Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 5587–5590
Tetrahedron Letters

$NaIO_4$-mediated C–H activation of alkylbenzenes and alkanes with LiBr

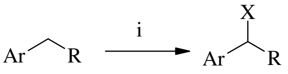
Tanveer M. Shaikh and Arumugam Sudalai*

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India

Received 2 December 2004; revised 26 May 2005; accepted 6 June 2005
Available online 1 July 2005

Abstract—$NaIO_4$ oxidizes lithium bromide efficiently under acidic conditions to functionalize alkylbenzenes and alkanes and produce the corresponding bromo and acetoxy derivatives in excellent yields. The protocol also demonstrates the direct conversion of cyclohexane into *trans*-1,2-dibromocyclohexane in moderate yield.

The selective and efficient activation of unreactive C–H bonds in aliphatic hydrocarbons is particularly difficult and constitutes one of the major challenges in organic chemistry.[1] In recent years, several catalytic methods have been developed for the oxidation of aliphatic hydrocarbons using enzymes, transition metal complexes, processes involving halogenations, etc.[2] In particular, oxidation at the benzylic position of alkylbenzenes assumes importance due to their oxygenated derivatives such as peroxides, alcohols and carbonyl compounds being useful as speciality chemicals in industry.[3] Generally, C–H activation at benzylic positions is achieved using peroxides as oxidants and a variety of transition metal salts as catalysts.[4] However, several drawbacks are associated with these processes including: (i) the toxicity of some transition metals, (ii) stoichiometric reaction conditions and (iii) non-generality. Recently, we reported that sodium periodate ($NaIO_4$) oxidizes alkali metal halides efficiently in aqueous medium for halogenation of alkenes and aromatics and produces the corresponding halo derivatives with excellent regio and stereoselectivity.[5] In this letter, we wish to report that $NaIO_4$ oxidatively functionalizes the C–H bonds of alkylarenes and alkanes in combination with lithium bromide as the halogen source under acidic conditions (Scheme 1). When toluene was heated with lithium bromide (1.1 m equiv) and conc. H_2SO_4 (2 M equiv) in the presence of catalytic $NaIO_4$ (25 mol%) in MeOH at 65 °C, the corresponding benzylic bromide **1** and methyl ether **2** were obtained as a mixture in good overall yield (Table 1).



X = Br, OMe or OAc

Scheme 1. Reagents and conditions: (i) alkylarene (5 mmol), $NaIO_4$ (25 mol%), LiBr (5.5 mmol), MeOH, H_2SO_4 or glacial AcOH, 65–110 °C, 24 h.

Surprisingly, no reaction took place when other halide sources such as NaBr, NaI, LiCl and KI were employed. In the absence of $NaIO_4$, no reaction took place; lowering the molar ratio of $NaIO_4$ also resulted in reduced yield. It was found that the use of 25 mol% $NaIO_4$ and the correct choice of solvent under acidic conditions (H_2SO_4 or AcOH) were critical in achieving high levels of conversion of the alkylarenes with high product selectivity. While in the case of isobutylbenzene the corresponding methyl ether was obtained as the sole product (42%), only the benzylic bromo compound (31%) was obtained when acetonitrile was used as solvent.

Table 2 shows[6] examples of the $NaIO_4$-mediated oxidative bromination/acetoxylation of several alkylbenzenes and arenes with LiBr in glacial acetic acid as solvent. Interestingly, high yields (60–87%) and selective

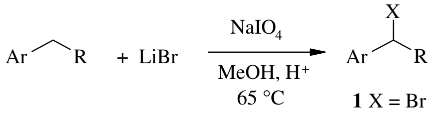
---

Keywords: C–H activation; Alkylbenzenes; Alkanes; $NaIO_4$; Lithium bromide.

* Corresponding author. Tel.: +91 020 25893300; fax: +91 020 25893359; e-mail: a.sudalai@ncl.res.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.033

Table 1. $NaIO_4$-mediated oxidative bromination and methoxylation of alkylarenes with metal halides[a]

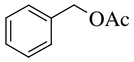
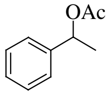
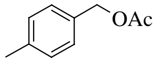
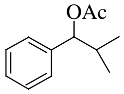
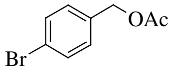
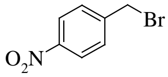
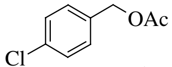
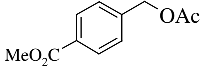
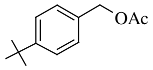


1 X = Br
2 X = OMe

Entry	Substrate	Metal halide	Solvent	Temp (°C)	Yield[b] (%)	
					1	2
1	Toluene	LiBr	MeOH	65	47	36
		LiBr	CH_3CN	80	31	—
		NaBr	MeOH	65	NR	—
2	Ethylbenzene	LiBr	MeOH	65	36	43
3	*p*-Xylene	LiBr	MeOH	65	45	30
4	Isobutylbenzene	LiBr	MeOH	65	—	42

[a] Conditions: substrate (10 mmol), $NaIO_4$ (25 mol%), metal bromide (11 mmol), concd H_2SO_4 (0.5 mL, 20 mmol), solvent (15 mL), 24 h.
[b] Isolated yield after chromatographic purification.

