Regioselective iodination of arenes in ionic liquids mediated by the Selectfluor™ reagent F-TEDA–BF_4

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Dedicated to Professor Domenico Spinelli on his 70th birthday
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Abstract
A variety of aromatic compounds was regioselectively iodinated with iodine and F-TEDA in imidazolium- and pyridinium- based ionic liquids, [bmim][PF_6] and [bpyr][BF_4]. Iodination was *para*- directed when possible, otherwise it occurred in the *ortho*- position. The substrate selectivity measured in competitive experiments is in agreement with a polar mechanism.

Keywords: Aromatic iodination, iodoarenes, ionic liquids

Introduction

In recent years, iodo-aromatic compounds have assumed increasing importance in organic synthesis because, being more reactive than the respective bromides and chlorides, they can be easily functionalized through metal-catalyzed cross-coupling reactions.[1] Moreover, they are able to form a large variety of stable aromatic polyvalent iodine compounds, which have found increasing application in modern synthetic procedures.[2] Finally, iodo-aromatic derivatives are also used as bio-active compounds.[3] The direct introduction of iodine into aromatic molecules is the most used methodology although the addition of activating agents is necessary, owing to the low electrophilicity of I_2. Several methods using iodonium donating agents have therefore been developed, such as iodine–tetrabutylammonium peroxydisulfate,[4] BuLi–CF_3CH_2I,[5] iodine–nitrogen dioxide,[6] iodine–F-TEDA–BF_4,[7] iodine–iodine pentoxide,[8] iodine monochloride,[9] NIS–CF_3SO_3H,[10] iodine–mercury salts,[11] and NaOCl–NaI.[12] Most of these methods require toxic reagents or solvents and the reactions often occur with a low regioselectivity giving, besides the mono-iodo adducts, mixtures of poly-iodination products. However, concern over the health hazards and environmental pollution caused by organic solvents has prompted chemists to look for "greener" media for syntheses generally carried out in molecular organic solvents. One intriguing alternative to molecular solvents, that has recently received a good deal of attention, is

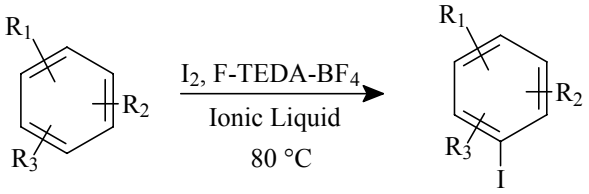
represented by the use of ionic liquids.[13] These solvents, mainly owing to their high thermal stability and lack of measurable vapor pressure, appear to be ideal media for performing reactions under, "eco-friendly" conditions.

Herein we report an efficient method for the iodination of representative aromatic rings using iodine and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate), F-TEDA–BF_4, in two ionic liquids, [bmim][PF_6] and [bpyr][BF_4]. The use of Selectfluor™ (F-TEDA–BF_4) in ionic liquids has recently been reported[14] as a "green" method for fluorination of aromatic compounds. However, F-N type reagents not only are able to fluorinate arenes but also possess oxidizing properties. F-TEDA–BF_4 has indeed been used for the iodination of anisoles in acetonitrile, and for the α-iodination of ketones in methanol.[7,15]

The present study was therefore undertaken to determine the efficacy of this iodinating system in an ionic liquid and to obtain, from comparison with molecular solvents, further information about the properties of these new reaction media.

Results and Discussion

F-TEDA–BF_4 and I_2 were slowly dissolved, using an ultrasonic bath, in the ionic liquids [bmim][PF_6] (1-butyl-3-methylimidazolium hexafluorophosphate) and [bpyr][BF_4] (1-butyl-pyridinium tetrafluoro-borate) at room temperature. In the case of [bmim][PF_6] dissolution of F-TEDA–BF_4 is accompanied by counter-anion exchange but this did not affect iodination. After addition of the substrate the solution was warmed at 70–80°C. The products were extracted with Et_2O and analyzed by NMR. When [bmim][PF_6] was used as solvent, after the extraction of the reaction product, washing with water gave a pure ionic liquid (NMR) which may be re-used at least twice without significant modification in yield and selectivity. A number of different aromatic substrates was subjected to the iodination reaction to test the generality of this method, and the results are reported in Table 1.



