(Diacetoxyiodo)benzene-Lithium Bromide as a Convenient Electrophilic Br^+ Source

D. Christopher Braddock,*[a] Gemma Cansell,[a] Stephen A. Hermitage[b]

[a] Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, UK

[b] GlaxoSmithKline Ltd, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK
Fax +44(207)5945805; E-mail: c.braddock@imperial.ac.uk

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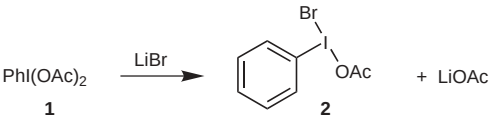
Abstract: A mild and versatile procedure for the bromination of olefins and activated arenes by in situ generation of 'Br^+' using (diacetoxyiodo)benzene and lithium bromide is presented. The reactions were carried out in open vessels at room temperature and were typically complete in 30 minutes. The brominated products were isolated by column chromatography, which also allowed for the isolation of the iodobenzene by-product for recycle.

Key words: electrophilic aromatic substitution, electrophilic addition, bromine, alkenes, hypervalent iodine

Aryl bromides and alkyl bromides are fundamental to organic chemistry, finding use as key intermediates for subsequent reactions such as metal-catalysed carbon–carbon bond formation (aryl bromides)[1] and nucleophilic substitution reactions (alkyl bromides).[2] Typically aryl bromides are generated by electrophilic substitution of an aromatic with molecular bromine.[3] Alkyl halides, are often generated from the alcohol by activation of the hydroxyl group and subsequent displacement with bromide anion (e.g., the well-known CBr_4–PPh_3 system), but for the generation of 1,2-dibromides, the electrophilic addition of molecular bromine to an alkene via a bromonium ion[4] remains the method of choice. However, despite the widespread use of molecular bromine as an electrophilic reagent it is a toxic, difficult to handle, low-boiling lachrymatory liquid, causing severe burns on contact with skin.[5] Moreover, since molecular bromine is a strong oxidizing agent, attempted bromination of complex organic substrates can be hampered by undesired competing oxidation processes.[6] In the electrophilic substitution of arenes with Br_2, the stoichiometric by-product (HBr) is toxic and leads to strongly acidic aqueous waste streams. These concerns over selectivity, handling and toxicity issues associated both with Br_2 and HBr have fuelled research into new strategies for the electrophilic bromination of organic substrates.[7]

Hypervalent iodine compounds have recently gained increasing popularity for a number of synthetically valuable transformations, exemplified by oxidation chemistry with the Dess–Martin periodinane,[8] and the so-called IBX reagent.[9] We were drawn to investigate whether an iodine(III) compound – specifically, (diacetoxyiodo) benzene, $PhI(OAc)_2$ **1** (DIB) – could be used as a synthetically useful co-reagent with anionic bromide for electrophilic bromination of arenes and alkenes. From a practical perspective, DIB is a readily available compound,[10] which also benefits from being an air-stable, crystalline solid, with good reactivity at ambient temperature. Mechanistically, it was envisaged that electrophilic 'Br^+' could be generated in situ by the reaction of the bromide anion with DIB and displacement of acetate to give putative intermediate **2** (Scheme 1). The resulting Br–I(III) bond of **2** should render the bromine atom electrophilic.



Scheme 1

The use of DIB has previously been reported to facilitate electrophilic bromination of selected substrates in combination with trimethylsilyl bromide or quaternary ammonium bromide salts.[11–15] Rho has reported the use of DIB and $TMSBr$[11a] or Bu_4NBr[11b] for the 3-bromination of flavones, and Evans used the former in the related bromination of dihydropyrans.[12] Bromoacetoxylation of 1,4-dimethoxynapthalenes using TMS-Br,[13a,b] of glycals using polymer-bound R_4NBr,[14] and of cyclic olefins with tetraethylammonium bromide[15] have also been reported but none of these methods can be considered general. Herein we now report a convenient and general method for the rapid bromination of activated aromatics, heteroaromatics and bromolactonisation or dibromination of olefins using LiBr and DIB in THF solvent. The method is practically simple, using air-tolerant reagents, with fast reaction times, giving good-to-excellent yields of the brominated products. Additionally, the iodobenzene, which is liberated as a side-product, can in principle be re-isolated and re-oxidised to DIB for further use.

