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ScienceDirect
Journal of Fluorine Chemistry 129 (2008) 217–221
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Fluorination of activated aromatic systems with Selectfluor™ F-TEDA-BF_4 in ionic liquids

Mohammad Reza Poor Heravi *

Chemistry Department, Payame Noor University, P.O. Box 97, Ahar, Iran

Received 21 October 2007; received in revised form 8 November 2007; accepted 14 November 2007
Available online 22 November 2007

Abstract

Selectfluor™ was shown to be soluble in ionic liquid, thus allowing the 'green' electrophilic fluorination of activated aromatic systems compounds in high chemoselectivity and yields.

Keywords: Fluorination; Ionic liquids; Activated aromatic systems; Selectfluor™

1. Introduction

The replacement of toxic organic solvents is one of the most important issues in green chemistry [1–3]. Their use in organic synthesis inevitably leads to solvent emission and/or waste. Especially, fluorination reactions have been recognized as being useful in organic synthesis, their reactions commonly employed organic solvents (such as DMF, CH_3CN, DMSO, etc.), and in many cases they are removed from the final reaction mixture by a water quench which leads to an aqueous waste stream [4]. Recently, studies of reusable media such as fluorous fluid [5] and ionic liquids [6–10] are having an important impact on organic reactions. Synthesis of mono and *gem*-difluorinated molecules using [C_8mim][PF6] ionic liquid as a recyclable solvent medium with diethylaminosulfur trifluoride (DAST) as the fluorinating reagent, is reported [11]. In the fluorine chemistry, replacements of safety handling are one of the most important issues.

In this paper, we would like to describe the utility of ionic liquids as a solvent for fluorination in good yields without the need for conventional aqueous work-up procedures.

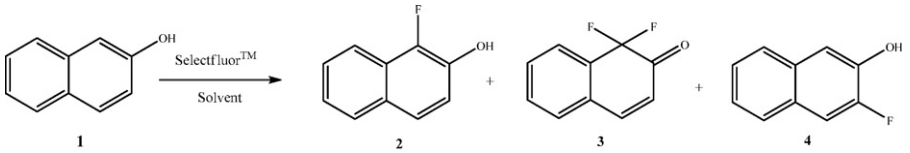
2. Results and discussion

Fluorinated activated aromatic systems such as β-naphtol is targets of important in the field of organofluorine compounds. 1,1-Difluoronaphthalen-2(1H)-one **3** are especially interesting as synthetic intermediates and tools for elucidating biological processes. In this context, a recent report described the access to the target compounds via a direct fluorination of β-naphtol **1** by means of commercially available Selectfluor™ in acetonitrile (Scheme 1) [12]. The method gave fairly good results (yields **2**, 55%, **3**, 22% and **4**, 12% with 1.1 eq Selectfluor™ and yields **2**, 19%, **3**, 68%, **4**, 10% with 2.1 eq Selectfluor™ for fluorination **1**.

In connection with our studies on electrophilic chemoselective fluorination, we now report the fluorination of β-naphtol **1** in various conditions including the use of ionic liquids as solvents. Ionic liquids present many advantages in the green chemistry context and we assumed that they could be powerful solvents for electrophilic fluorination since Selectfluor™ is a charged compound. Ionic liquids as solvents are much polar than classical organic solvents such as acetonitrile. So, 2-naphtol much better can tautomerise to keto form in ionic liquids. In conclusion, we will have a high regioselectivity in the fluorination of 2-naphtol in ionic liquids as compared with low regioselectivity in acetonitrile. Our results are reported in Table 1. Interestingly, very high conversions were observed. The reaction in ionic liquid minimises the protonated β-naphtol **1**. When using methanol or ethanol as cosolvent. Thus, both

* Tel.: +98 242522 4021; fax: +98 242522 6932.
E-mail address: heravimr@yahoo.com.

0022-1139/$ – see front matter
doi:10.1016/j.jfluchem.2007.11.006



Scheme 1.

