Available online at www.sciencedirect.com

ScienceDirect

Journal of Fluorine Chemistry 128 (2007) 674–678

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/fluor

Short communication

Photochemical Schiemann reaction in ionic liquids

Jorge Heredia-Moya, Kenneth L. Kirk *

Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health,
Department of Health and Human Services, Bethesda, MD 20892, United States

Received 29 January 2007; received in revised form 9 March 2007; accepted 10 March 2007
Available online 16 March 2007

Abstract

Photochemical Schiemann reactions of imidazole derivatives **1** and **4** were carried out in 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid [bmim][BF_4] as solvent. The effects of temperature, co-solvent and wavelength on the rate of the reaction and product yield were examined. The use of ionic liquid increases the yield of the photochemical fluorodediazoniation reaction of **2** at 0 °C. Careful temperature control is necessary to minimize the photodecomposition of the ionic liquid in order to increase the yield of product.

Keywords: Photochemistry; Ionic liquid; Imidazole; Schiemann reaction

1. Introduction

The Balz–Schiemann reaction was one of the first methods developed for the synthesis of fluorinated aromatic compounds and is still widely used. In this reaction the fluorinated compound is formed by thermal decomposition of an aryl diazonium tetrafluoroborate or hexafluorophosphate salt [1]. This is a valuable transformation that has made available many new aryl fluorides. However, the original procedure had reproducibility problems and gave yields that were quite dependent on the arene substrate. Furthermore, the high temperatures often required to effect cleavage of the diazonium salt carbon–nitrogen bond can lead to thermal destruction of product or starting material. Thus, in repeated attempts to prepare ring-fluorinated imidazoles by thermal decomposition of imidazole diazonium fluoroborates, we were unable to detect any trace of desired fluorinated product despite destruction of starting material [2].

Faced with lack of success with thermal decomposition of imidazole diazonium fluoroborates we explored the option of providing selective energy to the diazonium chromophore by carrying out a photochemical reaction. We found that under very mild conditions, UV irradiation promoted efficient extrusion of nitrogen, thermal side reactions were avoided, and fluoroimidazoles were delivered in satisfactory yields [2]. Advantages of this procedure include its generality and the fact that it can be done *in situ* without isolation of the diazonium salt [3]. Using this photochemical variation of the Schiemann reaction, we subsequently prepared many fluorinated analogues of biologically important imidazoles for extensive biological evaluation [4].

A limitation of the photochemical Schiemann reaction stems from competing reaction with solvent nucleophiles. Studies of the dediazoniation reactions of diazonium salts have revealed a heterolytic mechanism for both photochemical and thermal dediazoniation [5]. Thus, the fate of the aryl cation formed in the reaction can be strongly affected by the solvent. As an example, water and alcohols can compete with fluoride as a nucleophile and form phenols and aryl ethers, respectively [5a,6].

Ionic liquids are suitable media for stabilization of charged transition states favoring those mechanisms occurring through charge separation [7]. We reasoned that in the dediazoniation reaction the absence of protic nucleophiles in ionic liquids should eliminate side reactions that result from competing reactions with solvent and thus improve the yield of the fluoroproduct.

A few studies have recently addressed the use of ionic liquids in photochemistry, focusing on use of photochemical probes such as Nile Red to assess polarity [8] in studies of photoinduced electron transfer features [7,9] in characterization of radical ions [10] and in photochemical degradation of

---

* Corresponding author.
E-mail address: kennethk@intra.niddk.nih.gov (K.L. Kirk).

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.03.012

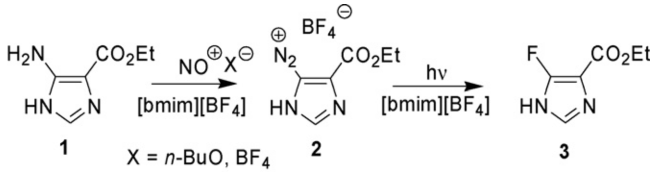
environmental contaminants [11]. However, their use in preparative organic photochemistry has been limited to dimerization [12], photoisomerization [13], and photoreduction reactions [14].

In the literature, imidazolium ionic liquids are generally regarded as optically transparent liquids possessing no absorption in the UV–vis range (above 250 or 300 nm). Any absorption beyond this wavelength has been ascribed to the presence of impurities. However, recent studies not only suggest that these ionic liquids have significant absorption in the UV region, but also that they have fluorescence that covers a large part of the visible region [15]. The lack of transparency of most imidazolium ionic liquids below 320 nm may explain the limited use of ionic liquids in photochemistry [9a].

