Solvent-Free Iodination of Arenes at Room Temperature

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This work is dedicated to the late Dr. B. M. Khadilkar.

Abstract: Silica supported bismuth(III)nitrate pentahydrate [BNP-SiO_2] was prepared under simple co-grinding condition. The iodination of aromatic compounds using BNP-SiO_2 and molecular iodine under solvent-free conditions is described. The reaction occurred in the solid state at room temperature, yielding the corresponding mono-iodo derivative in good yields. However, less activated aromatics required longer reaction time with comparatively less yield.

Key words: aromatic iodination, solvent-free, bismuth nitrate pentahydrate, molecular iodine, co-grinding

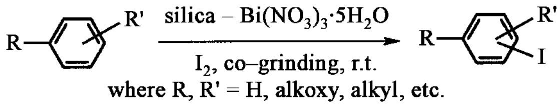
Halogenated aromatic compounds constitute an important class of molecules in synthetic organic chemistry. Iodoarenes are important intermediates[1] with wide practical applicability that range from preparation of functionalised aromatic compounds to aryl organometallic reagents. Many iodoorganic compounds are biologically active molecules often used in medicine as drugs or in diagnostic aids as radioactively labeled markers or contrastors and thus their related chemistry has attracted broad interest.[2] Despite significant improvements for direct bromination and chlorination of aromatics with the respective molecular halogens,[3] limitations still exist for aromatic iodination reaction.

Iodine is a weak electrophile when compared to bromine or chlorine. Moreover, electrophilic iodination often generates hydrogen iodide, which is both a strong reducer as well as a strong acid which can cause protolytic cleavage of the formed aryl iodide. Iodination of hydrocarbons is a reversible process and besides requiring electrophilic I^+ species, requires an oxidising agent to oxidise the hydriodic acid formed in the reaction. For this purpose, a variety of reaction systems involving molecular iodine along with oxidants such as, oleum,[4a] iodic acid,[4b] periodic acid,[4c] peracetic acid,[4d] mixture of nitric and sulfuric acid,[4e] $KMnO_4$,[4f] MnO_2,[4f] sodium periodate,[4g] CrO_3,[4h] $Pb(OAc)_4$,[4i] antimony(V)chloride,[4j] Hg salts,[4k] nitrogen dioxide,[4l] CF_3SO_3Ag,[4m] silver sulfate,[4n] tetrabutylammonium peroxydisulfate,[4o] diiodine pentoxide,[4p] etc. were reported. Recent milder modifications employ quaternary ammonium salts[5] prepared either by using the corrosive and moisture sensitive iodine monochloride or by a series of steps performed under controlled temperature conditions. Thus, in general, most reactions described in the literature are carried out either with excess of the reactant or by using chlorinated hydrocarbons or acetonitrile as solvent, sometimes at room and often at elevated temperatures. In this regard, an efficient construction of this aromatic scaffold employing molecular iodine at room temperature is always appealing.

Recently, we have reported the iodination of activated arenes using silica supported ferric(III)nitrate and molecular iodine, in dichloromethane.[6] It should be noted that Fe^{+3} functions as a Lewis acid and also can participate in some redox reactions. Sakae and co-workers have already demonstrated aromatic iodination and bromination with antimony(V)chloride and molecular halogens using chlorinated hydrocarbons as solvents.[4j] Bi(III) salts have gained increasing attention for a variety of organic transformations.[7] Bismuth(III)nitrate pentahydrate [BNP] i.e. $Bi(NO_3)_3 \cdot 5H_2O$ is an inexpensive, commercially available reagent and requires no special care during its handling. The potentials of this reagent for aromatic nitration,[8a] oxidation of alcohols,[8b] deprotection of oximes[8c] and conversion of thiocarbonyls to the corresponding carbonyl compounds[8d] have been recently explored.

Reactions carried out under solvent-free conditions have received immense popularity in recent years.[9] The mild reaction conditions, low reaction times, sometimes enhanced selectivity and clean products are the salutary features of this approach. On the basis of all the above rationale, we thought it would be worthwhile to prepare and study the application of this reagent [BNP-SiO_2] for direct iodination of arenes in presence of molecular iodine. Thus, in sharp contrast to the volume of literature,[1–4] we herein disclose the first report for aromatic iodination under solvent-free conditions, using molecular iodine (Scheme 1). This protocol is mild as compared to the existing methods using solvents.

Our initial experiments focused on the iodination of an activated arene like anisole. It was observed that with 0.5



Scheme 1 Solvent-free iodination of aromatics using BNP-SiO_2 and molecular iodine, at room temperature

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equivalents of this oxidant 95% of the *p*-iodoanisole was isolated within 5 minutes under the reaction condition.[10] On decreasing the amount of the oxidant to 0.3 equivalents, 92% of the iodo product was isolated in the same period. These exciting results prompted us to carry out all further studies using 0.3 equivalents of the oxidant with respect to the substrate used.