A series of arenes and alkenes were selected for attempted bromination. In the event, it was found that a stoichiometric combination of DIB and LiBr in THF smoothly brominates a variety of substrates in 30 minutes at room temperature (Table 1).[16,17] Inspection of the results gathered in the Table 1 reveals that this combination of reagents is effective for the monobromination of electron-rich aromatics (entries 1–4) and heteroaromatics (entries

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5 and 6), although *m*-xylene represents the lower limit of reactivity (entry 8). Additionally, it was found that this combination of reagents is capable for the transformation of a 2,4,6-trisubstituted phenol into the corresponding 4-bromodienone (entry 9), γ-unsaturated carboxylic acids into bromolactones (entry 10), and for the dibromination of olefins when additional LiBr is present. Interestingly, it is effective for both unfunctionalised olefins (entry 11) and electron deficient ones (entry 12). Furthermore, in the case of the bromination of anisole we demonstrated the iodobenzene side-product could be recovered by chromatography (93%).

Mechanistically, several possibilities for the de facto electrophilic bromine source can be considered for the above system. In the DIB–TMSBr manifold, molecular bromine is generated as evidenced by UV–Vis experiments.[13] Rho has invoked AcOBr, when using Bu_4NBr–DIB.[11b] Alternatively, Kirschning has suggested double acetate transfer from iodine(III) in DIB to bromide to form a bromate(I) anion.[15]

In the LiBr–DIB system, the DIB is added portionwise to a homogeneous solution of LiBr and substrate in THF. An immediate bright orange colour is observed along with precipitation (LiOAc). The orange colour tends to fade as the reaction progresses. The observation of the bright orange colour could easily be interpreted as liberation of molecular bromine. However, when 4-pentenoic acid is treated with bromine, instead of essentially quantitative conversion to the bromolactone with LiBr–DIB (Table 1, entry 10), a considerable quantity of 1,2-dibromoacid **3**[18] (ca 50%) was produced alongside the bromolactone. Moreover, ageing experiments of LiBr–DIB combinations versus Br_2 in THF before the addition of anisole reveal that molecular bromine retains its activity much longer than the species resulting from DIB–LiBr (Table 2).[19] The reactive intermediate that is generated becomes considerably less active over time giving only a 56% conversion of anisole to 4-bromoanisole after 1 hour ageing of reagents, followed by a 0.5 hour reaction time cf. 98% for 5 minutes ageing.

The above experiments therefore do not support the generation of molecular bromine as the major pathway. The generation of AcOBr (from reductive elimination from putative intermediate **2**) was also considered as the possible electrophilic Br^+ source in this system. However, treatment of 4-pentenoic acid with authentically generated AcOBr[20] gave only a 50% conversion to the bromolactone, with the remainder of the product mixture comprised of 25% dibromoacid **3** (Figure 1), and a further 25% of an unidentified component.

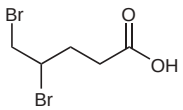

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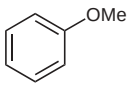
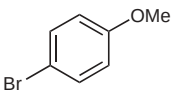
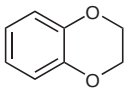
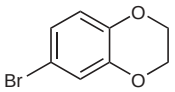
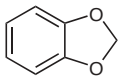
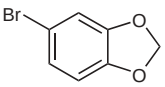
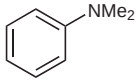
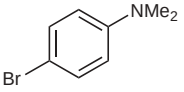
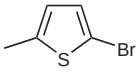
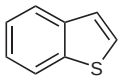
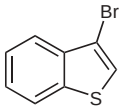
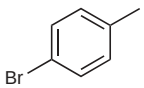
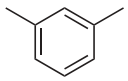
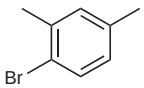
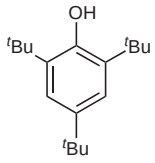
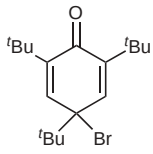
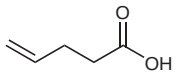
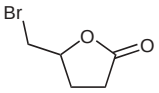
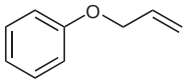
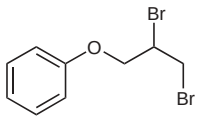
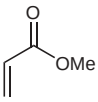
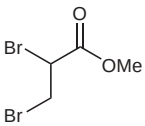
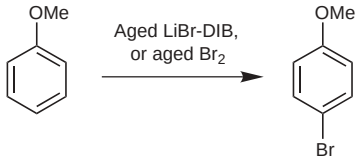
Figure 1