In this paper, we report our studies on the photochemical fluorodediazoniation of imidazole derivatives in ionic liquid. We have examined the effects of temperature and wavelength on the rate of the reaction and product yield.

2. Results

Previous attempts to carry out the thermal Balz–Schiemann reaction of imidazole-4-diazoniumfluoroborate-5-carboxylic esters **2** resulted in decomposition of starting material but no trace of fluorinated imidazole could be detected [2]. However, photochemical decomposition proceeded smoothly and the photochemical decomposition of **2** provided the first synthesis of ring fluorinated imidazoles. This reaction remains the only general route to this important class of compounds. The initial procedure consisted of reaction of a solution of the amine **1** in HBF_4 with $NaNO_2$ at 0 °C followed by irradiation of the mixture with a UV lamp until evolution of nitrogen ceases. With this procedure, the fluoroimidazole **3** was reported in 39% yield [2a]. The results of reaction in ionic liquid (Scheme 1) are described below.



Scheme 1. One-pot diazotization-photochemical fluorodediazoniation in $[bmim][BF_4]$.

2.1. Effect of temperature

In our first attempt (Scheme 1), we reduced the amount of water in the media by replacing aqueous sodium nitrite with *n*-BuONO in an equivalent of 48% HBF_4 and used $[bmim][BF_4] > 97\%$ of purity to replace 48% aqueous HBF_4 (Table 1, entries 1–5) as solvent. This reaction initially was done at room temperature in a micro photochemical reactor using a quartz immersion well. After 1.5 h the initial yellow color of the solution changed to red and the yield of **3** was only of 11%. The same yield was obtained using an equivalent of 48% HBF_4 and 1.5 equivalents of *n*-BuONO. When the temperature of the reaction was reduced to −78 °C the mixture solidified and the evolution of nitrogen was almost negligible. Every hour the mixture was warmed 0 °C to allow mixing and removal of generated nitrogen and then cooled again to −78 °C for continued irradiation. After 9 h of reaction the solution remained yellow and **3** was obtained in 41% yield. The reaction at 0 °C affords **3** in 30% yield after 1 h of reaction.

Table 1
Diazotization-fluorodediazoniation of **2** in [bmim][BF4] (Quartz jacketed immersion well, unless indicated)

Entry	Amine	Solvent	Nitrile source		T (°C)	Time (h)	Yield[a] (%)
			HBF_4/*n*-BuONO	$NOBF_4$			
1	1	$[bmim][BF_4]$	1.2/1.20	–	rt	1.5	11
2	1	$[bmim][BF_4]$	1.0/1.5	–	rt	3	11
3	1	$[bmim][BF_4]$	1.5/1.5	–	0	1	30
4	1	$[bmim][BF_4]$	1.5/1.5	–	−10	1	20
5	1	$[bmim][BF_4]$	1.5/1.5	–	−78	9	41
6	1	$[bmim][BF_4]$	–	1.1	0	9	31
7	1	$[bmim][BF_4]$	–	1.1	0	11	37
8	1	$[bmim][BF_4]$	–	1.5	0	2	52
9	1	$[bmim][BF_4]$	–	1.7	0	6	51
10	1	$[bmim][BF_4]$	–	1.5	0	8	57
11	1	$[bmim][BF_4]$	–	1.5	0	9	58
12	1	$[bmim][BF_4]$	–	1.5	0	24	62
13	1	Acetonitrile:$[bmim][BF_4]$ 1:1	–	1.5	0	6	45
14	1	Acetonitrile:$[bmim][BF_4]$ 1:1	–	1.5	0	8	44
15	1	Acetonitrile:$[bmim][BF_4]$ 1:1	–	1.5	−50	6	46
16	1	$[bmim][BF_4]$[b]	–	1.5	0	168	70
17	1	$[bmim][BF_4]$[b]	–	1.5	rt	168	63
18	4	$[bmim][BF_4]$	–	1.5	0	24	56[c]

[a] Yield of **3**.

[b] Borosilicate glass jacketed immersion well.

[c] Yield of **5**.

2.2. Source of nitrite

In a similar study of the thermal Schiemann reaction, Laali and Gettwert [16] used $NOBF_4$ in the diazotization reaction. This permits complete elimination of water in the reaction mixture as a strategy to increase the yield, a strategy we adopted in our next experiments. We explored both the thermal and the photochemical reactions.

