IONIC LIQUIDS AS MEDIA FOR NUCLEOPHILIC RING OPENING FLUORINATION OF AZIRIDINES

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Abstract: We have developed an efficient methodology for nucleophilic ring opening fluorination of aziridines by $KF{\cdot}2H_2O$ or KHF_2 in an ionic liquid without any external sources, which resulted in a convenient route to β-fluoro amines. The ionic liquid acts not only as a solvent but also as a phase transfer catalyst in the reaction.

Keywords: fluorination, fluorine, aziridine, ionic liquid, β-fluoro amine

Introduction

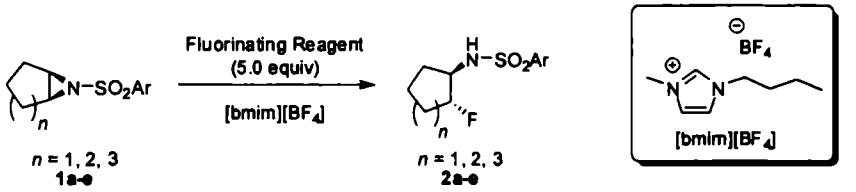
There is enormous interest in the development of efficient synthetic approaches to fluoro-organic compounds, particularly those which hold chiral C-F units in their structures [1,2]. As part of our research program for the stereoselective synthesis of fluoro-organic compounds [3-17], we have an interest in developing a simple and effective method for nucleophilic ring opening fluorination of aziridines. Aziridines can be utilized as important building blocks for the synthesis of biologically active amine derivatives, such as amino acids, β-lactam antibiotics and alkaloids, and considerable efforts have been made to open aziridine rings by nucleophlic substitution reaction [18-23]. A ring opening reaction of aziridines by fluoride anion is one of the most straightforward ways to access β-fluoro amines [24-33]. There are many methods available for the nucleophilic ring opening fluorination of aziridines, using hydrogen fluoride, hydrogen fluoride-pyridine, and diethylaminosulfur trifluoride [24-33]; however, practical and convenient methods are quite restricted. In 2004, Hou and co-workers reported that a potassium fluoride with tetrabutylammonium bisulfate in THF is quite an effective reagent system for conversion from aziridines to β-fluoro amines in high yields [34]. They also reported another procedure on the preparation of β-fluoro amines by the ring-opening reaction of aziridines using $BF_3{\cdot}Et_2O$ in CH_2Cl_2 [35]. Although both methods take place under mild conditions, more environmentally benign procedures are truly required.

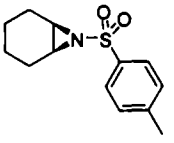
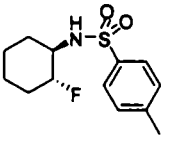
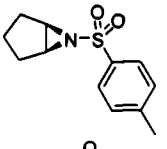
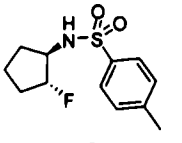
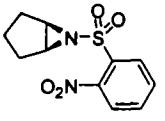
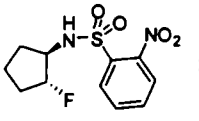
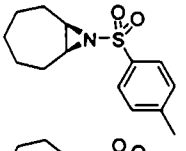
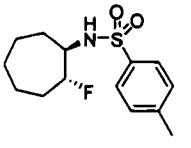
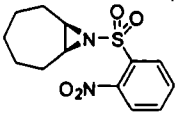
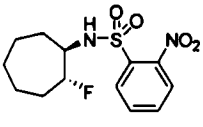
Incidentally, organic reactions in ionic liquids are becoming more and more important because of their great potential in environmentally benign organic synthesis [36-41]. The advantages of using ionic liquids as reaction media are not only from a green

