Aromatic Fluorination by Decomposition of Triazenes in Ionic Liquids

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Received November 24, 2004

The aromatic fluorination method involving the acid-catalyzed decomposition of a triazene in an ionic liquid is a very convenient and efficient way to prepare a variety of aromatic fluorides in a lab-scale. It should be particularly useful for the preparation aryl fluorides substituted with electron withdrawing substituents. Fluorination of triazene **1** (1.0 mmol) and *p*-toluenesulfonic acid (1.2 mmol) in an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4], 2.5 mL) proceeds very smoothly at 80 °C with or without an external source of fluoride, providing 73% yield in 30 min. Unlike diazonium salts, triazene precursors are stable enough to be stored for a long period of time without a noticeable decomposition.

Key Words : Aromatic fluorination, Triazine, Ionic liquid, Balz-Schiemann reaction

Introduction

Because of the unique chemical and physiological properties of fluorine, monosubstituted fluoro compounds have been one of major interest to organic and medicinal chemists.[1-4] Although many methods for the synthesis of fluoro aromatic compounds have been developed, such as the Balz-Schiemann reaction, diazotization-fluorination, aromatic nucleophilic and electrophilic substitution,[5-7] there are still limitations to practical and efficient application of these chemical processes. Thus, there is considerable interest in developing new and improved methods for aromatic fluorination.

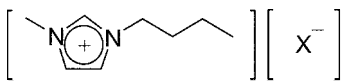
Methods for the introduction of fluorine into aromatic rings in a regiospecific manner are the Balz-Schiemann reaction and aromatic nucleophilic substitution. The Balz-Schiemann reaction, one of the most frequently used methods, involves the thermal decomposition of an aryl diazonium tetrafluoroborate or hexafluorophosphate salts.[5,8] In similar manner, fluorine can be introduced into aromatic systems by the so-called diazotization-fluorination method, which involves diazotization of an aniline using $NaNO_2$, followed by fluorination using HF-pyridine.[9] In nucleophilic aromatic substitution, a halogen, nitro, and trimethylammonium group is used as a leaving group,[10-13] the reaction being efficient only in electron-deficient aromatic systems and thus of rather limited scope.

Aryl diazonium tetrafluoroborates or hexafluorophosphates, used as precursors for the Balz-Schiemann reaction, are more stable than either diazonium chorides or diazonium hydrogen sulfates. However, because all of these aryl diazonium salts are relatively unstable, aryl triazenes, which are easily prepared from aryl diazonium chlorides and alkylamines, have been used as precursors for aromatic fluorination.[14-18] In fact, this method, which has been called the "Wallach reaction", based on the name of the lead author of the original report of this method, and it predates the Balz-Schiemann reaction.[19,20]

The fluorination of aryl triazenes can be affected by their thermal decomposition in acidic medium in the presence of fluoride ion. Typically, HF is generated in this conversion by the reaction a fluoride salt with an acid. As acid is required to decompose the aryl triazene, a major byproduct is typically the arene substituted with the counterion of acid used. Higher yields of the fluoride product can be obtained when greater amounts of the fluoride source are added, but substantial yields of the non-fluorinated byproduct are typically also produced.[16] To avoid competitive formation of the byproduct, decomposition of aryl diazosulfide using silver fluoride was attempted.[18]

Ionic liquids containing imidazolium cations and their counter anions (Figure 1) are alternative reaction media of increasing interest and are regarded as an eco-friendly alternatives, of potential use in place of the volatile organic solvents typically used in current chemical processing methods.[21-24] Recently, we reported a highly efficient nucleophilic aliphatic fluorination using metal fluoride in the presence of an ionic liquid such as 1-*n*-butyl-3-methylimidazolium cation [bmim] and its counter anions – [bmim][X].[25-27] In 2001, Laali and Gettwert used ionic liquids as solvents for the Balz-Schiemann reaction.[28] Fluorodediazoniation of aromatic diazonium salts (ArN_2BF_4) and one-pot diazotization-fluorodediazoniation using $NOPF_6$ or $NOBF_4$ in ionic liquids such as 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF_4]) or [bmim][PF_6] were achieved in excellent yield. We have also applied ionic liquids as solvents for aromatic fluorination, but we have used the more convenient and stable aryl triazenes as precursors.