In the thermal reaction of **2** using 1.5 equiv. of $NOBF_4$ at 110 °C no reaction was observed after 5 h. The tlc showed only starting material. After 12 h of reaction at 120 °C no reaction was observed, but the ionic liquid had visibly decomposed. The thermal stability of imidazolium based ionic liquids will be significantly reduced in the presence of nucleophiles, especially at extended times at high temperature [17] or in the presence of fluoride ion [18]. After 7 h at 140 °C the diazonium salt disappeared but no fluoroimidazole **3** was observed. This result is consistent with our original observations during attempts to synthesize ring-fluorinated imidazoles by a thermal Schiemann reaction [2].

The ionic liquid used is a mobile liquid at room temperature, but at 0 °C it becomes very viscous. However, it remains mobile enough to permit stirring and evolution of nitrogen during the irradiation. Using 1.5 equiv. of $NOBF_4$, the reaction affords **3** in 62% yield after 1 day (Table 1, entry 12). When the equivalents of $NOBF_4$ are less than 1.5 (Table 1, entries 6 and 7) the yield decreased and when higher than this (Table 1, entry 9) the yield did not change, even with a higher time of reaction.

2.3. Addition of co-solvent

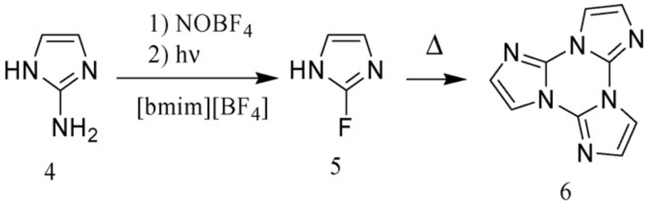
In order to decrease viscosity, we used a mixture of acetonitrile: [bmim][BF_4] 1:1 as solvent (Table 1, entries 13–15). In this case the yields of **3** after 6 h at 0 °C and −50 °C were 45% and 46%, respectively. Additionally, at −50 °C it was possible to obtain 1% yield of a solid that was identified as 5-diazoimidazole-4-carboxylic acid ethyl ester by ^{1}H NMR and MS.

2.4. Wavelength

We also investigated the effect of wavelength on the reaction (Table 1, entries 16 and 17). Using a borosilicate glass jacketed immersion well in the photochemical reactor led to a slower rate of conversion but increased the yield. After 7 days of reaction at 0 °C, **3** was obtained in a 70% yield. In addition, under these conditions of longer wavelength irradiation it was possible to carry out the reaction at room temperature with only a small decrease in the yield (63%) after the same reaction time.

2.5. Alternate substrate

A suspension of 2-aminoimidazole sulfate (**4**) was treated with the $NOBF_4$ and irradiated at 0 °C overnight using a quartz jacketed immersion well to afford 2-fluoroimidazole **5** (Table 1, entry 18). Due the reactivity of 2-fluoroimidazole [19], it was isolated as imidazole cyclic trimer **6** that corresponded to a yield of **5** of 56% (Scheme 2). In an attempt to improve the solubility of the sulfate in [bmim][BF_4], a small amount of water was added, but this resulted in a lower yield.



Scheme 2. Diazotization-photochemical fluorodediazoniation reaction of **4** in [bmim][BF_4].

3. Discussion

The use of ionic liquids in the photochemical fluorodediazoniation of diazonium salt **2** has been examined as a strategy to increase the yield of fluoroimidazole **3** by eliminating side reactions related to competing reactions with protic solvents. We found that temperature control is critical and that the reaction must be carried out below 0 °C if a quartz well is used, otherwise, photodecomposition of the ionic liquid increases and the yield of product decreases. The photodecomposition of the ionic liquid can be reduced using a borosilicate well but this necessitates an increase in reaction time. This increase in reaction time does not affect the yield.

One of the major advantages of ionic liquids is that they can be easily recycled. However, recent studies have shown that imidazolium-based ionic liquids suffer degradation by UV-light and the degree of degradability is dependent on the nature of *n*-alkyl chain [20]. This degradation increases with the duration of irradiation [11a] and is enhanced by the presence of reactive species [20].