chemistry point of view, but also from their rate-enhancement effects of the chemical reactions owing to their high polarity and the ability to solubilize both organic and inorganic compounds [36-41]. In the area of fluorine chemistry, many kinds of nucleophilic fluorination in ionic liquids have been developed [42-47] including ring opening reaction of epoxides [48,49], however, few nucleophilic fluorination reactions of aziridines in ionic liquids have been reported, except for one study by Kroutil and Jenistova in 2005 [50]. They revealed that the nucleophilic ring opening of *N*-nosylaziridines with fluoride anion was successfully achieved by the use of a mixed nucleophile system in an ionic liquid, *N*-methylpyridinium tosylate. In this method, KHF_2 was used as the main nucleophile and difluorostannate complex, and $Bu_4N[Ph_3SnF_2]$ as the co-nucleophile. However, it required preparation of the difluorostannate complex in advance. In this paper, we disclose our preliminary results of a simple and efficient protocol for the preparation of β-fluoro amines by the nucleophilic ring opening fluorination of aziridines. In ionic liquid, aziridines are efficiently opened by $KF{\cdot}2H_2O$ or KHF_2 without any externals in good to high yields.

Results and Discussion

Table 1: Nucleophilic Ring Opening Fluorination of Aziridines in an Ionic Liquid.[1)]



Entry	Substarate	(1)	Fluorinating Reagent	Temp. (°C)	Time (h)	Product	(2)	Yield (%)
1		1a	KF	60	24		2a	53
2			$KF{\cdot}2H_2O$	40	24			96
3		1b	$KF{\cdot}2H_2O$	80	24		2b	18
4			KHF_2	80	24			59
5		1c	$KF{\cdot}2H_2O$	60	2		2c	85
6		1d	$KF{\cdot}2H_2O$	80	24		2d	N.R.
7			KHF_2 ii)	80	120			52
8		1e	$KF{\cdot}2H_2O$	60	2		2e	70

i) A substrate concentration range of 0.2-0.4 M was used in the reaction.
ii) KHF_2 (10 equiv) was used.

We first attempted the ring opening fluorination of cyclohexyl *N*-tosylaziridine (**1a**) (Table 1). The **1a** was treated with KF as a fluorinating reagent took place at 60 °C in ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4). The yield of cyclohexyl fluoro amine derivative **2a** was moderate, 53% (Table 1, entry 1). Ring opening fluorination of **1a** smoothly proceeded at 40 °C when $KF{\cdot}2H_2O$ was used instead of KF to afford the corresponding **2a** in an excellent yield of 96% (entry 2). In the case of cyclopentyl *N*-tosylaziridine **1b**, however, only 18% of product **2b** was obtained under these conditions (entry 3). The low yield of **2b** was partially improved to 59% by the use of KHF_2 as a fluorinating reagent (entry 4). By comparison to the reaction of **1a** and **1b**, the aziridine with a seven membered-ring, **1d**, required drastic conditions. The reaction of **1d** did not start at all under the $KF{\cdot}2H_2O$ condition at

80 °C for 1 day, and the use of an excess amount of KHF_2 under 80 °C for 5 days provided the corresponding β-fluoro amino compound **2d** in 52% yield (entries 6 and 7). Since it is known that the reactivity of the aziridines towards nucleophiles is significantly influenced by the electronic nature of the aromatic substituent of nitrogen [51], the 2-nitrobenzensulfonyl (nosyl) protecting group in aziridines **1c** and **1e** were selected as aryl groups in the next experiments. The reactivity of the aziridines should be improved resulting from the strong electron withdrawing nature of the nitro group on the benzene ring. A nosyl group is also useful as a sulfur-assisted removable protecting group [52-54]. We were particularly pleased to find that both the five- and seven-membered aziridines **1c** and **1e** gave high yields of the ring opening fluorination adducts **2c** and **2e** in high yields by use of $KF{\cdot}2H_2O$ at 60 °C for 2 days (entries 5 and 8). The *trans* configuration of compound **2a** was assigned on the basis of the H_1 and H_2 ($J_{H1,H2}$ = 9.2 Hz) values of the ^1H NMR coupling constant, compared with known compounds [34, 35, 55]. The fact that $J_{H1,F}$ is too small to be detected whereas the other two vicinal coupling constants ($J_{H1,H2}$, $J_{H2,H3}$) both amount to 9.2 Hz indicates that the two protons H_1 and H_2 occupy diaxial positions and that fluorine and the *N*-tosyl group are equatorial (Figure 1). The corresponding *cis* isomer was not detected. The *trans* configuration of other compounds was tentatively assigned by the similarity of the reaction mechanism. These results indicate that the *trans* isomer **2** should be accounted for via a S_N2 backside attack by the fluoride ion.