Herein, we report the detailed characteristics of an aromatic fluorination method based on the acid-catalyzed decomposition of triazenes conducted in ionic liquids. This method is convenient, and it operates efficiently under appropriate conditions. Additionally, the triazene precursors are much more stable than are diazonium salts, and they can conveniently be stored for long periods of time without



[bmim][X] {X = BF_4, PF_6, SbF_6, OTf, OAc}

Figure 1. Ionic Liquids.

decomposition. Furthermore, the ionic liquids that are the solvent – and in some cases reagents – in these reactions, can be regenerated and recovered. Thus, this method should be particularly useful for the preparation of small amounts of aryl fluorides substituted with electron withdrawing substituents.

Results and Discussion

The four triazenes used in this study were prepared from the corresponding aryl amines, according to known procedures: The treatment of the aryl diazonium chlorides, generated from the arylamines, with dialkyl amines such as piperidine, provided these triazenes very efficiently.[14,15,18] The four aryl amines we selected have acetyl, methyloxycarbonyl, phenyl, and isopropyl groups in *para* position. From prior studies, it is known that the diazonium ion derived from triazene with electron deficient substituents on the aromatic ring would undergo decomposition via a radical path, whereas the diazonium ion derived from triazenes with electron rich substitutents would decompose predominantly *via* a heterolytic decomposition.[16,29,30] Thus, 1-(4-acetylphenyl)-3,3-(pentanediyl)triazene (**1a**) was selected as the first compound to characterize this decomposition-fluorination reaction; Table 1 shows the results of the fluorinations of all of the triazenes.

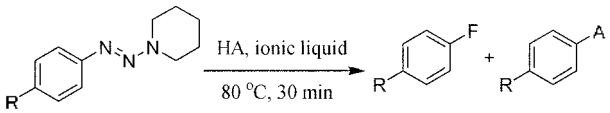
The fluorination with KF, CsF, and *t*-butylammonium fluoride (TBAF) as fluoride sources in [bmim][BF_4] in the presence of *p*-toluenesulfonic acid (*p*-TsOH) provided the fluoroarenes in similar yields, 73, 71, and 68%, respectively (entries 1-3). Surprisingly, however, the reaction yields were influenced by the nature of the counter anion. While fluorination reactions in either [bmim][BF_4] or [bmim][PF_6] gave quite high yields (entries 1 and 4), reaction yields in [bmim][OTf] and [bmim][NTf_2] were much lower (entries 5 and 6). Curiously, we found that the yield of the fluoroarene decreased with the addition of excess KF, and when more acid was added, the increased levels of the byproduct resulting from arene substitution with the acid counterion were obtained.[16,17]

When we performed the reaction without the addition of a fluoride source such as KF or CsF, we were pleased to find that we obtained the desired product in even a slightly better yield than before (entry 7). This result means that the anion [BF_4] of the ionic liquid plays the same role as it does in the aromatic diazonium salts [ArN_2][BF_4] used for the Balz-Schiemann reaction.[28] The actual isolated yield of fluoroarene for this reaction, when run on a 1.0 mmol reaction scale, was 73%, with only 7% of byproduct **3** isolated (entry 8). However, when 7.5 equiv of acid was used, byproduct **3** was essentially the only material isolated (93% yield, entry 9). This result indicates that by using this method, we can overcome one of the principal problems associated with fluorination methods that involve decomposition of aryl diazonium ions: byproduct formation by competitive substitution with other, non-fluoride, counterions.

