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Iodination of activated arenes using silfen: an improved protocol

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Abstract—A simple and direct method for the iodination of activated arenes, using molecular iodine and silfen (silica supported ferric nitrate nonahydrate) as an oxidant, is presented. The reactions are performed at 20°C in dichloromethane. The method provides an easy access to the corresponding iodinated products in good yields. The observed orientation effects are in agreement with those based on general aromatic electrophilic substitution theory. © 2002 Elsevier Science Ltd. All rights reserved.

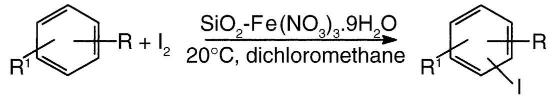
Iodoarenes are valuable and versatile synthetic intermediates with wide applications in medicine and biochemistry.[1] Recent progress in organotransition metal chemistry has renewed the importance of these iodoarenes. The transformations of iodine in iodoarenes, to diverse functional groups, by transition metal catalysts, has been a popular and fruitful area of investigation.[2] Despite the importance of iodoarenes and the long history of aromatic electrophilic halogenation, the lack of reactivity of molecular iodine has hindered extensive progress towards their efficient synthesis.

Synthetic methods involving a source of positive iodine i.e. I^+ as the reactive species, seem to be the most convenient procedure for the direct iodination of arenes.[3] A wide array of reagents and methods involving molecular iodine, in combination with oleum,[4] CrO_3,[5] F_2,[6] Pb $(OAc)_4$,[7] Hg salts,[8] nitrogen dioxide[9] and CF_3SO_3Ag[10] have been documented. However, most of these methods require large volumes of mineral acids, high reaction temperatures, the use of expensive/non-ecofriendly/sensitive metallic reagents and the generation of large amounts of toxic waste. Hence, a convenient method involving mild reaction conditions is highly desirable.

During the past decade, the technique of surface-mediated reactions has gained much interest and popularity. In comparison to their homogeneous counterparts, the advantages of these reactions include mild conditions enhanced selectivity and increased yields.[11] It has also been demonstrated that attempts to carry out the same reactions in solvents, without a support, either frequently fail or result in the formation of mixtures of products.

Over the last few years, we have been actively involved in utilising surface-mediated reactions and have found them useful in carrying out various synthetic organic transformations.[12] We have already published our results on oxidation of alcohols and aromatisation of 1,4-dihydropyridines using silfen (silica supported ferric nitrate nonahydrate) as a mild oxidant.[13] Silfen is prepared under solvent-free conditions and possesses no handling and storage problems.[14] In continuation of our progressive investigation into the applications of this mild oxidant, we herein wish to report a mild, efficient and regioselective monoiodination of activated arenes, using molecular iodine and silfen.[15] This communication deals with the scope and limitations of this newly developed iodination method (Scheme 1).

To gain some preliminary information on this synthetically useful reaction, control experiments were performed. For all these studies, an activated arene i.e. anisole was the substrate of choice. We studied the influence of different factors on the reaction kinetics. Thus, solvent and the amount of oxidant were varied.



where R, R' = -H, alkoxy, alkyl, aryloxy, halogen etc.

Scheme 1. Iodination of activated arenes using molecular iodine and silfen as an oxidant.

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† This work is dedicated to our research guide, the late Dr. B. M. Khadilkar.

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Table 1. Effect of solvent on the reaction time at 20°C, using silfen (5 mmol content of $Fe(NO_3)_3 \cdot 9H_2O$)

Solvent	CH_3CN	CH_2Cl_2	PhMe	Et_2O	THF
Reaction time (h)	4.5	3.5	6	10	12

Our observations revealed that, amongst the various solvents used, dichloromethane was the most effective, giving a short reaction time and clean product. Basic solvents such as diethyl ether and tetrahydrofuran were found to be detrimental to this reaction, most probably due to complexation to the oxidant. The results are compiled in Table 1.

However, when the same reaction was performed at reflux temperature, along with the formation of the major *p*-iodoanisole, a considerable amount of nitration product was obtained. This prompted us to carry out all further investigations at 20°C, as it was found to favour the iodination reaction. (Conversions monitored by GC).[16]

In an attempt to optimise the reaction conditions, we examined the effect of the oxidant loading on the silica gel. For this purpose, the molar ratios of ferric nitrate nonahydrate on silica gel were varied. The results are compiled in Table 2.

During the course of our studies, we found that when anisole, iodine and ferric nitrate supported on silica gel were taken (entry 1) along with 80% of *p*-iodoanisole, 20% of the nitrated product was obtained. When the molar ratio was 1.0:0.55:0.50 respectively, 95% of *p*-iodoanisole was obtained exclusively (entry 2). However, after further decreasing the $Fe(NO_3)_3 \cdot 9H_2O$ content, it was observed that on isolation, only 80% of the iodinated product was obtained after 3.5 h (entry 3). Hence, all further reactions were performed with the most effective molar ratio, i.e. 1.0:0.55:0.50, respectively. To our surprise, in a blank reaction performed without supporting the $Fe(NO_3)_3 \cdot 9H_2O$ on silica gel, anisole was found to remain unconsumed even after 7 h. On isolation, only 50% of *p*-iodoanisole was obtained. Thus, the role of silica gel as an inexpensive support is justified.

