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An Unexpected Oxidation of Unactivated Methylene C−H Using DIB/TBHP Protocol

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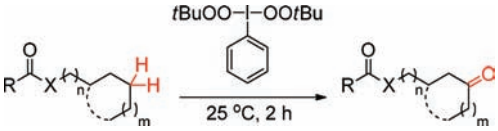
ABSTRACT



An in situ generated hypervalent iodine species, bis(*tert*-butylperoxy)iodobenzene, was used as a peroxy radical source for the oxidation of unreactive, remote, and isolated alkyl (cyclic or aliphatic) esters and amides to the corresponding keto compounds under very mild conditions.

Unactivated sp^3 C−H oxidation is an important class of organic transformation. Inexpensive hydrocarbons from petrochemical feedstocks can be functionalized as high-value building blocks and intermediates.[1] In addition, the direct functionalization of the inert carbons can often shorten the synthetic sequences,[2] which is of particular interest to the manufacturing sectors.[3] Despite the importance and the power of this class of reaction, this research area remains challenging and a major obstacle is the high energy of the unactivated C−H bond that makes it very inert toward many reagents.[4] Over the past decades, significant endeavors have been dedicated involving the use of metallic[5,6] and nonmetallic[7,8] reagents/catalysts.[9] Herein we describe an unexpected and unprecentented oxidation of unreactive, remote, and isolated sp^3 methylene C−H to ketone using a diacetoxyiodobenzene (DIB) (**1**)/*tert*-butylhydroperoxide (TBHP) (**2**) protocol.

Diacetoxyiodobenzene (DIB) (**1**), a commercially available and inexpensive reagent, is frequently used as the stoichiometric oxidant in many reactions, including the

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(1) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514. (c) Godula, K.; Sames, D. *Science* **2010**, *312*, 67–72.

(2) (a) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223–226. (b) Hoffmann, R. W. *Synthesis* **2006**, 3531–3541. (c) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824–828. (d) Ishihara, Y.; Baran, P. S. *Synlett* **2010**, *12*, 1733–1745.

(3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J., Jr.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411–420.

(4) (a) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255–263. (b) Chen, K.; Eschenmoser, A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9705–9708.

(5) (a) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566–571. (b) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783–787. (c) Gomez, L.; Garcia-Bosch, I.; Company, A.; Benet-Buchholz, J.; Polo, A.; Sala, X.; Ribas, X.; Costas, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5720–5723. (d) Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. *Nature Chem.* **2010**, *2*, 478–483. (e) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379–3394. (f) McNeill, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202–10204. (g) Murahashi, S. I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490–1501. (h) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560–564. (i) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149–8150. (j) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (k) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655. (l) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(6) (a) Yiu, S.-M.; Wu, Z.-B.; Mak, C.-K.; Lau, T.-C. *J. Am. Chem. Soc.* **2004**, *126*, 14921–14929. (b) Nehru, K.; Kim, S. J.; Kim, I. Y.; Seo, M. S.; Kim, Y.; Kim, S.-J.; Kim, J.; Nam, W. *Chem. Commun.* **2007**, 4623–4625. (c) Lindsay Smith, J. R.; Shul'pin, G. B. *Tetrahedron Lett.* **1998**, *39*, 4909–4912.

(7) (a) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1–9. (b) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247–7249. (c) Litvinas, N. D.; Brodsky, B. H.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4513–4516. (d) DesMarteau, D. D.; Donadelli, A.; Montanari, V.; Petrov, V. A.; Resnati, G. *J. Am. Chem. Soc.* **1993**, *115*, 4897–4898. (e) Wirth, T., Ed. *Hypervalent Iodine Chemistry*; Topics in Current Chemistry; Springer, Berlin, 2003, Vol. 224. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (g) Ochiai, M. *Coord. Chem. Rev.* **2006**, *250*, 2771–2781.

(8) (a) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247–7249. (b) Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. *Nature Chem.* **2010**, *2*, 478–483.

(9) For an excellent review, see:Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374.

