] salt.
2. The [bmim][PF$_6$]: after several runs allowing [HNEt*i*Pr$_2$][PF$_6$] to build-up in the ionic liquid, it was washed with propyl acetate to remove most of [HNEt*i*Pr$_2$][PF$_6$] salt (propyl acetate extracted some of the ionic liquid).

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