Ionic Liquid = [bmim][PF_6] or [BPyr][BF4]

Under the reaction conditions, aromatic fluorination did not compete with iodination. Iodination always gave monosubstitution products, even with activated aromatic compounds, *e*.g., anisoles, phenols, and aniline. Furthermore, the reactions occurred with high regioselectivity in both the ionic liquids tested to give, with the exception of toluene, practically a single product.

Iodination was *para*- directed when possible (runs 7, 8, 11 and 14–16), otherwise it occurred in the *ortho*-position (runs 9, 10 and 17). The nature of the ionic liquid affected only the reaction rate; with the exception of 3,4-dimethoxyacetophenone, the reactions carried out in [bmim][PF_6] generally showed higher conversions than those in [bpyr][BF_4]. In both solvents, the reactivity of the substrates seemed to be associated with the electron density of the aromatic rings (run 1, 2 and 11–17). Introduction of a nitro group at the *para* position in phenol markedly reduced the reactivity (runs 17).

3,4-Dimethoxyacetophenone was converted in both ionic liquids into the α-iodocarbonyl derivative. The formation of α -iodoketones by reaction of aryl alkyl ketones with iodine–F-TEDA–BF_4 has been observed recently using methanol as solvent.[15] In the molecular solvents the regioselectivity (α-iodocarbonyl derivatives *vs.* iodoarenes) appears to be regulated by the solvent: in acetonitrile only iodoarenes are formed, independently of the ketone structure, while in methanol the reaction gives exclusively the corresponding α -iodocarbonyl derivatives. It is worthy of note that, in the two ionic liquids used, only the α-iodocarbonyl derivative was formed from 3,4-dimethoxyacetophenone.

Related to the applicability of this reaction it must be stressed that the purity of the ionic liquid, and in particular the absence of halogen anion (Br^- or Cl^-) which may be present in traces as a consequence of an incomplete metathesis reaction, is an important feature for obtaining exclusively iodo- derivatives. The presence of bromide or chloride ions gave, under the reaction conditions, relevant amounts of the corresponding bromo- or chloro- derivatives besides the iodo- adducts. F-TEDA–BF_4 is indeed able to convert these anions very effectively to the equivalent of an X^+ electrophile (formally Br^+ or Cl^+),[16] which is able to compete with I^+ to give the corresponding substitution products.

$$F^+ + X^- \longrightarrow F^- + X^+ \qquad (1)$$

Experiments carried out in [bmim][PF_6] at 70–80 °C, but using NaBr or NaCl instead of I_2 as source of the electrophile, show that the reaction between equimolar amounts of anisole and Br^- was >90% complete after 24h, while the reaction with anisole and Cl^- was 45% complete after the same time. Furthermore, while the reaction involving Br^+ gave the *para*- adduct as the sole reaction product, a *ca*. 45:55 mixture of the *para*-/*ortho*- isomers was obtained with Cl^+.

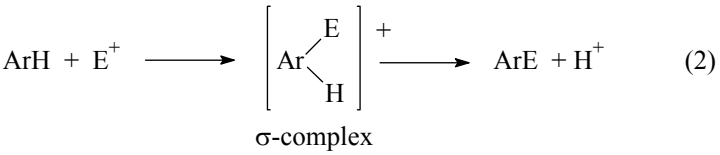
Finally, concerning the mechanism of this synthetically useful reaction, some preliminary observations can be made. As in acetonitrile and in methanol, under the reported reaction conditions, we did not observe any reaction between elemental I_2 and F-TEDA–BF_4. Although F-TEDA–BF_4 is a very efficient reagent for fluorination of aromatic compounds in the presence of I_2 it is not able to react with arenes. Therefore, it seems that the function of F-TEDA–BF_4 is that to activate the I_2–arene system through a process that starting from oxidation of I_2 proceeds with the attack of the electrophile at the most reactive position of the aromatic ring.

