



Ionic liquids as solvents of choice for electrophilic fluorination: fluorination of indoles by F-TEDA-BF₄

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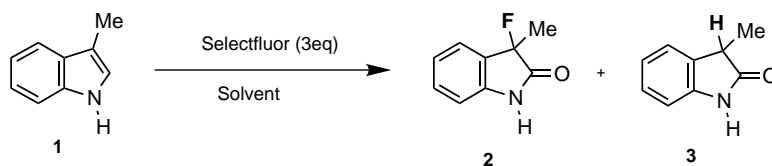
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Abstract—Selectfluor™ was shown to be soluble in ionic liquid, thus allowing the ‘green’ electrophilic fluorination of indole compounds in high chemoselectivity and yields. © 2002 Elsevier Science Ltd. All rights reserved.

Fluorinated five and six-membered heterocycles are targets of importance in the field of organofluorine compounds.¹ 3-Fluorooxindoles are especially interesting as synthetic intermediates and tools for elucidating biological processes. In this context, a recent report from Takeuchi's group described the access to the target compounds via a direct fluorination of several 3-substituted indoles by means of commercially available Selectfluor™ in acetonitrile (Scheme 1).² The method gave fairly good results (yields 71% for fluorination of **1** and in the 64–92% range for other 3-alkyl indoles), although it led to the oxoindole **3** as a side product.

In connection with our studies on electrophilic enantioselective fluorination,³ we now report the fluorination of 3-methyl indole **1** in various conditions including the use of ionic liquids as solvents. Ionic liquids present many advantages in the green chemistry context,⁴ and we assumed that they could be powerful solvents for electrophilic fluorination since Selectfluor™ is a charged compound. A recent report from Laali and Borodkin regarding the electrophilic fluorination of arenes in those solvents prompts us to disclose our own results.⁵ Our main results are reported in Table 1.



Scheme 1.

Table 1. Electrophilic fluorination in ionic liquids

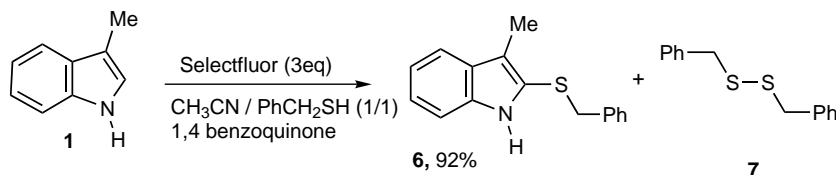
Solvent	Cosolvent (1/1)	T (°C)	Time (h)	2 (%)	3 (%)
Acetonitrile ^a	Water	rt	Overnight	71	Side product
[bmim] [PF ₆]	MeOH	20	3	99	–
[bmim] [BF ₄]	MeOH	20	3	99	–
[bmim] [PF ₆]	EtOH	20	12	88	12
[bmim] [BF ₄]	EtOH	20	12	92	8

^a Data taken from Ref. 2.

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Scheme 2.



Scheme 3.

Interestingly, very high conversions were observed. The reaction in ionic liquid minimizes the protonated oxindole **3**, when using methanol or ethanol as cosolvent. Thus, both chemoselectivity and yield appear to be highly increased when using ionic liquid as solvent. This study, as well as the recent results from Laali and Borodkin,⁵ clearly demonstrates the unique properties of this new class of ‘green’ solvents in the field of electrophilic fluorination. We also realized a set of experiments in which a nucleophilic reagent was added in acetonitrile in order to test the role of this additive in the fluorination process. When applied to *N*-alkylated compounds **4**, the use of 2-propanol led to high transformation into the fluorinated targets **5**, especially for the *N*-methyl substrate (Scheme 2).

Substantially different results were observed in the presence of thiols (Scheme 3).

The reaction stopped at the intermediate **6** in good yield, an observation which supports Takeuchi mechanism,² since **6** is not obtained in the absence of Selectfluor. Indeed, the excess of thiol is oxidized into **7**, thus reducing Selectfluor and preventing the subsequent fluorination of **6**. When using only 2 equiv. of thiol, the fluorinated oxindole **2** is obtained (63%). This part of our work gives an interesting methodology for the access to the sulfur substituted indoles of type **6**.⁶

Conclusion

In this study, we have demonstrated that modifications of experimental conditions can either improve or mod-

ify the electrophilic fluorination of indoles. Worth noting are the results obtained in ionic liquids, in which high yields and chemoselectivity were observed. An interesting access to thio-substituted indoles was also discovered.

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