Table 2. $NaIO_4$-mediated oxidative bromination and acetoxylation of alkylarenes with LiBr[a]

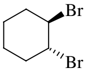
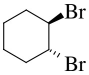
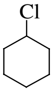
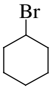
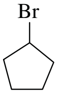
Entry	Substrate	Temp[b] (°C)	Product[c]	Yield[d] (%)
1	Toluene	110		87 (31,[e] 83,[f] 37[g])
2	Ethylbenzene	90		85
3	*p*-Xylene	100		75
4	Isobutylbenzene	110		80
5	4-Bromotoluene	110		60
6	4-Nitrotoluene	110		80
7	4-Chlorotoluene	110		80
8	Methyl 4-methyl benzoate	110		66
9	4-*tert*-Butyltoluene	110		60

[a] Conditions: substrate (10 mmol), $NaIO_4$ (25 mol%), LiBr (11 mmol), glacial acetic acid (15 mL), 24 h.
[b] Oil bath temperature.
[c] All products were characterized by ^1H and ^{13}C NMR, GC–MS and IR.
[d] Isolated yields after column chromatographic purification.
[e] Yield corresponds to when 20 mol% of LiBr was used.
[f] Yield corresponds to the use of Br_2 (2 equiv) as the halogen source. However, in the absence of $NaIO_4$, only benzyl bromide (60%) was formed.
[g] Yield corresponds to the use of NaBr (1.1 equiv) as halide source.

acetoxylation at the benzylic position were observed with all the alkylarenes studied except for 4-nitrotoluene (Table 2, entry 6), where the corresponding benzyl bromide was obtained as the sole product. We observed that both LiBr and $NaIO_4$ were required in the oxidation of the alkylarenes at the benzylic position. Also when the quantity of $NaIO_4$ was reduced to 5 mol%, the yield of benzyl acetate was reduced considerably (9%). Furthermore, *p*-toluic acid failed to undergo oxidative bromination at the benzylic position.

Table 3 shows the results of $NaIO_4$-mediated oxidative bromination of alkanes with LiBr as the bromide source. Surprisingly, cyclohexane underwent oxidative bromination to produce *trans*-1,2-dibromocyclohexane

Table 3. $NaIO_4$-mediated oxidative halogenation of alkanes using LiBr[a]

Entry	Substrates	Halides (equiv)	Temp (°C)	Product	Yield[b] (%)
1	Cyclohexane	LiBr (1.1)	80		28
		LiBr (2.1)	80		40
		LiBr (2.1)	25	No reaction	—
	Cyclohexane[c]	Cl_2 excess	80		60
		Br_2 (2.1)	80		13[d]
2	Cyclopentane	LiBr (2.1)	60		37
3	Octane	LiBr (2.1)	100	Bromooctane[e]	41
4	Heptane	LiBr (2.1)	90	Bromoheptane[e]	30

[a] Conditions: substrate (10 mmol), LiBr (11 or 22 mmol), $NaIO_4$ (25 mol%), glacial AcOH (15 mL), 80 °C, 24 h.

[b] Isolated yield.

[c] $NaIO_4$ (25 mol%) and excess chlorine gas was bubbled through the reaction mixture at 80 °C for 5 h.

[d] Yield of cyclohexyl bromide when no $NaIO_4$ was used.

[e] Isomeric mixtures of bromoalkanes.

$$\begin{array}{rcl} 8\,\mathrm{Br}^- & \longrightarrow & 4\,\mathrm{Br}_2 + 8\,e^- \\ \mathbf{IO_4}^- + 8\,\mathrm{H}^+ + 8\,e^- & \longrightarrow & \mathbf{I}^- + 4\,\mathrm{H_2O} \\ 4\,\mathrm{Ar\text{-}CH_3} + 4\,\mathrm{Br_2} & \longrightarrow & 4\,\mathrm{Ar\text{-}CH_2Br} + 4\,\mathrm{HBr} \\ 4\,\mathrm{Ar\text{-}CH_2Br} + 4\,\mathrm{AcOH} & \longrightarrow & 4\,\mathrm{Ar\text{-}CH_2OAc} + 4\,\mathrm{HBr} \\ \hline 4\,\mathrm{Ar\text{-}CH_3} + \mathbf{IO_4}^- + 8\,\mathrm{Br}^- + 8\,\mathrm{H}^+ + 4\,\mathrm{AcOH} & \longrightarrow & 4\,\mathrm{Ar\text{-}CH_2OAc} + \mathbf{I}^- + 8\,\mathrm{HBr} + 4\,\mathrm{H_2O} \end{array}$$

Scheme 2.

in 28% isolated yield. Notably, a higher isolated yield (40%) of *trans*-1,2-dibromocyclohexane was obtained when 2.1 equiv of LiBr were employed. However, in the case of cyclopentane (Table 3, entry 2), only monobromocyclopentane was obtained in 37% yield. Interestingly, when linear alkanes such as *n*-octane and *n*-heptane were subjected to oxidative bromination with equimolar LiBr, a mixture of three bromoalkanes in the ratio ca. 1:1:1 was obtained (confirmed by GC–MS), which were difficult to isolate in pure form.