With a better understanding of the reaction variables, a series of arenes were subjected to iodination in the presence of molecular iodine and silfen.[15] Electronically rich arenes were iodinated smoothly, while benzene and electron-deficient arenes such as chlorobenzene and bromobenzene were recovered unchanged even after 48 h. The results are compiled in Table 3.

The products obtained, after the reaction, resulted from the regioselective iodination of the aromatic ring. The

Table 2. Effect of variation of the oxidant loading on the silica gel (4 g); reaction performed at 20°C in dichloromethane for 3.5 h

Entry	Molar ratios (anisole:iodine:$Fe(NO_3)_3 \cdot 9H_2O$)	Yield[a] (%)	
		Iodination	Nitration
1	1.0:0.55:1.0	80	20
2	1.0:0.55:0.50	95	–
3	1.0:0.55:0.25	80	–

[a] Isolated yields.

Table 3. Iodination of activated arenes using molecular iodine and silfen as an oxidant

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	Methoxybenzene	3.5	1-Iodo-4-methoxybenzene	95
2	Ethoxybenzene	4	1-Iodo-4-ethoxybenzene	90
3	1-Methoxy-2-methylbenzene	2.5	4-Iodo-1-methoxy-2-methylbenzene	84
4	1-Methoxy-4-methylbenzene	2.5	2-Iodo-1-methoxy-4-methylbenzene	80
5	2-Chloro-1-methoxybenzene	6	2-Chloro-4-iodo-1-methoxybenzene	84
6	2-Methoxynaphthalene	6	1-Iodo-2-methoxynaphthalene	85
7	Diphenyl ether	28	4,4′-Diiododiphenyl ether	80
8	Thiophene	2	2-Iodothiophene	47
9	1,4-Dimethoxybenzene	14	2-Iodo-1,4-dimethoxybenzene	84
10	1,3,5-Trimethylbenzene	2	2-Iodo-1,3,5-trimethylbenzene	92
11	1,4-Dimethylbenzene	24	2-Iodo-1,4-dimethylbenzene	60
12	Benzene	48	–	–
13	Chlorobenzene	48	–	–
14	Bromobenzene	48	–	–

[a] Isolated yields.

regioselectivity observed may be explained from the result that iodination occurs at a more electron rich and less sterically hindered position. This character is strongly reflected in the iodination of anisole, phenetole, 2-methylanisole and 2-chloroanisole (entries 1, 2, 3 and 5), where the iodination occurred at the *p*-position to the alkoxy group. As anticipated, *o*-iodination occurred only when the *p*-position was occupied (entry 4). Regioselective diiodination of diphenyl ether, a binuclear arene (entry 7) has been achieved by controlling the stoichiometry. Also, α-iodination of an activated heterocycle, thiophene (entry 8) was obtained. Monoiodothiophene serves as a useful intermediate in the synthesis of conjugated materials, self-assembled monolayers and as bioactive reagents in antitumour therapy.[17]

Attempts to gain an insight into the mechanistic details of this reaction have not yet been achieved. Presumably, the electrophile I^+ is generated in situ by the reaction of molecular I_2 and silfen. The spent material obtained after iodination, is found to be effective in Friedel–Crafts alkylation, another industrially important reaction.[18]

In conclusion, we have established silfen as an economical, efficient, ecofriendly oxidant for regioselective monoiodination. The ease of this present protocol is expected to make this methodology useful in the field of synthetic organic chemistry. To enhance the synthetic utility of this method, its applications to other heterocycles are being pursued.

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14. For the present studies, silfen was prepared as follows: $Fe(NO_3)_3 \cdot 9H_2O$ (2 g, 5 mmol) was cogrinded with silica gel (4 g, SRL 230–400 mesh, BET surface 385.6 $m^2\ g^{-1}$, pore volume 0.65 $cm^3\ g^{-1}$) in an agate mortar. A pale yellow free flowing mixture was obtained, which was used without any further activation.
15. Silfen was prepared as cited in Ref. 14. In a representative procedure, to 10 mmol of substrate and 5.5 mmol of iodine in 15 ml dichloromethane, silfen (5 mmol content of $Fe(NO_3)_3 \cdot 9H_2O$) was added. The reaction was then stirred for the specified time, at 20°C. On completion (monitored by TLC and GC) the reaction mixture was filtered and the organic solution successively washed with aqueous sodium thiosulphate solution. The combined organic extracts were dried using anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography (silica gel) to furnish the pure iodo products. The products are characterised by their physical constants, IR, NMR and GC–MS.
16. Conversions in all cases were monitored with respect to the decay of anisole on GC. An Eshika chromatograph equipped with FID was employed for the analysis. The detector temperature was maintained at 300°C. The column was programmed with an initial temperature at 100°C and was increased thereafter to 250°C at the rate of 10°C min^{-1}. The column used was SE-30 (length 2 metres).
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18. In an unoptimised reaction, benzene (20 ml) and benzyl chloride (10 mmol) were stirred at 80°C in the presence of spent reagent (1 g) for 30 min, to obtain 50% of monoarylated product. Further studies are ongoing.