The presence of BF_3 and HF in the reaction could produce new species similar to those observed in *N*-methylimidazole treated with HCl or CF_3COOH [15] that could absorb incident photons. These new species could interfere in the photochemical reaction and favor the photodecomposition of the ionic liquid especially with temperatures over 0 °C. Even at 0 °C the absorbance of [bmim][BF_4] before and after the

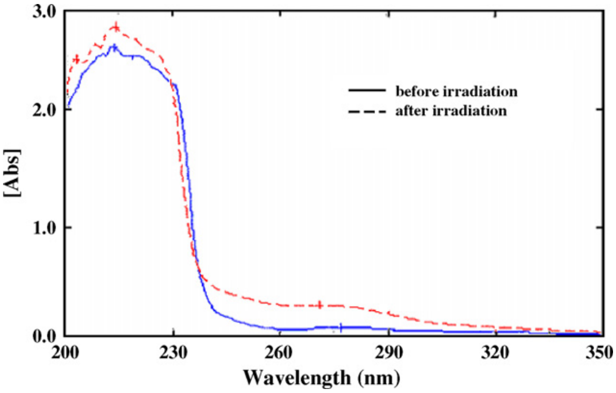


Fig. 1. Absorbance of [bmim][BF_4]: (a) before and (b) after irradiation.

reaction (Fig. 1) show the same pattern observed in the photodecomposition of 1-ethyl-3-methylimidazolium bis(perfluoroethylsulfonyl) imide ([emim][beti]) and [bmim][PF_6] [11a].

The presence of impurities in the ionic liquids clearly could affect the rate and product formation in our photochemical procedure, for instance by interfering with light transmission in the solution. It is interesting that competition between impurities and ionic liquid for photon absorption has been cited as a protective factor that enhances the stability of the solvent during irradiation [11a]. We have not investigated these factors in our own work.

4. Conclusion

The photochemical Schiemann reaction in ionic liquid leads to a somewhat improved yield compared to the reaction done in aqueous HBF_4. On the other hand, technical problems related to viscosity at low temperatures suggest that the increased yield may not outweigh other disadvantages.

5. Experimental

5.1. General

All the reagents were from Aldrich and used without further purification. NMR spectra were run in $CDCl_3$ on a Varian Gemini 300 MHz spectrometer. Mass spectra were determined using a Jeol SX-102 instrument. The temperature was controlled with a Neslab CC100 cooling machine. All the reaction were made in a micro photochemical reactor using a jacketed immersion well, in either quartz or borosilicate glass and a quartz Pen-Ray 5.5 W, low pressure, cold cathode, mercury lamp.

5.2. 5-Fluoro-1H-imidazole-4-carboxylic acid ethyl ester (3)

To a solution of 226.8 mg of 5-amino-1*H*-imidazole-4-carboxylic acid ethyl ester (**1**) (1.46 mmol) in 2.0 mL of [bmim][BF_4] at 0 °C was added slowly a cooled suspension of 255.2 mg of $NOBF_4$ (2.18 mmol) in 1.0 mL of [bmim][BF_4] while N_2 was bubbled into the solution. Additional [bmim][BF_4] (1.0 mL) was used to transfer all the $NOBF_4$ into the reactor. After 90 min, the reaction mixture was irradiated using the quartz (overnight) or borosilicate glass (7 days) jacketed immersion well. Water (10 mL) was added and the solution was extracted with ether. The organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by column chromatography (KP-Sil column, 20–50% EtOAc in Hexane, UV 235–245 nm) to afford 142.9 mg, 62% (quartz) and 153.9 mg, 70% (borosilicate glass) of 5-fluoro-1*H*-imidazole-4-carboxylic acid ethyl ester (**3**) as a white solid. The ^1H NMR and MS were in complete agreement with the data reported in the literature [2a]. Traces of 5-diazoimidazole-4-carboxylic acid ethyl ester also were found (see results).

5.3. Imidazole Cyclic Trimer (6)

To a solution of 308.9 mg of 2-aminoimidazole sulfate 98% (**4**) (194.3 mg, 2.29 mmol) in 2.0 mL of [bmim][BF_4] at 0 °C was added slowly a cooled suspension of 399.9 mg of $NOBF_4$ (3.42 mmol) in 1.0 mL of [bmim][BF_4] while N_2 was bubbled into the solution. Additional [bmim][BF_4] (1.0 mL) was used to transfer all the $NOBF_4$ into the reactor. After 90 min, the reaction mixture was irradiated overnight using the quartz jacketed immersion well. Water (10 mL) was added and the solution was extracted with ether. The organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was heated to complete conversion of 2-fluoro-1H-imidazole (**5**) to trimer **6** and then purified by column chromatography (KP-Sil column, 20–50% MeOH in CH_2Cl_2, UV 220–245 nm) to afford 85.1 mg of imidazole cyclic trimer **6** that corresponds to 110.9 mg, 56% of 2-fluoro-1*H*-imidazole (**5**). The ^1H NMR and MS were in complete agreement with the data reported in literature [19].