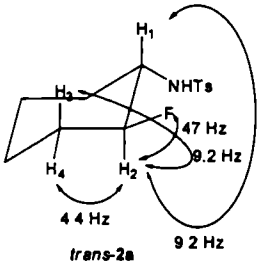


Figure 1: ^1H NMR coupling constants of *trans*-**2a**.

Conclusion

In summary, we describe an efficient method for the synthesis of β-fluoro amines by stereoselective ring opening of aziridines with $KF{\cdot}2H_2O$ or KHF_2 in an ionic liquid as reaction media without any additives. The ionic liquid acts not only as a solvent but also presumably as a phase transfer catalyst. The mild reaction conditions, simplicity in operation and recyclability of ionic liquids make it a useful process for the synthesis of β-fluoro amines.

Experimental

General

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Solvents were transferred *via* syringe and were introduced into the reaction vessels through a rubber septum. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or *p*-anisaldehyde in ethanol/ heat. Column chromatography was carried out on a column packed with silica gel 60N spherical neutral size 63-210 μm. The ^{1}H NMR (200 MHz) and ^{19}F NMR (188 MHz) spectra for solution in $CDCl_3$, were recorded on a Varian Gemini-200. ^{13}C NMR (150.9 MHz) spectra were recorded on a BRUKER 600 UltraShield^{TR}. Chemical shifts (δ) are expressed in ppm downfield from internal TMS or $CHCl_3$. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A (EI-MS). Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer.

Synthesis

General Procedure for Ring-Opening Reaction of Aziridines with KF·2H$_2$O in [bmim]BF$_4$; *N*-(2-Fluorocyclohexyl)-4-methylbenzenesulfonamide (2a):

To a stirred solution of aziridine **1a** (50 mg, 0.199 mmol) in [bmim][BF_4] (1.0 mL, 0.2 M) was added KF·2H_2O (94 mg, 0.995 mmol, 5.0 equiv), and the resulting mixture was stirred at 40 °C for 1 day. Water was added into the reaction mixture and the mixture was extracted by AcOEt (3 mL×3). The combined organic phase was washed with brine, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (benzene:AcOEt=9:1) to give product **2a** (51.6 mg, 96%) as a white solid.

mp 95-97 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19-1.74 (m, 6H), 1.94-2.06 (m, 2H), 2.41 (s, 3H), 3.15-3.22 (m, 1H), 4.08 and 4.32 (double multiplet, $^{2}J_{H\text{-}F}$ = 48.0 Hz, 1H), 5.20 (d, J = 6.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H). 7.77 (d, J = 8.0 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$) δ –177.1 (double multiplet, $^{2}J_{H\text{-}F}$ = 48.0 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 143.67, 137.93, 129.91, 127.47, 93.28 (d, J = 179 Hz), 56.79 (d, J = 19.5 Hz), 31.54, 30.92 (d, J = 17.5 Hz), 23.65, 23.06 (d, J = 9.7 Hz), 21.87; IR (KBr) 3304, 2951, 1598, 1496 cm^{-1}; EI-MS *m/z* 271 (M^+).

N-(2-Fluorocyclopentyl)-4-methylbenzenesulfonamide (2b):

The reaction of **1b** (50 mg, 0.212 mmol) with KHF_2 (82.3 mg, 1.06 mmol, 5.0 equiv) in [bmim][BF_4] (0.53 mL, 0.4 M) gave **2b** (32.4 mg, 59%) as a pale yellow solid.

mp 75-77 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33-1.46 (m, 1H), 1.58-2.12 (m, 5H), 2.44 (s, 3H), 3.53-3.67 (m, 1H), 4.73 and 5.00 (double multiplet, $^{2}J_{H\text{-}F}$ = 54.0 Hz, 1H),

5.07 (d, J = 6.0 Hz) 7.31 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 7.8 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$) δ-175.9 (double multiplet, $^2J_{H\text{-}F}$ = 54.0 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 144.11, 137.22, 130.17, 127.59, 98.85 (d, J = 179 Hz), 60.0 (d, J = 27.8 Hz), 31.32, 30.73 (d, J = 20.4 Hz), 21.91, 21.34; IR (KBr) 3265, 3029, 1597, 1326 cm^{-1}; EI-MS m/z 257 (M+).