Table 1 Electrophilic Bromination of Substrates Using LiBr and DIB[a]

Entry	Substrate	Product	Yield[b]
1			88%
2			74%
3			71%
4			73%[c]
5			88%[d]
6			79%
7			0%
8			25%[e]
9			87%[f]
10			89%
11			87%[g]
12			80%[g,h]

[a] All the reactions were carried out on a 5 mmol scale using 1.1 equiv of both LiBr and $PhI(OAc)_2$, in THF solvent for 30 min at r.t.
[b] Isolated yields after chromatography.
[c] 18% of 2,4-dibromo-*N*,*N*-dimethylaniline was isolated.
[d] Contaminated with ca 15% PhI and ca 17% 2,4-dibromo-5-methylthiophene after chromatography.
[e] Product not isolated, crude conversion by NMR and MS.
[f] Iodobenzene was removed by distillation of the crude product leaving the product as the residue.
[g] 2.2 equiv of LiBr used.
[h] Isolated material eliminates HBr to give α-bromomethylacrolate on standing.

Table 2 Ageing Experiments in the Bromination of Anisole[a]



Time (min)	LiBr–DIB	Br_2
0	100	100
5	98	100
10	97	100
30	89	95
60	56	84

[a] The reagents (1.1 equiv.) were aged for the appropriate time in THF solvent, anisole was added, and the reaction quenched after 0.5 h.

In the light of the above experiments, we propose that the de facto electrophilic bromine source in this system is hypervalent iodine compound **2** with an I–Br bond as proposed in Scheme 1. Its mode of action may involve nucleophilic attack first at iodine followed by reductive elimination by anology with e.g., Koser's reagent,[21] or by direct electrophilic bromine transfer with concomitant loss of acetate and generation of iodobenzene.

In conclusion, we have developed a mild, rapid and efficient method for electrophilic bromination of a wide range of arene and alkene substrates using stoichiometric amounts of LiBr and (diacetoxyiodo)benzene (DIB). Irrespective of the actual mechanism, the practical simplicity of this method, avoiding the hazards of molecular bromine, and the selectivity profile for bromolactonisation compared to Br_2 makes it attractive for synthesis.

Acknowledgment

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(16) **A Typical Procedure for DIB–LiBr Bromination**: To a solution of substrate (5 mmol) and LiBr (0.48 g, 5.5 mmol) stirring in anhyd THF at r.t. in an open vessel DIB was added portionwise over 5 min (1.77 g, 5.5 mmol). The suspension was stirred for a further 25 min, water added (10 mL) and the reaction mixture extracted with CH_2Cl_2 (20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo, and chromatographed (isooctane–Et_2O) to give the brominated product.
(17) **4-Bromanisole** (Table 1, entry 1): Yield: 88%; colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 9.0 Hz, 2 H, ArH), 6.76 (d, *J* = 9.0 Hz, 2 H, ArH), 3.76 (s, 3 H, CH_3). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 158.7, 132.4, 115.8, 112.9, 55.4. MS (EI): *m*/*z* = 186, 188 [M^+·]. HRMS: *m*/*z* calcd for $C_7H_7O^{79}Br$: 185.9680; found: 185.9697. **6-Bromo-2,3-dihydrobenzo[1,4]dioxine** (Table 1, entry 2): Yield: 74%; Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 2.4 Hz, 1 H, ArH), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1 H, ArH), 6.72 (d, *J* = 8.8 Hz, 1 H, ArH), 4.20 (br s, 4 H, CH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 142.9, 124.3, 120.3, 118.6, 112.8, 64.3, 64.2. MS (EI): *m*/*z* = 214, 216 [M^+·]. HRMS: *m*/*z* calcd for $C_8H_7O_2{}^{79}Br$: 213.9629; found: 213.9628. **5-Bromobenzo[1,3]dioxole** (Table 1, entry 3): Yield: 71%; colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (m, 2 H, ArH), 6.66 (d, *J* = 8.8 Hz, 1 H, ArH), 5.95 (s, 2 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 147.0, 124.3, 113.1, 112.3, 109.6, 101.7. MS (EI): *m*/*z* = 200, 202 [M^+·]. HRMS: *m*/*z* calcd for $C_7H_5O_2{}^{79}Br$: 199.9473; found: 199.9473. **4-Bromo-*N*,*N*-dimethylaniline** (Table, entry 4): Yield: 73%; colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H, ArH), 6.55 (d, *J* = 8.7 Hz, 2 H, ArH), 2.89 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 131.7, 114.1, 108.5, 40.6. MS (ES): *m*/*z* = 200, 202 [MH^+]. HRMS: *m*/*z* calcd for $C_8H_{11}NBr$: 200.0075; found: 200.0084. **2-Bromo-5-methylthiophene** (Table 1, entry 5): Yield: 88%; colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 3.7 Hz, 1 H, ArH), 6.51 (d, *J* = 3.7 Hz, 1 H, ArH), 2.42 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 129.6, 125.5, 108.5, 15.5. MS (EI): *m*/*z* = 176, 178 [M^+·]. HRMS: *m*/*z* calcd for $C_5H_5S^{79}Br$: 175.9295; found: 175.9336. **3-Bromo-benzo[*b*]thiophene** (Table 1, entry 6): Yield: 79%; colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.80 (m, 2 H, ArH), 7.40 (t, *J* = 7.4 Hz, 1 H, ArH), 7.35–7.32 (m, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 137.6, 127.6, 125.1, 123.6, 123.2, 122.8, 107.8. MS (EI): *m*/*z* = 212,

