

## Grindstone chemistry: (diacetoxyiodo)benzene-mediated oxidative nuclear halogenation of arenes using NaCl, NaBr or I<sub>2</sub>

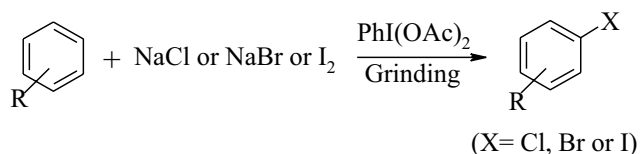
N.N. Karade\*, G.B. Tiwari, D.B. Huple and T.A.J. Siddiqui

School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded – 431606, Maharashtra, India

A technique of “Grindstone chemistry” is applied to the solvent-free halogenation of arenes with NaCl, NaBr or I<sub>2</sub> using (diacetoxyiodo)benzene as the oxidant. Improved yields and higher purities of the products are observed compared with those from established methods.

**Keywords:** grindstone chemistry, (diacetoxyiodo)benzene, nuclear halogenation

Halogenated aromatic compounds have been extensively used as intermediates for the synthesis of many industrially valuable products such as drugs, pharmaceuticals, agrochemicals, pigments and photographic materials.<sup>1</sup> Recent progress in organo-transition metal chemistry has also renewed the importance of haloarenes because they can be easily functionalised through metal-catalysed cross-coupling reactions.<sup>2</sup> Therefore, there are several known methods available in the literature that have been developed for the chlorination, bromination and iodination of aromatic compounds. However, classical direct chlorination and bromination involve the use of potentially hazardous, difficult to store and handle elemental halogens, Cl<sub>2</sub> or Br<sub>2</sub> which generate toxic and corrosive hydrohalic acids as side-products, thereby causing serious environmental pollution.<sup>3</sup> Also, the direct iodination of arenes with elemental iodine is extremely difficult due to the low reactivity of iodine compared with the other halogens in aromatic substitution. Therefore, molecular iodine has to be used in combination with mineral acids, high reaction temperatures and metallic reagents, which in turn generate toxic waste.<sup>4</sup> To overcome these drawbacks with elemental halogens, several other methods for chlorination, bromination and iodination of arenes have been developed using different reagents.<sup>5</sup> Among these, *N*-halosuccinimides have been extensively utilised for achieving nuclear halogenation of arenes under different reaction conditions.<sup>6</sup> Alternatively, the generation of electrophilic halogen from halide salts or hydrohalic acid, under oxidative conditions, has also resulted in nuclear halogenation of arenes.<sup>7</sup> Despite the availability of a variety of methods for the reaction, there is growing need for green methodologies that obviate the use of copious amounts of heavy metal oxidants, toxic Cl<sub>2</sub>/Br<sub>2</sub> and environmentally unfriendly organic solvents.<sup>8</sup> From this point of view, the reactions of hypervalent iodine reagents under solvent-free conditions are highly attractive.<sup>9</sup> (Diacetoxyiodo)benzene (DIB) is the most extensively utilised hypervalent iodine (III) reagent. It is easy to handle, non-toxic, commercially available and is similar in reactivity to heavy metal oxidants.<sup>10</sup> Previously, DIB was used in the bromination of flavones, dihydropyrans and 1,4-dimethoxynaphthalenes using TMSBr or Bu<sub>4</sub>NBr.<sup>11</sup> Similarly molecular iodine combined with DIB was employed for the iodination of selected substrates such as alkyl benzene or thiophene derivatives.<sup>12</sup> The other hypervalent iodine reagent *i.e.* (dichloroiodo)benzene, PhICl<sub>2</sub> has been documented for chlorination of arenes.<sup>13</sup> All these halogenation reactions have been carried out in an organic solvent such as dichloromethane, DMSO, acetic acid, acetonitrile or THF. We find similar or even better yields of the halogenated arenes using the “Grindstone chemistry” technique, which has recently received a good deal of attention.<sup>14</sup> In 1987, Toda *et al.* showed that many reactions (but not all) can be conducted in high yields under solvent-



**Scheme 1**

free conditions by just grinding the reactants together.<sup>15</sup> Usually these reactions were carried out on a very small scale in an agate pestle and mortar. It has been of interest to us to extend this approach to the halogenation of arenes. Following our continued interest in hypervalent iodine reagents,<sup>16</sup> here we report an application of ‘Grindstone Chemistry’ to the nuclear chlorination, bromination and iodination of arenes with NaCl, NaBr or I<sub>2</sub> respectively, using DIB as oxidant (see Scheme 1).