N-(2-Fluorocyclopentyl)-2-nitrobenzenesulfonamide (2c):

The reaction of **1c** (52 mg, 0.193 mmol) with $KF{\cdot}2H_2O$ (88.3 mg, 0.938 mmol, 5.0 equiv) in [bmim][BF_4] (0.48 mL, 0.4 M) gave **2c** (47.3 mg, 85%) as a pale yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42-1.55 (m, 1H), 1.66-2.15 (m, 5H), 3.75-3.87 (m, 1H), 4.78 and 5.03 (double multiplet, $^2J_{H\text{-}F}$ = 50.0 Hz, 1H), 5.31 (d, J = 5.8 Hz, 1H), 7.70-7.80 (m, 2H), 7.82-7.88 (m, 1H), 8.15-8.20 (m, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ –174.8 (double multiplet, $^2J_{H\text{-}F}$ = 50.0 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 148.32, 134.17, 133.98, 133.31, 131.82, 125.81, 98.92 (d, J = 180 Hz), 60.69 (d, J = 27.9 Hz), 31.12 (d, J = 2.1 Hz), 30.66 (d, J = 21.7 Hz), 21.25; IR (KBr) 3301, 2965, 1541, 1366 cm^{-1}; EI-MS m/z 288 (M^+).

N-(2-Fluorocycloheptyl)-4-methylbenzenesulfonamide (2d):

The reaction of **1d** (50 mg, 0.188 mmol) with KHF_2 (148 mg, 1.88 mmol, 10.0 equiv) in [bmim][BF_4] (0.47 mL, 0.4 M) gave **2d** (27.9 mg, 52%) as a pale yellow solid.

mp 64-66 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25-2.04 (m, 10H), 2.42 (s, 3H), 3.32-3.36 (m, 1H), 4.24 and 4.48 (double multiplet, $^2J_{H\text{-}F}$ = 48.0 Hz, 1H), 4.99 (d, J = 6.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$) δ –168.5 (double multiplet, $^2J_{H\text{-}F}$ = 48.0 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 143.71, 137.73, 129.93, 127.53, 96.60 (d, J = 174 Hz), 59.49 (d, J = 21.7 Hz), 31.35 (d, J = 21.0 Hz), 30.56 (d, J = 6.8 Hz), 27.85, 23.70, 21.88, 21.30 (d, J = 8.3 Hz); IR (KBr) 3265, 3066, 2937, 1898 cm^{-1}; EI-MS m/z 285 (M^+).

N-(2-Fluorocycloheptyl)-2-nitrobenzenesulfonamide (2e):

The reaction of **1e** (50 mg, 0.169 mmol) with $KF{\cdot}2H_2O$ (79.3 mg, 0.842 mmol, 5.0 equiv) in [bmim][BF_4] (0.42 mL, 0.4 M) gave **2e** (37.2 mg, 70%) as a pale yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26-2.04 (m, 10H), 3.52-3.69 (m, 1H), 4.26 and 4.49 (double multiplet, $^2J_{H\text{-}F}$ = 46 Hz, 1H), 5.59 (d, J = 7.4 Hz, 1H), 7.66-7.77 (m, 2H), 7.84-7.90 (m, 1H), 8.12-8.16 (m, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ –166.1 (double multiplet, $^2J_{H\text{-}F}$ = 48.0 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 147.98, 135.10, 133.61, 133.18, 131.27, 125.74, 97.17 (d, J = 175 Hz), 60.69 (d, J = 22.0 Hz), 31.52 (d, J =

7.8 Hz), 30.41 (d, J = 21.0 Hz), 27.70, 23.95, 21.28 (d, J = 8.5 Hz); IR (KBr) 3350, 2937, 1530, 1159 cm^{-1}; EI-MS m/z 316 (M^+).

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