Table 1
Electrophilic fluorination β-naphtol **1** in ionic liquids

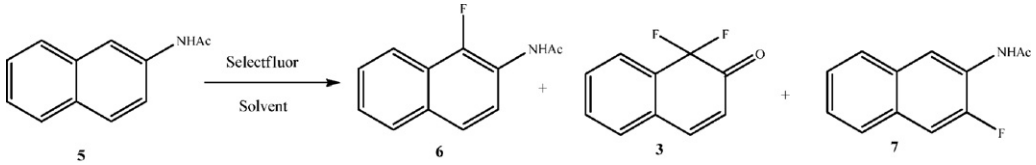
Selectfluor™ (eq)	Solvent	Cosolvent (1/1)	*T* (°C)	Time (h)	Yield **2** (%)[a]	Yield **3** (%)[a]	Yield **4** (%)[a]
1.1	Acetonitrile[b]	–	rt	6	55	22	12
1.1	[bmim][PF_6]	MeOH	20	1	97	2	1
1.1	[bmim][BF_4]	MeOH	20	1	98	2	0
1.1	[bmim][PF_6]	EtOH	20	3	98	2	0
1.1	[bmim][BF_4]	EtOH	20	3	94	3	1
2.1	Acetonitrile[b]	–	rt	7	19	68	10
2.1	[bmim][PF_6]	MeOH	20	1	1	98	1
2.1	[bmim][BF_4]	MeOH	20	1	1	99	0
2.1	[bmim][PF_6]	EtOH	20	3	2	98	0
2.1	[bmim][BF_4]	EtOH	20	3	2	97	1

[a] Isolated yield.
[b] Data taken from Ref. [12].

chemoselectivity and yield appear to be highly increased when using ionic liquid as solvent (Scheme 1, Table 1).

N-(Naphthalen-2-yl)acetamide **5** showed similar behaviour with Selectfluor™ (1.1 eq) in ionic liquids, forming predominantly *N*-(1-fluoronaphthalen-2-yl)acetamide **6** and lesser amounts of 1,1-difluoronaphthalen-2(1H)-one **3** and *N*-(3-fluoronaphthalen-2-yl)acetamide **7**, and fluorination with Selectfluor™ (2.1 eq) in ion liquids, forming predominantly 1,1-difluoronaphthalen-2(1H)-one **3,** lesser amounts of *N*-(3-fluoronaphthalen-2-yl)acetamide **7** and *N*-(1-fluoronaphthalen-2-yl)acetamide **6**. The method gave fairly good results using the best ionic liquid [bmim][PF_6] with EtOH as cosolvent (1/1) (yields **6**, 97%, **3**, 2% and **7**, 0% with 1.1 eq Selectfluor™ and yields **6**, 2%, **3**, 98%, **7**, 0% with 2.1 eq Selectfluor™ for fluorination **5** (Scheme 2, Table 2).

13-Methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthrene-3,17-diol **8** reacted with Selectfluor™ (1.1 eq) in ionic liquids to give 2-fluoro-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthrene-3,17-diol **9** and 4-fluoro-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthrene-3,17-diol **10**. Using ionic liquid [bmim][BF_4] with MeOH as cosolvent (1/1) yields **9**, 88%, **10**, 11% with 1.1 eq Selectfluor™**.** Compound **9** is produced in higher yield from

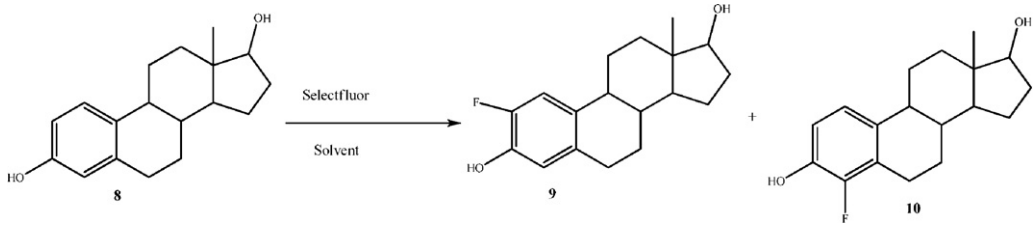


Scheme 2.