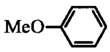
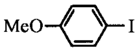
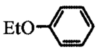
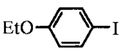
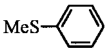
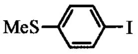
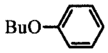
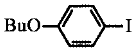
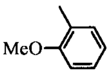
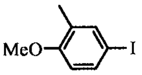
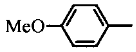
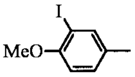
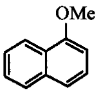
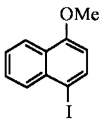
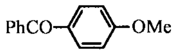
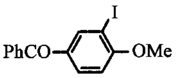
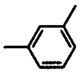
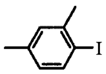
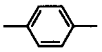
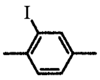
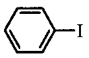
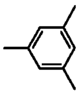
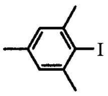
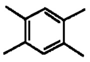
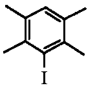
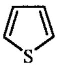
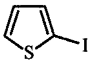
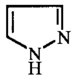
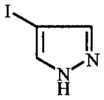
Nitration of aromatic compounds using BNP/K10 clay has been reported.[8a] However, in the present protocol the formation of nitro derivatives was not observed in spite of increasing the amount of BNP-SiO_2. Subsequently, supported reagents like BNP/K10 and BNP/KSF were prepared following the co-grinding procedure. The reagents were mixed with anisole and allowed to stand. The formation of the nitro derivative was not observed even after half an hour. To see the implication of reactivity of aromatic compounds in the interplay of iodination and nitration, 1,4-dimethoxybenzene was co-grinded with the BNP-SiO_2 and molecular iodine. However, in this case nitration was observed within few minutes. Thus, it is apparent that the method can be extended for the nitration of highly activated arenes.

To demonstrate the scope of the solvent-free iodination reaction, we subjected a range of substituted aromatic ethers to the present conditions. Most of the substituted aromatic ethers were rapidly converted to the corresponding iodo derivatives in good yields. To further generalise this methodology, arenes like benzene, some of its alkyl derivatives and a few heterocycles were subjected to the reaction conditions. Xylenes, mesitylene and durene were readily converted to the corresponding mono-iodo products, in a relatively short reaction time. In an unoptimised reaction, iodination of benzene led to the formation of iodobenzene with 37% yield after 3 days. Also, few heterocycles like pyrazole and thiophene were iodinated, though some optimisation is required. The unoptimised results are summarised in Table 1.

As anticipated, the products obtained after the reaction resulted from the regioselective iodination of the aromatic ring. The observed regioselectivity was in accordance with the electronic consideration and steric factor. However, in case of activated arenes like naphthalene, methoxy naphthalenes and acetanilide, formation of trace amounts of the corresponding nitro product was observed under the present reaction conditions (TLC analysis).

In conclusion, a highly novel, mild, inexpensive and solvent-free protocol for iodination of activated arenes is described. This practically simple method led to the corresponding iodo derivatives in short reaction times under extremely mild conditions. The ease of this protocol is of general interest as these iodo derivatives have wide potential applications in synthetic and combinatorial chemistry. Attempts to exploit the catalytic performance of this oxidant and few other metallic nitrates in polar solvents like ionic liquids have been accomplished and will be published in due course.

Table 1 Solvent-Free Iodination of Aromatics Using BNP-SiO_2 and Molecular Iodine, at Room Temperature

Entry	Substrate	Product	Time	Yield[a] (%)
1			5 min	92
2			5 min	91
3			10 min	84
4			5 min	89
5			5 min	82
6			5 min	84
7			10 min	84
8			12 h	69
9			2 h	76
10			5 h	70
11			3 days	37
12			5 min	90
13			5 min	87
14			10 min	58
15			10 min	52

[a] Isolated yields after chromatographic separation.

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(10) **General Experimental Procedure:** To a pre-weighed sample of silica-gel[11] (2.5 g) was added $Bi(NO_3)_3{\cdot}5H_2O$ (1.7 mmol) and iodine (3.0 mmol) which was then co-grinded in an agate mortar.[12] To the free flowing powder thus obtained, was added the organic substrate (5.0 mmol) and the contents were carefully ground to obtain a fine homogenous powder. This mixture was allowed to stand for the specified time (Table 1), at r.t. On completion (TLC or GC analysis[13]) the reaction mixture was desorbed by dichloromethane (3 × 10 mL). The organic extracts were successively washed with aq $Na_2S_2O_3$ solution, dried over anhyd Na_2SO_4 and then evaporated under reduced pressure. The crude product was purified by column chromatography to furnish the pure iodides. All products are well known in literature. The products were characterised by their physical constants and spectral analysis.

(11) SiO_2 (SRL, 230–400 mesh, BET surface 385.6 m^2g^{-1}, pore volume 0.65 cm^3g^{-1}) was used for all reactions without any prior activation. To a pre-weighed sample of silica-gel (2.5 g) is added the commercially available $Bi(NO_3)_3{\cdot}5H_2O$ (0.3 or 0.5 equiv) which is co-grinded in an agate mortar. The contents are carefully ground to obtain a fine homogenous powder. BNP/K10 and BNP/KSF were prepared in a similar manner.

(12) **CAUTION:** Special care must be taken when iodine is co-grinded along with the other contents in an agate mortar. This is because it is known that iodine vapours irritate all parts of the respiratory system.

(13) An Eshika Gas chromatograph equipped with FID and SE-30 column (length 2.0 m) was employed for analysis.