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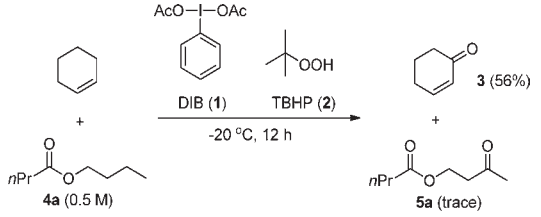
activated sp^3 C−H functionalization, which has been applied in the synthesis of useful building blocks and biologically active molecules.[7e,f] In contrast, limited cases were reported on the unreactive C−H activation using hypervalent iodine(III) reagents.[10] To the best of our knowledge, up to now, there is no report regarding to the oxidation of the unactivated, remote, and isolated methylene sp^3 C−H to ketone using hypervalent iodine reagent.

Very recently, we have reported a novel method in the generation of a reactive but controllable *t*BuOO• radical and its application to allylic oxidation.[11] Ester solvent was found to be necessary in the reaction, and an ester-coordinated hypervalent iodine intermediate was proposed. In fact, trace amount of side product was obtained consistently in each of the allylic oxidation reaction (e.g., Scheme 1, cyclohexene→**3**). After a very careful study, the side product was identified as keto-ester **5a**, which seemed to be a consequence of the C−H oxidation of ester solvent **4a** (Scheme 1).

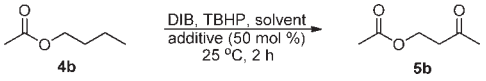
Scheme 1. DIB/TBHP Allylic Oxidation



This unexpected product led us to further investigate the possibility of using the DIB/TBHP protocol in the unreactive C−H oxidation. An initial experiment was performed using the structurally simpler *n*-butyl acetate (**4b**) under the same allylic oxidation conditions in the absence of olefin (Table 1). After 12 h at 25 °C, 10% of the desired product **5b** was obtained. Encouraged by this result, further optimizations were performed using **4b** as the stoichiometic reagent. Various solvents were screened, and acetonitrile was found to afford 38% of the keto-ester product (Table 1, entry 5). Interestingly, the yield was increased to 48% when the nonaqueous TBHP was changed to 70% aqueous TBHP (Table 1, entry 6). Unlike the allylic oxidation reaction, neither a base nor an acid additive can enhance the C−H oxidation; in fact, somewhat deteriorating effects on the reaction yields were observed (Table 1, entries 8−10). Finally, the reaction was equally smooth on a 1 mmol scale (Table 1, entry 7).

Having identified the appropriate conditions, other esters were subjected to the investigation and the results are summarized in Table 2.[12,13] Reactions using *n*-butyl alkanoates/benzoate proceeded smoothly to yield the corresponding keto-esters with good positional selectivities and conversions (Table 2, entries 1−3). For the esters with cycloalkane skeletons, position-selective products were also isolated (Table 2, entries 4, 5, 7, and 8). Other than the esters, alkanes with tosylate substituents could also be converted to the corresponding keto products (Table 2, entries 6 and 8). The selectivity appears to follow the inherent substrate preferences that were discovered in some studies.[5−8]

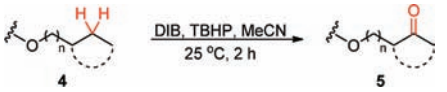
Table 1. Optimization of the DIB/TBHP C−H Oxidation

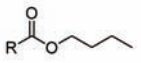
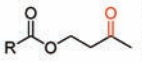
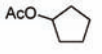
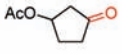
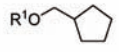
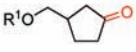
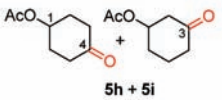
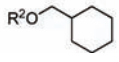
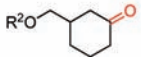


entry[a]	solvent	additive	isolated yield (%)
1	EtOAc		trace
2	CH_2Cl_2		trace
3	H_2O		14
4	$MeNO_2$		25
5	MeCN		38
6[b]	*MeCN*		*48*
7[b,c]	MeCN		46
8[b]	MeCN	K_2CO_3	48
9[b]	MeCN	$Mg(OAc)_2 \cdot 4H_2O$	29
10[b]	MeCN	AcOH	29

[a] Reactions were carried out with *n*-butyl acetate **4b** (0.5 mmol), DIB (**1**) (1.5 mmol), TBHP (**2**) (6 M in decane, 2.0 mmol), and additive (0.25 mmol) in solvent (0.5 mL). [b] 70% TBHP (**2**) in water was used. [c] Reaction was perform on a 1 mmol scale.