Table 2
Electrophilic fluorination *N*-(naphthalen-2-yl)acetamide **5** in ionic liquids

Selectfluor™ (eq)	Solvent	Cosolvent (1/1)	*T* (°C)	Time (h)	Yield **6** (%)[a]	Yield **3** (%)[a]	Yield **7** (%)[a]
1.1	[bmim][PF_6]	MeOH	20	1	97	2	1
1.1	[bmim][BF_4]	MeOH	20	1	96	2.5	1.5
1.1	[bmim][PF_6]	EtOH	20	2	98	2	0
1.1	[bmim][BF_4]	EtOH	20	2	96	3	1
2.1	[bmim][PF_6]	MeOH	20	1	3	96	1
2.1	[bmim][BF_4]	MeOH	20	1	3	95	2
2.1	[bmim][PF_6]	EtOH	20	2	2	97	1
2.1	[bmim][BF_4]	EtOH	20	2	2	98	0

[a] Isolated yield.



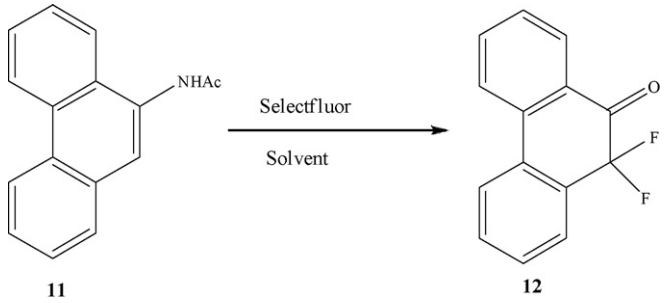
8 9 10

Scheme 3.

Table 3
Electrophilic fluorination 13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthrene-3,17-diol **8** in ionic liquids

Selectfluor™ (eq)	Solvent	Cosolvent (1/1)	*T* (°C)	Time (h)	Yield **9** (%)[a]	Yield **10** (%)[a]
1.1	[bmim][PF_6]	MeOH	20	0.5	87	11
1.1	[bmim][BF_4]	MeOH	20	0.5	88	11
1.1	[bmim][PF_6]	EtOH	20	1	82	12
1.1	[bmim][BF_4]	EtOH	20	1	86	10

[a] Isolated yield.



11 12

Scheme 4.

the reaction of **8** with Selectflour™, Both fluorinated isomers **9**, **10** were useful in the study of cancer therapy with estrogens [15–17] (Scheme 3, Table 3).

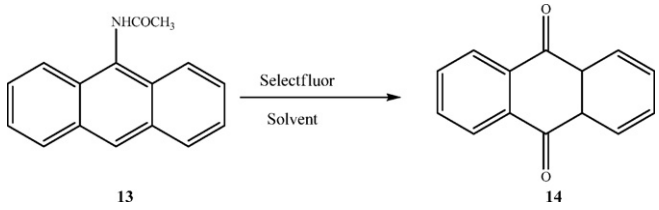
N-(Phenanthren-9-yl)acetamide **11** fluorinated with Selectflour™ in ionic liquids and produced 10,10-difluorophenanthren-9(10H)-one **12** as main product. Using ionic liquid [bmim][PF_6] with MeOH as cosolvent (1/1) in optimization condition, yield 69%, **12** at 5 h with 1.1 eq Selectfluor™ (Scheme 4, Table 4).

N-(Anthracen-9-yl)acetamide **13** is not fluorinated with Selectflour™ in ionic liquids; instead cause oxidation to produce anthracene-9,10-dione **14**. Using ionic liquid [bmim][PF_6] with MeOH as cosolvent (1/1) yields in optimization condition, yield 96%, **14** at 0.5 h with 1.1 eq Selectfluor™ (Scheme 5, Table 5).

Table 4
Electrophilic fluorination *N*-(phenanthren-9-yl)acetamide **11** in ionic liquids

Selectfluor™ (eq)	Solvent	Cosolvent (1/1)	*T* (°C)	Time (h)	Yield **12**(%)[a]
1.1	[bmim][PF_6]	MeOH	30	5	69
1.1	[bmim][BF_4]	MeOH	30	5	67
1.1	[bmim][PF_6]	EtOH	30	6	65
1.1	[bmim][BF_4]	EtOH	30	6	65

[a] Isolated yield.



13 14

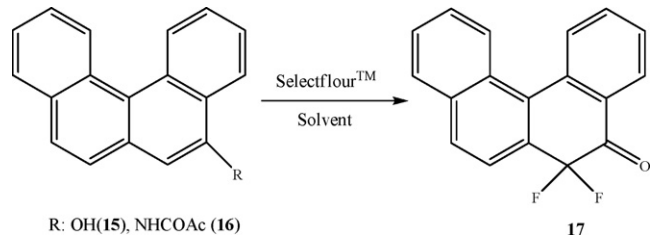
Scheme 5.