In a typical experimental procedure, a homogeneous mixture of arene (2 mmol), (diacetoxyiodo)benzene (2.2 mmol) and NaCl or NaBr (2 mmol) was gently ground for 30 minutes using a pestle and mortar. The wetting of the reaction mixture along with a red or yellow colouration was observed. After completion of reaction (monitored by TLC by taking a small amount of the mixture and dissolving it in ethyl acetate), the solid residue was washed with diethyl ether (5 ml), concentrated *in vacuo* and chromatographed to give chlorinated and brominated arenes in good to excellent yields. However, the yields of iodination reaction of arenes under similar experimental conditions were relatively poor using NaI and DIB in equimolar quantities. However, a combination of DIB and molecular iodine in 1: 0.6 molar ratio gave excellent yields of iodinated arenes. Therefore, we have selected NaCl and NaBr for chlorination and bromination, while molecular iodine for iodination of a range of arenes using DIB as oxidant. The results are summarised in the Table 1.

It follows from Table 1 that highly activated methoxy-benzenes (Entries a–e) and moderately activated alkyl benzenes (Entries f–h) underwent halogenation in good to excellent yields. It is very interesting and remarkable that monohalogenation products were observed in all the cases. One of the most important features of this methodology is its regioselectivity. Thus, halogenation of anisole, *N,N*-dimethyl aniline and acetanilide (Entries a, i and j) occurred exclusively at the *para*-position. The yields of chlorination products were found relatively poor compared to the yields of the bromination and iodination reactions.

Mechanistically, the ligand exchange reaction between PhI(OAc)<sub>2</sub> and bromide or chloride anion will form a putative intermediate PhI(OAc)X (where X is Cl or Br). The overwhelming tendency of iodobenzene for reductive elimination from PhI(OAc)X will generate electrophilic chlorine or bromine responsible for the chlorination and

\* Correspondent. E-mail: nnkarade@rediffmail.com

**Table 1** Halogenation of arenes with NaCl, NaBr or I<sub>2</sub> using (diacetoxyiodo)benzene as oxidant under solvent-free conditions<sup>a</sup>

Entry	Arene	Product <sup>b</sup>	Yield (%) of the product <sup>b</sup> for X = Cl, Br or I		M.P./°C	Lit. M.P./°C
a			Cl	84	Oil	Oil <sup>6b</sup>
			Br	94	Oil	Oil <sup>6b</sup>
			I	96	51	50–53 <sup>6b</sup>
b			Cl	80	Oil	Oil <sup>6b</sup>
			Br	91	Oil	Oil <sup>6b</sup>
			I	90	76	76–78 <sup>6b</sup>
c			Cl	81	36	34–36 <sup>18</sup>
			Br	93	Oil	Oil <sup>18</sup>
			I	91	40	37–41 <sup>18</sup>
d			Cl	78	Oil	Oil <sup>17</sup>
			Br	88	Oil	Oil <sup>17</sup>
			I	89	Oil	Oil <sup>17</sup>
e			Cl	77	69	68–69 <sup>6b</sup>
			Br	87	Oil	Oil <sup>6b</sup>
			I	84	Oil	86–87 <sup>6b</sup>
f			Cl	69	Oil	Oil <sup>18b</sup>
			Br	78	Oil	Oil <sup>18</sup>
			I	81	Oil	Oil <sup>18b</sup>
g			Cl	71	Oil	Oil <sup>18</sup>
			Br	77	Oil	Oil <sup>18</sup>
			I	83	Oil	Oil <sup>18b</sup>
h			Cl	68	Oil	Oil <sup>18b</sup>
			Br	74	Oil	Oil <sup>18</sup>
			I	76	Oil	Oil <sup>4d</sup>
i			Cl	74	Oil	Oil <sup>18a</sup>
			Br	82	54	54–55 <sup>7e</sup>
			I	77	66	66–67 <sup>19</sup>
j			Cl	71	178	177–179 <sup>18b</sup>
			Br	84	167	167–169 <sup>18b</sup>
			I	76	154	153–156 <sup>18</sup>

<sup>a</sup>All the reactions were carried for 30 minutes.<sup>b</sup>Isolated yield.

bromination of arenes.<sup>10</sup> On the other hand, the reaction of DIB with molecular iodine will generate acetylhypiodite, which is an active source of electrophilic iodine responsible for the iodination of arenes.<sup>12</sup>

In summary, we have applied the “Grindstone Chemistry” approach to a mild and regioselective monohalogenation of aromatic compounds using inexpensive, non-toxic and readily available reagents. These reaction conditions are contributing to the development of sustainable techniques in organic synthesis and to the simplicity of reactions with hypervalent iodine reagents.