In order to gain insight into the mechanism, the following experiments were carried out: (i) when benzyl bromide was refluxed with either glacial acetic acid or methanol in the absence of $NaIO_4$, no reaction took place. However, addition of 25 mol% of $NaIO_4$ to the reaction mixture produced benzyl acetate in 72% yield. A further increase in the molar ratio of $NaIO_4$ (>30 mol%) did not produce any significant increase in yield. This probably indicates that the first step involves bromination at the benzylic position. (ii) KIO_3 and NaI have been found to be effective in mediating the transformation of benzyl bromide, thus producing benzyl acetate in 47% and 16% yield, respectively. (iii) A cyclic voltammogram study revealed[5] that Br_2 generated in situ from LiBr by oxidation with $NaIO_4$, is probably responsible for rapid bromination of the alkyl benzenes to produce bromo derivatives. Finally, benzyl bromide is solvolyzed[7] with AcOH and a rate enhancement in solvolysis was observed with the addition of either IO_4^-, IO_3^- or I^- salts. Scheme 2 shows a plausible mechanism for the formation of benzyl acetate from toluene.

In the case of cyclohexane the formation of *trans*-1,2-dibromocyclohexane probably indicates the involvement of cyclohexene as the intermediate, followed by bromine addition to the double bond.

In conclusion, we have described a simple and efficient $NaIO_4$-mediated oxidative bromination as well as acetoxylation procedure that allows the transformation of alkylbenzenes into their corresponding benzyl acetates in excellent yields. A novel feature of the present catalytic process is that cyclohexane could be converted directly into *trans*-1,2-dibromocyclohexane in a single step in 40% isolated yield.

Acknowledgements

T.M. thanks the Department of Science and Technology, New Delhi for financial support of this work (Sanction No. SR/S1/OC-22/2002) and the authors thank Dr. B. D. Kulkarni, Head, CE-PD, for his constant encouragement.

References and notes

1. (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932; (b) Hill, C. L. *Activation and Functionalization of Alkanes*; John Wiley: New York, 1989; (c) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437–2450; (d) Schreiner, P. R.; Fokin, A. A. *Chem. Rec.* **2004**, *3*, 247–257; (e) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.
2. (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032–1033; (b) Sels, B.; Vos, D. D.; Buntinx, M.; Pierard, F.; Mesmaekar, A. K.; Jacobs, P. A. *Nature* **1999**, *400*, 855–857; (c) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Fokin, A. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2786–2788; (d) Schreiner, P. R.; Lauenstein, O.; Kolomitsyn, I. V.; Nadi, S.; Fokin, A. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1895–1897; (e) Asadullah, M.; Kitamura, T.; Fujiwara, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 2475–2478; (f) Barluenga, J.; Gonzalez-Bobes, F.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2556–2558; (g) Jones, C. J.; Taube, D.; Ziatdinov, V. R.; Periana, R. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4626–4629; (h) Barton, B.; Hlohloza, N. S.; McInnes, S. M. *Org. Process Res. Dev.* **2003**, *7*, 571–576; (i) Barton, B.; Logie, C. G.; Schoones, B. M.; Zeelie, B. *Org. Process Res. Dev.* **2005**, *9*, 62–69; (j) Barton, B.; Logie, C. G.; Schoones, B. M.; Zeelie, B. *Org. Process Res. Dev.* **2005**, *9*, 70–79.
3. (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639; (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1769.
4. (a) Bergman, J.; Engman, L. *Tetrahedron Lett.* **1978**, *35*, 3279–3282; (b) Minisci, F.; Araneo, S.; Recupero, F. *J. Chem. Soc., Chem. Commun.* **1994**, 1823–1824; (c) Feldberg, L.; Sasson, Y. *Tetrahedron Lett.* **1996**, *37*, 2063–2066; (d) Nikalje, M. D.; Sudalai, A. *Tetrahedron* **1999**, *55*, 5903–5908; (e) Ebitani, E.; Choi, K.; Mizugaki, T.; Kaneda, K. *Langmuir* **2002**, *18*, 1849–1855; (f) Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* **2003**, *44*, 8955–8957; (g) Benhmid, A.; Narayana, K. V.; Martin, A.; Lucke, B. *Chem. Commun.* **2004**, 2118–2119; (h) Miyafuji, A.; Katsuki, T. *Synlett* **1997**, *7*, 836–838.
5. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501–4504.
6. To a stirred mixture of alkylbenzene (10 mmol) and LiBr (11 mmol) in glacial acetic acid (15 mL), $NaIO_4$ (25 mol%) was added and reaction mixture heated to 90–110 °C. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water (30 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with a dilute solution of sodium thiosulfate, 5% $NaHCO_3$ and brine then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, petroleum ether and ethyl acetate (9:1) as eluent) to afford the pure product.
7. Bergman, J.; Engman, L. *J. Org. Chem.* **1982**, *47*, 5191–5196.