Table 5
Electrophilic fluorination *N*-(anthracen-9-yl)acetamide **13** in ionic liquids

Selectfluor™ (eq)	Solvent	Cosolvent (1/1)	*T* (°C)	Time (h)	Yield **14** (%)[a]
1.1	[bmim][PF_6]	MeOH	30	0.5	96
1.1	[bmim][BF_4]	MeOH	30	0.5	97
1.1	[bmim][PF_6]	EtOH	30	0.5	91
1.1	[bmim][BF_4]	EtOH	30	0.5	92

[a] Isolated yield.

N-(Benzo[*c*]phenanthren-5-yl)acetamide **15** and benzo[*c*]-phenanthren-5-ol **16** react with Selectflour™ in ionic liquids to give the 6,6-difluorobenzo[*c*]phenanthren-5(6H)-one **17**. Using ionic liquid [bmim][PF_6] with MeOH as cosolvent (1/1) in optimization condition, yields 56% and 67%, **17** at 8, 7 h with 1.1 eq Selectfluor™ (Scheme 6, Table 6).



R: OH(**15**), NHCOAc (**16**) **17**

Scheme 6.

Table 6
Electrophilic fluorination *N*-(benzo[*c*]phenanthren-5-yl)acetamide **15** and benzo[*c*]phenanthren-5-ol **17** in ionic liquids

Substrate	Selectfluor™ (eq)	Solvent	Cosolvent (1/1)	*T* (°C)	Time (h)	Yield **17** (%)[a]
16, 17	1.1	[bmim][PF_6]	MeOH	40	8, 7	56, 67
16, 17	1.1	[bmim][BF_4]	MeOH	40	8, 7	53, 58
16, 17	1.1	[bmim][PF_6]	EtOH	40	9, 11	51, 56
16, 17	1.1	[bmim][BF_4]	EtOH	40	10, 13	52, 54

[a] Isolated yield.

3. Experimental

3.1. General

All commercially available reagents were without further purification. Chemical shifts of ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using Bruker DRX500 machine at room temperature in ppm (δ) and spectra were measured using deuterochloroform as solvent using residual solvent as an internal standard and $CFCl_3$ as an internal standard for ^{19}F NMR. Mass spectra were obtained using a Micro mass LCT machine in ES or EI mode. Infra-red spectra were measured on a PerkinElmer Paragon100 FT-IR spectrophotometer. Melting point was determined using a Liukam HF591 heating stage, used in conjunction with a TC92 controller and are uncorrected. All reaction solvents used were HPLC grade or distilled; petroleum ether refers to the fraction which boils in the range 40–60 °C. TLC plates were visualized by UV light (254 nm).

3.2. 1-Fluoronaphthalen-2-ol (*2*)

A mixture solution of 2-naphtol (**1**) (324 mg, 2 mmol) and Selectfluor™ (365 mg, 1.1 mmol) in mixture of (1/1) [bmim][PF_6] (2 g) and CH_3OH (2 g) was stirred for 1 h at 20 °C. The product was extracted with diethyl ether (10 × 20 ml), and ionic liquid was recovered, and then the organic layer was dried over anhydrous $MgSO_4$, on removal of the solvent. 1-Fluoronaphthalen-2-ol (**2**) was purified by column chromatography on silica gel using a mixture of petroleum ether-ethyl acetate (10:2) as an eluent. mp 71 °C (Ref. [13] mp 71–73 °C), ^{1}H NMR (250 MHz, CDCl3) δ ppm 5.77 (s, 1H), 7.21 (t, *J* = 8.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 9.3 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (63 MHz, CDCl3) δ ppm 94.2, 118.7, 118.8, 124.2, 126.6, 127.5, 129.0, 139.1 (d, *J* = 13.2 Hz), 142.8, 146.7. ^{19}F NMR (235 MHz, CDCl3) δ ppm −144.6 (s, 10 Hz, 6 Hz, 1F). IR (neat, cm^{-1}): 3347, 3121, 1565. HRMS (EI) found: M^+, 162.0277; $C_{10}H_7OF$ requires M^+, 162.0316; LRMS *m/z* (EI): 163 (25% M^+), 162(100%); ES+: MNa^+, 185, MH^+, 186; Elemental analysis: found (%): C, 73.89; H, 4.47; calcd. for $C_{10}H_7OF$: C, 74.07; H, 4.35.