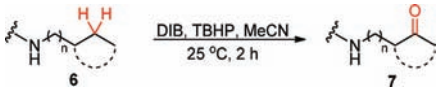
Table 2. DIB/TBHP C−H Oxidation of Alkyl Esters **4**[a]

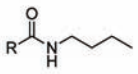
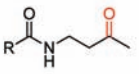
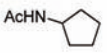
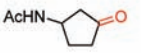
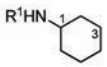
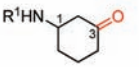
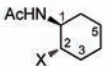
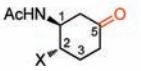


entry	substrate	product	% yield[b]
1		 **5a** (R = *n*Pr)	55(42)
2		**5c** (R = Et)	56(42)
3		**5d** (R = Ph)	53(43)
4		 **5e**	32(49)
5		 **5f** (R^1 = Ac)	40(33)
6		**5g** (R^1 = Ts)	40(47)
7[c]		 **5h + 5i**	52(45)[c]
8		 **5j** (R^2 = Ac)	42(45)
9		**5k** (R^2 = Ts)	42(46)

[a] Reactions were carried out with substrate **4** (0.5 mmol), DIB (**1**) (1.5 mmol), TBHP (**2**) (70% in water, 2.0 mmol) in MeCN (0.5 mL). [b] The yield of the isolated product **5**. The amount of unreacted starting material **4** was determined by ^{1}H NMR and indicated in the parentheses. [c] **5h**:**5i** = 1:2 determined by ^{1}H NMR.

Table 3. DIB/TBHP C−H Oxidation of Alkyl Amides **6**[a]

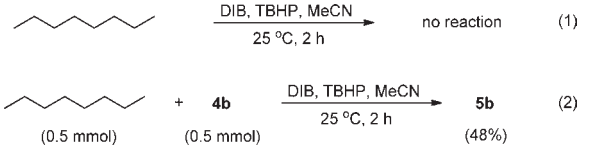


entry	substrate	product	% yield[b]
1			
2		**7a** (R = Me) **7b** (R = Ph)	36(36) 36(50)
3			
		7c	41(40)
4			
5		**7d** (R^1 = Ac) **7e** (R^1 = Boc)	43(40) 40(38)
6		**7f** (R^1 = Ts)	45(42)
7			
8		**7g** (X = Cl) **7h** (X = Br)	40(46) 35(50)

[a] Reactions were carried out with substrate **6** (0.5 mmol), DIB (**1**) (1.5 mmol), TBHP (**2**) (70% in water, 2.0 mmol) in MeCN (0.5 mL). [b] The yield of the isolated product **7**. The amount of unreacted starting material **6** was determined by ^{1}H NMR and indicated in the parentheses.

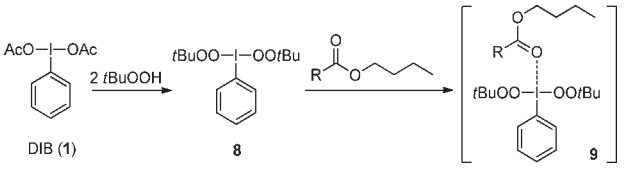
Other than esters, amides with similar skeletons were also examined (Table 3). The desired keto-amides were furnished (Table 3, entries 1−4). In addition to amides, carbamate and *N*-tosylate substrates could be also utilized in this reaction (Table 3, entries 5 and 6). It is worthwhile to note that the amide could be oxidized to the *N*-oxide product when dioxirane oxidant was used.[14] Nevertheless, the amides in the present study could tolerate the DIB/TBHP oxidation environment. In the case of using haloamides **6g** and **6h**, C(5) oxidized products **7g** and **7h** were isolated as the only isomers which could be attributed to the deactivation of C(3) position by the halogens both sterically and electronically (Table 3, entries 7 and 8).