Acknowledgement

This work was supported by the intramural research program of NIDDK, NIH.

References

[1] G. Balz, G. Schiemann, Chem. Ber. 60 (1927) 1186.

[2] (a) K.L. Kirk, L.A. Cohen, J. Am. Chem. Soc. 93 (1971) 3060–3061;
(b) K.L. Kirk, L.A. Cohen, J. Am. Chem. Soc. 95 (1973) 4619–4624;
(c) K.L. Kirk, W. Nagai, L.A. Cohen, J. Am. Chem. Soc. 95 (1973) 8389–8392.

[3] B. Langlois, in: B. Baasner, H. Hagemann, J.C. Tatlow (Eds.), Methods of Organic Chemistry (Houben-Weyl). Organo-Fluorine Compounds, vol. 10a, Thieme, Stuttgart, 2000, pp. 686–740.

[4] K.L. Kirk, L.A. Cohen, in: R. Filler (Ed.), Biochemistry of the Carbon-Fluorine Bond, ACS Symposium Series, 1976, 23–36.

[5] (a) A. Milanesi, M. Farnoni, A. Albini, J. Org. Chem. 70 (2005) 603–610;
(b) P.S.J. Canning, K. McCrudden, H. Maskill, B. Sexton, J. Chem. Soc., Perkin Trans. 2 (1999) 2735–2740.

[6] K.L. Kirk, J. Org. Chem. 41 (1976) 2373–2376.

[7] M. Alvaro, E. Carbonell, B. Ferrer, H. García, J. Herance, J. Photochem. Photobiol. 82 (2006) 185–190.

[8] A.J. Carmichael, K.R. Seddon, J. Phys. Org. Chem. 13 (2000) 591–595.

[9] (a) S. Marquis, B. Ferrer, M. Alvaro, H. García, H. Roth, J. Phys. Chem. B 110 (2006) 14956–14960;
(b) M. Alvaro, B. Ferrer, H. García, M. Narayana, Chem. Phys. Lett. 362 (2002) 435–440;
(c) C.M. Gordon, A.J. McLean, Chem. Commun. (2000) 1395–1396;
(d) C. Lee, T. Winston, A. Unni, R.M. Pagni, G. Mamantov, J. Am. Chem. Soc. 118 (1996) 4919–4924.

[10] A. Marcinek, J. Zielonka, J. Gębicki, C.M. Gordon, I.R. Dunkin, J. Phys. Chem. A 105 (2001) 9305–9309.

[11] (a) Q. Yang, D.D. Dionysiou, J. Photochem. Photobiol. A: Chem. 165 (2004) 229–240;
(b) Q. Yang, D.D. Dionysiou, in: R.D. Rogers, K.R. Seddon (Eds.), Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities, ACS Symposium Series 902, American Chemical Society, Washington, DC, 2005, pp. 182–198.

[12] G. Hondrogiannis, C.W. Lee, R.M. Pagni, G. Mamantov, J. Am. Chem. Soc. 113 (1993) 9828–9829.

[13] (a) S.C. Hubbard, P.B. Jones, Tetrahedron 61 (2005) 7425–7430;
(b) J. Ding, V. Desikan, X. Han, T.L. Xiao, R. Ding, W.S. Jenks, D.W.

Armstrong, Org. Lett. 7 (2005) 335–337;
(c) R. Ozawa, H. Hamaguchi, Chem. Lett. 30 (2001), 736-736.
[14] J.L. Reynolds, K.R. Erdner, P.B. Jones, Org. Lett. 4 (2002) 917–919.
[15] A. Paul, P.K. Mandal, A. Samanta, Chem. Phys. Lett. 402 (2005) 375–379.
[16] K.K. Laali, V.J. Gettwert, J. Fluorine Chem. 107 (2001) 31–34.
[17] A.G. Glenn, P.B. Jones, Tetrahedron Lett. 45 (2004) 6967–6969.
[18] C.B. Murray, G. Sandford, S.R. Korn, J. Fluorine Chem. 123 (2003) 81–84.
[19] Y. Takeuchi, K.L. Kirk, L.A. Cohen, J. Org. Chem. 44 (1979) 4243–4246.
[20] P. Stepnowski, A. Zaleska, J. Photochem. Photobiol. A: Chem. 170 (2005) 45–50.