3.3. 1,1-Difluoronaphthalen-2(1H)-one (*3*)

A mixture solution of 2-naphtol (**1**) (324 mg, 2 mmol) and Selectfluor™ (730 mg, 2.1 mmol) in mixture of (1/1) [bmim][PF_6] (2g) and CH_3OH (2 g) was stirred for 1 h at 20 °C. The product was extracted with diethyl ether (10 × 20 ml), and ionic liquid was recovered, and then the organic layer was dried over anhydrous $MgSO_4$, on removal of the solvent. 1-Fluoronaphthalen-2-ol (**3**) was purified by column chromatography on silica gel using a mixture of petroleum ether-ethyl acetate (10:2) as an eluent. mp 50 °C (Ref. [13] mp 53–54 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 6.22 (td, *J* = 10.1, 2.7 Hz, 1H), 7.82 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.53 (dd, *J* = 6.2, 2.6 Hz, 2H), 7.44 (d, *J* = 10.1 Hz, 1H), 7.37 (dd, *J* = 6.4, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 105.5 (t, *J* = 244.7 Hz, 1C), 123.4, 127.7, 129.9, 130.2, 131.0, 132.1, 133.2, 145.6, 187(C=O). ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm −101.51 (s, 1F). IR (neat, cm^{-1}): 3144, 2997, 1688 (C=O), 1572. HRMS (EI) found: M^+, 180.0388; $C_{10}H_6OF_2$ requires M^+, 180.0401; LRMS *m/z* (EI): 180 (25% M^+), 161 (100%); ES+: MNa^+, 203, MH^+, 181; Elemental analysis: found (%): C, 66.50; H, 3.18; calcd. for $C_{10}H_6OF_2$: C, 66.67; H, 3.36.

3.4. N-(1-Fluoronaphthalen-2-yl) acetamide (*6*)

mp 118–120 °C (Ref. [14] mp 120–121 °C); ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −141.7 (s, 1F).

3.5. 2-Fluoro-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (*9*)

mp 174–175 °C (Ref. [15] mp 173–175 °C); ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −138.4 (d, 1F).

3.6. 4-Fluoro-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (*10*)

mp 189–190 °C (Ref. [15] mp 189–191 °C); ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −137.0 (m, 1F).

3.7. 10,10-Difluorophenanthren-9(10H)-one (*12*)

Purification on alumina (benzene), mp 93–94 °C (Ref. [16] mp 100–102 °C), ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −103.6 (S, 2F).

3.8. Anthracene-9,10-dione (*14*)

mp 283–284 °C (authentic sample mp 283–284 °C).

3.9. 6,6-Difluorobenzo[c]phenanthren-5(6H)-one (**17**)

Chromatography on alumina (benzene), mp 93–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.47–8.64 (m, ArH, 10H); ^{13}C NMR (125, $CDCl_3$) δ ppm: 108.5 (t, J = 246 Hz), 121.5, 126.1, 126.7, 128.3, 128.7, 129.5, 130.6, 181.4 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −110.75 (S, 2F). HRMS m/z $[M]^+$; calcd. for $C_{18}H_{10}F_2O$ 280.0754, found: 280.0743. Elemental analysis: found (%): C, 77.31; H, 3.64; calcd. for $C_{18}H_{10}F_2O$: C, 77.14; H, 3.57.

4. Conclusions

In this study, I have demonstrated that modifications of experimental conditions can either improved or modify the electrophilic fluorination of activated aromatic systems. Worth noting are the results obtained in ionic liquids, in which high yields and chemoselectivity were observed. I am hopeful that new useful fluorination in various fields will b born through our fluorination technologies.

Acknowledgements

I thank Payame Noor University, Iran, for financial support and The University of Sheffield, UK, for take of ^{1}H, ^{13}C NMR spectra (special thanks from Prof. R.F.W. Jackson).

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