As the reaction proceeds in a similar manner with or without the addition of excess fluoride ion, we tested the effect of the nature of the acid. While triflic (TfOH) and methanesulfonic acids (MsOH) gave similar yields, trifluoroacetic acid gave a slightly lower yield, and acetic acid gave no product (entries 10-13). Recently, Pages and Langlois reported the fluorination of triazene **1a** with CsF in acidic medium (not in ionic liquid); in the presence of triflic acid, they obtained product **2a** in 24% yield after 60 min at 80 °C (entry 17).[17] Thus, our method gives greatly improved yields compared to this earlier work.

In our hands, using the ionic liquid, the reaction of 1-(4-methoxycarbonylphenyl)-3,3-(pentanediyl)triazene (**1b**) and 1-(4-biphenyl)-3,3-(pentanediyl)triazene (**1c**) gave the corresponding fluoroarenes in 60 and 63% isolated yields, respectively (entries 14 and 15). On the other hand, 1-(4-isopropylphenyl)-3,3-(pentanediyl)triazene (**1d**) did not give

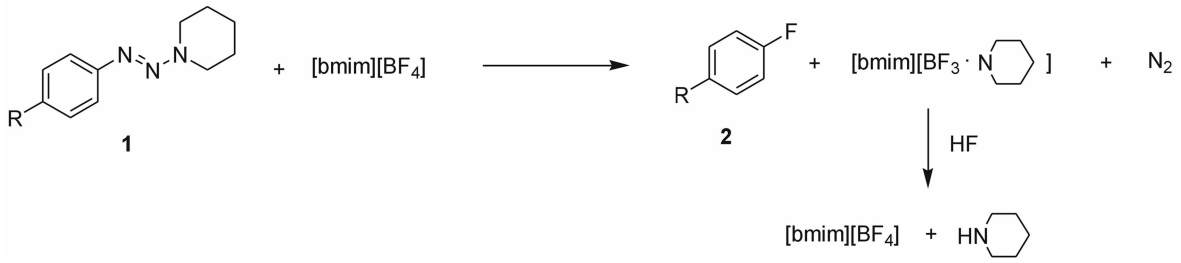
Table 1. Fluorination by decomposition of triazenes[a]



1 2 3

Entry	R	[bmim][X]	HA (1.5 equiv)	Fluoride (equiv)	Yield 2	Yield 3
1	Ac	[BF_4]	*p*-TsOH	KF (1.5)	73	15
2	Ac	[BF_4]	*p*-TsOH	CsF (1.5)	71	13
3	Ac	[BF_4]	*p*-TsOH	TBAF (1.5)	68	12
4	Ac	[PF_6]	*p*-TsOH	KF (1.5)	71	12
5	Ac	[OTf]	*p*-TsOH	KF (1.5)	29	26
6	Ac	[NTf_2]	*p*-TsOH	KF (1.5)	22	28
7	Ac	[BF_4]	*p*-TsOH	–	77	12
8[b]	Ac	[BF_4]	*p*-TsOH (1.2)	–	73	7
9	Ac	[BF_4]	*p*-TsOH (7.5)	–	0	93
10	Ac	[BF_4]	TfOH	–	65	10
11	Ac	[BF_4]	MsOH	–	70	9
12	Ac	[BF_4]	TFA	–	56	22
13	Ac	[BF_4]	AcOH	–	0	0
14[b]	MeOCO	[BF_4]	*p*-TsOH (1.2)	–	60	10
15[b]	Ph	[BF_4]	*p*-TsOH (1.2)	–	63	8
16[b]	*i*-Pr	[BF_4]	*p*-TsOH (1.2)	–	–	30
17[c]	Ac	–	TfOH (4.0)	CsF (5.0)	24	11
18[d]	Ac	–	HF-pyridine	AgF (1.0)	29	NA

[a]Reactions were carried out on a 0.1 mmol reaction scale of triazene 1 and acid (0.15 mmol) using 0.15 mmol of MF in ionic liquid (0.25 mL) at 80 °C for 30 min. The yields were obtained by NMR using an internal standard. [b]Reactions were carried out on a 1.0 mmol reaction scale of triazene 1 and acid (1.2 mmol) in ionic liquid (2.5 mL) at 80 °C for 30 min. The isolated yield was obtained. [c]Data from ref. 17. [d]Data from ref. 18. The amount of compound **3** was not available.