Table 1. Iodination of aromatic compounds with I_2–F-TEDA–BF_4 in ionic liquids

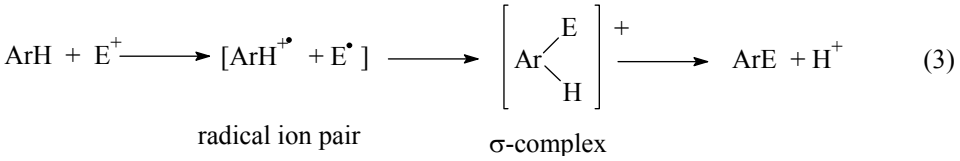
No.	Substrate	Solvent	Time (h)	Conv. (%)	Product distribution, mol %	Yield (%)
1	Toluene	[bmim][PF_6]	24	50	4-Iodotoluene, 65; 2-iodotoluene, 35	80
2	*p*-Xylene	[bpyr][BF_4]	24	100	2-Iodo-*p*-xylene	90
3	"	[bmim][PF_6]	24	100	"	90
4	Mesitylene	[bpyr][BF_4]	24	100	2-Iodo-mesitylene	90
5	"	[bmim][PF_6]	24	100	"	95
6	Durene	[bmim][PF_6]	25	45	3-Iododurene	95
7	Anisole	[bpyr][BF_4]	24	60	4-Iodoanisole	95
8	"	[bmim][PF_6]	24	75	"	94
9	*p*-Cresol	[bpyr][BF_4]	24	50	2-Iodo-*p*-cresol	95
10	"	[bmim][PF_6]	24	70	"	95
11	Phenol	[bmim][PF_6]	24	80	4-Iodophenol, 90; 2-iodophenol, 10	90
12	2,6-di-iso-Propyl-phenol	[bpyr][BF_4]	24	45	2,6-di-iso-Propyl-4-iodophenol	90
13	"	"	48	80	"	
14	"	[bmim][PF_6]	24	55	"	90
15	Aniline	[bpyr][BF_4]	24	30	4-Iodoaniline	85
16	"	[bpyr][BF_4]	24	70[a]	"	80
17	"	[bmim][PF_6]	24	50	"	80
18	*p*-Nitrophenol	[bpyr][BF_4]	24	15	2-Iodo-*p*-nitrophenol	85
19	3,4-Dimethoxy-acetophenone	[bpyr][BF_4]	24	90	α –Iodo-3,4-dimethoxy-acetophenone	90
20	"	[bmim][PF_6]	24	30	"	90

[a] [Aniline] = 1.2 *M*, [I_2] = [F-TEDA] = 0.6 *M*.

The mechanism of electrophilic aromatic iodination in molecular solvents is already an object of investigation and debate. Beside the "classical" polar route of substitution (path 2), *via* rate-limiting reaction of the electrophile and the aromatic substrate to form the σ-complex, an alternative mechanism (path 3), involving an initial electron-transfer to generate the aromatic cation radical ($ArH^{\bullet+}$), has been proposed more recently.[17–20]



(2)



(3)

Both mechanisms involve a σ-complex as the key intermediate: the main difference, however, is related to the structure of the transition state of the rate-determining step, which should be more similar to the σ-complex in the first mechanism, and more similar to the radical pair in the second one. Although these two possible reaction pathways are not easy to distinguish experimentally, there is recent evidence that in this dichotomy, both the substrate and the solvent probably have significant roles.[20] Important information in this respect has been obtained by the determination of the mesitylene-to-durene reactivity ratio. Mesitylene should be more reactive than durene in a "classical" electrophilic substitution, while durene should be more reactive if the transition state of the process is closer to the radical-ion pair. Although the use of this mechanistic probe has been debated,[21] the usefulness of these "intelligent" substrates for establishing the nature of the mechanism of the aromatic iodination has been stressed recently.[20] In order to obtain preliminary information about the mechanism of iodination with I_2/F-TEDA–BF_4 in ionic liquids we have therefore determined the substrate selectivity in competitive reactions using a 1:1 mixture of mesitylene and durene in [bmim][PF_6]. The k_{mes} / k_{dur} value, determined by GC–MS, was 54. An identical experiment performed in CH_3CN gave the k_{mes} / k_{dur} ratio as 61. It is worth noting that these values are very similar to that measured [20] for the reaction with ICl in CH_3CN (k_{mes} / k_{dur} = 46) suggesting, at least for iodination of alkyl substituted arenes with I_2/F-TEDA–BF_4 in ionic liquids, a polar mechanism occurring through a transition state having a pronounced σ-complex character.