## Experimental

### (a) For chlorination of arenes

A homogeneous mixture of arene (2 mmol), NaCl or NaBr (2 mmol) and DIB (2.2 mmol) was gently ground for 30 minutes using a pestle and mortar. The progress of the reaction was monitored by TLC by taking a small amount of the mixture and dissolving it in ethyl acetate. After completion of reaction, the solid residue was washed with diethyl ether (5 ml),

concentrated *in vacuo* and chromatographed (silica gel) to give chlorinated and brominated arenes.

### (b) For iodination of arenes

A homogeneous mixture of arenes (2 mmol), I<sub>2</sub> (1.2 mmol) and DIB (2.2 mmol) was gently ground for 30 minutes using a pestle and mortar. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 ml). The organic extract was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent and subsequent silica gel chromatography (petroleum ether and EtOAc) afforded the corresponding iodinated arene in the pure form.

The authors are thankful to Department of Science and Technology, New Delhi for financial support (No. SR/FTP/CS-77/2005)

Received 4 October 2005; accepted 12 December 2005  
Paper 05/3527

## References

- 1 (a) C. Christophersen, *Acta Chem. Scand. B*, 1985, **39**, 515; (b) A. Butler and J.V. Walker, *Chem. Rev.*, 1993, **93**, 1937; (c) K.C. Nicolaou, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1377.
- 2 (a) E. Negishi, C. Coperet, S. Ma, S. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365; (b) F. Diederich and P.J. Stang, *Metal Catalysed Cross Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998.
- 3 For recent examples of chlorination and bromination protocols see: (a) K. Smith, M. Butters, W.E. Paget, D. Goubet, E. Fromentin and B. Nay, *Green Chem.*, 1999, **1**, 83; (b) N.B. Barhate, A.S. Gajare, R.D. Wakharkar and A.V. Bedekar, *Tetrahedron*, 1999, **55**, 11127; (c) G. Rothenberg and J.H. Clark, *Org. Proc. Res. Dev.*, 2000, **4**, 270; (d) U. Bora, G. Bose, M.K. Chaudhuri, S.S. Dhar, R. Gopinath, A. Khan and B.K. Patel, *Org. Lett.*, 2000, **2**, 247; (e) N. Narender, K.V. V.K. Mohan, R.V. Reddy, P. Srinivasu, S.J. Kulkarni and K.V. Raghavan, *J. Mol. Catal. A*, 2003, **192**, 73.
- 4 For recent examples of iodination protocols see: (a) T. Mukaiyama, H. Kitagawa and J. Matsuo, *Tetrahedron Lett.*, 2000, **41**, 9383; (b) S.J. Garden, J.C. Torres, S.C. de Souza Melo, A.S. Lima, A.C. Pinto and E.L.S. Lima, *Tetrahedron Lett.*, 2001, **42**, 2089; (c) A.S. Castanet, F. Colobert and P.E. Broutin, *Tetrahedron Lett.*, 2002, **43**, 5047; (d) R.D. Tilve, V.M. Alexander and B.M. Khadilkar, *Tetrahedron Lett.*, 2002, **43**, 9457.
- 5 (a) V. Kavala, S. Naik and B.K. Patel, *J. Org. Chem.*, 2005, **70**, 4267; (b) M.Y. Park, S.G. Yang, V. Jadhav and Y.H. Kim, *Tetrahedron Lett.*, 2004, **45**, 4887; (c) M. Sosnowski, L. Skulski and K. Wolowik, *Molecules*, 2004, **9**, 617; (d) S.C. Roy, C. Guin, K.K. Rama and G. Maiti, *Tetrahedron Lett.*, 2001, **42**, 6941.