214 [M^+·]. HRMS: *m*/*z* calcd for $C_8H_5S^{79}Br$: 211.9295; found: 211.9285. **4-Bromo-2,4,6-tri-*tert*-butylcyclohexa-2,5-dienone** (Table 1, entry 9): Yield: 87%; orange crystalline solid; mp 71–73 °C [lit.[22] 80.5–81.5 °C]. IR (CH_2Cl_2): 1656, 1636 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 2 H, ArH), 1.25 [s, 18 H, 2- and 6-C$(CH_3)_3$], 1.14 [s, 9 H, C$(CH_3)_3$)]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0, 145.2, 139.9, 72.5, 40.0, 35.0, 29.4, 26.5. MS (CI^+): 341, 343 [MH^+]. HRMS: *m*/*z* calcd for $C_{18}H_{30}O^{79}Br$: 341.1480; found: 341.1472. **5-Bromomethyl-γ-butyrolactone** (Table, 1 entry 10): Yield: 89%; colourless oil. IR (thin film; NaCl): 1777 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 4.71 (m, 1 H, OC*H*), 3.51 (d, *J* = 5.1 Hz, 2 H, CH_2Br), 2.70–2.32 (m, 3 H, *CHHCH*$_2$), 2.17–1.96 (m, 1 H, CH*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 176.4, 78.0, 34.5, 28.5, 26.2. MS (CI^+): *m*/*z* = 196, 198 [M + NH_4^+]. MS (CI^-): 79, 81 [Br]. HRMS: *m*/*z* calcd for $C_5H_{11}{}^{79}BrNO_2$: 195.9973; found: 195.9971. **(2,3-Dibromopropoxy)benzene** (Table 1, entry 11): Yield: 87%; colourless oil. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.37 (dt, *J* = 7.6, 0.9 Hz, 2 H, ArH), 7.07 (t, *J* = 7.6 Hz, 1 H, ArH), 6.99 (d, *J* = 7.6, 2 H, ArH), 4.49–4.32 (m, 3 H), 4.02–3.91 (m, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 158.1, 129.6, 121.9, 115.0, 69.2, 48.0, 33.1. MS (EI): *m*/*z* = 292, 294, 296 [M]. HRMS: *m*/*z* calcd for $C_5H_{11}{}^{79}Br_2NO_2$: 291.9098; found: 291.9092. **Methyl 2,3-Dibromopropionate** (Table 1, entry 12): Yield: 80%; orange oil. ^1H NMR (270 MHz, $CDCl_3$): δ = 4.40 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.87 (dd, *J* = 11.2, 9.9 Hz, 1 H), 3.79 (s, 3 H, CH_3), 3.63 (dd, *J* = 9.9, 4.4 Hz, 1 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 168.2, 53.5, 40.8, 29.7.

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(19) However, ^1H NMR studies of LiBr–DIB in THF-d_8 failed to detect any new species: only $PhI(OAc)_2$ and PhI could be observed.
(20) (a) Beebe, T. R.; Wolfe, J. W. *J. Org. Chem.* **1970**, *35*, 2056. (b) This reagent was prepared in situ, and its activity confirmed by conversion of *cis*-cyclooctene to *trans*-1-bromo-2-acetoxy-cyclooctane.
(21) See for example:Stang, P. J.; Zadankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.
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