Scheme 1

the corresponding fluoroarenes, but rather byproduct **3**, together with unknown products (entry 16).

Laali and Gettwert have pointed out that a major concern in the use of ionic liquids is their relatively high cost, which makes their recycling (*i.e.*, recovery and reuse) an important issue.[28] According to the procedure reported for the preparation of [bmim][BF_4], this material is made from [bmim][Cl] and $NaBF_4$ by anion exchange. Scheme 1 shows the proposed mechanism of this fluorination reaction. From the balanced chemical equation for our fluorination reaction, the anion complex of [BF_3·piperidide] would be formed. As the ionic liquid in this reaction is used in excess, its recovery and reuse should be possible.[31,32] Thus, because the ionic liquid in this reaction is used in large excess, in practice, we have been able to reuse it directly (*i.e.*, without regeneration of the BF_4 counterion) at least three times, without any noticeable decrease in yield. There are reports by others that ionic liquids can be recycled for use in other reactions,[31,32] again, without the need for regeneration. Eventually, however, repeated recycling of the ionic liquid would require regeneration of the [BF_4] counterion by treatment of the anion complex in the product [BF_3·piperidide] with hydrogen fluoride; the piperidine that is freed could be removed by extraction.

Conclusion

The aromatic fluorination method that we present – involving the acid-catalyzed decomposition of a triazene in an ionic liquid – is a very convenient and efficient way to prepare the aromatic fluorides in the laboratory. Triazenes are much more stable than diazonium salts, and they can be stored for long time periods, and under appropriate conditions, the aryl fluorine product can be obtained conveniently and in high yield, without contamination by products resulting from competitive substitution with non-fluoride counterions. An additional convenience is that the ionic liquid can be used not just as solvent, but also as the source fluoride, and it can be used repeatedly without regeneration, with no loss in yield. This method should be particularly useful for the preparation of small amounts of aryl fluorides substituted with electron withdrawing substituents, and the expense of the ionic liquids can be offset by their recovery and reuse, and ultimately their regeneration.

Experimental Section

Ionic liquids were purchased from FutureChem Co., Korea and used as received. Other chemicals were purchased from Aldrich Chemical Co. Triazenes were prepared by known methods.[14,15,18] The products **2** and side products **3**[16,17] were identified by comparison of their physical properties with those for these materials reported in the literature.

General Procedure for the Acid-catalyzed Thermal Decomposition of Triazenes in the Presence of Ionic Liquids (Entry 8 in Table 1).

***p*-Fluoroacetophenone (2a):** *p*-Toluenesulfonic acid (1.2 mmol) was added to the solution of 1-(4-acetylphenyl)-3,3-(pentanediyl)triazenes[18] (1.0 mmol) in [bmim][BF_4] (2.5 mL). The mixture was heated at 80 °C for 30 min. After cooling to rt, the mixture was extracted with ethyl ether (10 mL × 3) and water (10 mL). The organic layer were washed with 1 N NaOH (10 mL), dried ($MgSO_4$), and concentrated, and purified by flash column chromatography (5% EtOAc/haxanes) to give **2a** (101 mg, 0.73 mmol, 73%) and *p*-toluenesufonyloxyacetophenone (20 mg, 0.07 mmol, 7%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.03-7.96 (m, 2H), 7.19-7.10 (m, 2H), 7.14 (t, J = 8.6 Hz, 2H), 2.60 (s, 3H); CAS No. [403-42-9].

Methyl *p*-Fluorobenzoate (2b): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.11-8.04 (m, 2H), 7.18-7.08 (m, 2H), 3.93 (s, 3H); CAS No. [403-33-8].

4-Fluorobiphenyl (2c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.65-7.37 (m, 7H), 7.16 (t, J = 9.3 Hz, 2H); CAS No. [324-74-3].

Acknowledgments. This work was supported by the National Research Laboratory Program in Korea (to D.Y.C) and the Department of Energy (DE FG02 86ER60401, to J.A.K).

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