In conclusion, the results of the present investigation show clearly the feasibility of performing aromatic iodination with I_2–F-TEDA–BF_4 in ionic liquids. Although temperatures around 70–80 °C are necessary to obtain complete transformation of the tested arenes in reasonable times, the yields are practically quantitative, the process involves no aqueous work-up, and the ionic liquid can be recycled and re-used. Moreover, the preliminary results relating to the reactions carried out with NaCl and NaBr show that this procedure is general, and that useful electrophiles in ionic liquids may be obtained from common anions. Finally, preliminary results obtained by competitive experiments suggest a polar mechanism for aromatic iodination with I_2–F-TEDA–BF_4 in ionic liquids.

Experimental Section

General Procedures. 1-Butylpyridinium tetrafluoroborate[bpyr][[BF_4],and1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF_6], were synthesized and purified as reported previously.[22] The Selectfluor^{TM} (F-TEDA–BF_4) was a sample from Aldrich. Liquid arenes were dried over molecular sieves. NMR spectra were recorded in $CDCl_3$ at 200 MHz using TMS as the internal reference. GC–MS analyses were performed with a Varian CP3800 instrument, equipped with an ion-trap detector, utilizing a 30 m DB5 capillary column.

Typical iodination procedure. F-TEDA–BF_4 (320 mg, 0.9 mmol) and I_2 (230 mg, 0.9 mmol) were added to 3 ml of the ionic liquid ([bpyr][BF_4] or [bmim][PF_6]) and the closed tube was placed inside an ultrasonic bath at room temperature for 30 min to increase solubility. After addition of arene (1.8 mmol) at room temperature, the mixture was stirred at 80 °C for 24 h. The organics were extracted with ether (2 ml x 3). The solvent was evaporated and the crude reaction mixtures were analyzed by NMR.

Bromination and chlorination of anisole. F-TEDA–BF_4 (320 mg, 0.9 mmol) and NaCl or NaBr (0.9 mmol) were added to 3 ml of [bmim][PF_6] and the closed tube was placed in an ultrasonic bath at room temperature for 30 min to increase solubility. After addition of anisole (0.9 mmol) at room temperature the mixture was stirred at 80 °C for 24 h. The organics were extracted with ether (2 ml x 3). The solvent was evaporated and the crude reaction mixtures were analyzed by NMR.

Competitive experiments

(a) In [bmim][PF_6]. To the ionic liquid (1.5 ml) containing I_2 (115 mg, 0.3 mmol) and F-TEDA–BF_4 (160 mg, 0.3 mmol) durene (120 mg, 0.6 mmol) and mesitylene (108 mg, 0.6 mmol) were added under argon. The reaction mixture was stirred at 80 °C for 24 h, following which the aromatics were extracted as described above and analyzed by MS–GC. The product ratio (1-iodo-2,4,6-trimethylbenzene: 1-iodo-2,3,5,6-tetramethylbenzene) was 54.

(b) In acetonitrile. I_2 (190 mg, 0.75 mmol), F-TEDA–BF_4 (260 mg, 0.3 mmol) durene (200 mg, 1.5 mmol) and mesitylene (180 mg, 1.5 mmol) were added under argon to a Schlenk tube containing MeCN (2.5 ml). The reaction mixture was stirred at 80 °C for 24 h, following which, after dilution with water, the aromatics were extracted with CH_2Cl_2 and analyzed by GC–MS. The product ratio (1-iodo-2,4,6-trimethylbenzene: 1-iodo-2,3,5,6-tetramethylbenzene) was 61.

Acknowledgements

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