- 6 (a) H.M. Meshram, P.N. Reddy, K. Sadashiv and J.S. Yadav, *Tetrahedron Lett.*, 2005, **46**, 623; (b) J.S. Yadav, B.V.S. Reddy, P.S.R. Reddy, A.K. Basak and A.V. Narsaiah, *Adv. Synth. Catal.*, 2004, **346**, 77; (c) R.A. Day, J.A. Blake and C.E. Stephens, *Synthesis*, 2003, **10**, 1586; (d) M.C. Carreno, J.L. Garcia Ruano, G. Sanz, M.A. Toledo and A.J. Urbano, *J. Org. Chem.*, 1995, **60**, 5328.
- 7 (a) D. Bogdal, M. Lukasiewicz and J. Pielichowski, *Green Chem.*, 2004, **6**, 110; (b) S.C. Roy, C. Guin, K.K. Rana and G. Maiti, *Tetrahedron Lett.*, 2001, **42**, 6941; (c) D. Roche, K. Prasad, O. Repic and T.J. Blacklock, *Tetrahedron Lett.*, 2000, **41**, 2083; (d) M. Zupan, J. Iskra and S. Stavber, *Tetrahedron Lett.*, 1997, **38**, 6305; (e) S.C. Roy, C. Guin, K.K. Rana and G. Maiti, *Tetrahedron Lett.*, 2001, **42**, 6941.
- 8 (a) T. Anastas and J.C. Warner, *Green Chemistry: Theory and Practice*. Oxford Science Publications, New York, 1998; (b) K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; (c) M. Eissen, J.O. Metzger, E. Schmidt and U. Schneidewind, *Angew. Chem. Int. Ed.*, 2002, **41**, 414.
- 9 (a) R.M. Moriarty, *J. Org. Chem.*, 2005, **70**, 2893; (b) T. Wirth, *Angew. Chem. Int. Ed.*, 2005, **44**, 3656; (c) P.J. Stang, *J. Org. Chem.*, 2003, **68**, 2997; (d) V.V. Zhdankin and P.J. Stang, *Chem. Rev.*, 2002, **102**, 2523.
- 10 (a) A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997, pp 6; (b) A. Varvoglis and S. Spyroudis, *Synlett*, 1997, 221.
- 11 (a) H.S. Rho, B-S Ko, H.K. Kim and Y-S. Ju, *Synth. Commun.* 2002, **32**, 1303; (b) P.A. Evans, J.D. Nelson and T. Manangan, *Synlett*, 1997, 968; (c) P.A. Evans and T.A. Brandt, *J. Org. Chem.*, 1997, **62**, 5321.
- 12 (a) E.B. Merkushev, N.D. Simakhina and G.M. Koveshnikova, *Synthesis*, 1980, 486; (b) M. D'Auria and G. Mauriello, *Tetrahedron Lett.*, 1995, **36**, 4883; (c) B. Panunzi, L. Ritiroti and M. Tingoli, *Tetrahedron Lett.*, 2003, **44**, 8753.
- 13 (a) R. Neu, *Ber. Deutsch. Chem. Ges.*, 1939, **72**, 1505; (b) V.G. Kostina, E.K. Rutkovskii and N.G. Feshchenko, *Zh. Obsch. Khim.*, 1984, **54**, 1001.
- 14 (a) A.K. Bose, S. Pednekar, S.N. Ganguly, G. Chakraborty and M.S. Manhas, *Tetrahedron Lett.*, 2004, **45**, 8351; (b) J.N. Moorthy, N. Singhal and P. Venkatakrishnan, *Tetrahedron Lett.*, 2004, **45**, 5419; (c) V.K. Balema, J.W. Wiench, M. Pruski and V.K. Pecharsky, *J. Am. Chem. Soc.*, 2002, **124** (22), 6244; (d) J.L. Scott and C.L. Raston, *Green Chem.*, 2000, **2**, 245; (e) F. Toda, T. Suzuki and S. Higa, *J. Chem. Soc. Perkin Trans. 1*, 1998, 3521.
- 15 F. Toda, K. Tanaka and A. Sekikawa, *J. Chem. Soc., Chem. Commun.*, 1987, 279.
- 16 (a) N.N. Karade, G.B. Tiwari and D.B. Huple, *Synlett*, 2005, **13**, 2039; (b) N.N. Karade, S.G. Shirodkar, B.M. Dhoot and P.B. Waghmare, *J. Chem. Res.(S)*, 2005, **4**, 274; (c) N.N. Karade, G.B. Tiwari, S.G. Shirodkar and B.M. Dhoot, *Synth. Commun.*, 2005, **35**, 1197; (d) N.N. Karade, S.G. Shirdokar, M.N. Patil, R.A. Potrekar and H.N. Karade, *Tetrahedron Lett.*, 2003, **44**, 6729.
- 17 S.M. Hubig, W. Jung and J.K. Kochi, *J. Org. Chem.*, 1994, **59**, 6233.
- 18 (a) Dictionary of Organic Compounds, Chapman & Hall: London, 6th edn, 1996; (b) Aldrich Catalogue of Chemicals, 2003.
- 19 A. Bachki, F. Foubelo and M. Yus, *Tetrahedron*, 1994, **50**, 5139.