Scheme 2. Attempts to Oxidize *n*-Octane



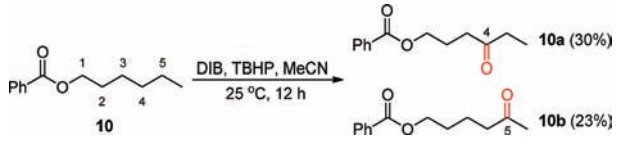
During our investigation, several clues were unearthed that may allow us to get a better understanding on the mechanistic picture. First, when *n*-octane was subjected to the standard DIB/TBHP oxidation conditions, no reaction was observed and the starting material was recovered quantitatively (Scheme 2, eq 1). A mixture of equal molar of *n*-octane and **4b** under the same conditions resulted in **5b** (48%), and no *n*-octane-associated product was detected (Scheme 2, eq 2).

Scheme 3. A Plausible Intermediate **9**



Second, we have compared the DIB/TBHP protocol with some common *tert*-butylperoxy radical sources including Cr,[15a] Mn,[15b] Pd/C,[15c] and $Pd(OH)_2/C$[15d] systems, and these protocols were unable to offer any C−H oxidation product. Although it is premature to draw a conclusion at this stage, the clues suggest that the carbonyl group of the substrates and the iodine-peroxy species **8**[11,16] may be important for the reactivity. One possibility is that an ester-coordinated hypervalent iodine species **9**, an intermediate that was proposed in the DIB/TBHP allylic oxidation, may also exist in this type of reaction (Scheme 3).[11]

Scheme 4. DIB/TBHP C−H Oxidation **10**



(10) (a) Tanner, D. D.; Van Bostelen, P. B. *J. Org. Chem.* **1967**, *32*, 1517–1521. (b) Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716–7730. (c) González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326–2328. (d) Francisco, C. G.; Herrera, A. J.; Kennedy, A. R.; Melián, D.; Suárez, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 856–858. (e) Barluenga, J.; González-Bobes, F.; González, J. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2556–2558. (f) Barluenga, J.; Campos-Gómez, E.; Rodríguez, D.; González-Bobes, F.; González, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5851–5854. (g) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

(11) Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128–2131.

(12) The details appear in the Supporting Information.

(13) Representative procedure: to a solution of *n*-butyl benzoate (**4d**) (89 mg, 0.5 mmol) in acetonitrile (0.5 mL) was added (diacetoxyiodo)benzene (483.1 mg, 1.5 mmol) at 25 °C under ambient atmosphere. The resultant suspension was vigorously stirred and a solution of *tert*-butylhydroperoxide (70% in water, 276 μL, 2.0 mmol) was added dropwise over 30 min. After the addition, the reaction mixture was stirred for 1.5 h followed by chromatography on silica gel with *n*-hexanes/diethyl ether (2:1) to yield 3-oxo-butyl benzoate (**5d**) as a yellow oil (51 mg, 52%).

(14) Annese, C.; D'Accolti, L.; De Zotti, M.; Fusco, C.; Toniolo, C.; Williard, P. G.; Curci, R. *J. Org. Chem.* **2010**, *75*, 4812–4816.

(15) (a) Pearson, A. J.; Chen, Y.-S.; Hsu, S.-Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235–1238. (b) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151. (c) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233. (d) Yu, J.-Q.; Wu, H.-C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415–1417.

(16) (a) Milas, N. A.; Plesničar, B. *J. Am. Chem. Soc.* **1968**, *90*, 4450–4453. (b) Dolenc, D.; Plesničar, B. *J. Am. Chem. Soc.* **1997**, *119*, 2628–2632.

(17) Similar long alkyl ester substrates were investigated in some studies (ref 5), which the terminal methylene C-H was more readily to be oxidized. It seems the result of oxidation of **10** in the present studies is not following the inherent properties and this unusual phenomenon is subjected to further investigation.

We have also attempted to apply the optimized protocol to a longer alkyl ester. Preliminary studies showed that the oxidation of **10** under the standard conditions gave **10a** (30%) and **10b** (23%) (Scheme 4).[17]

In summary, we have described a novel unactivated, remote, and isolated methylene C−H oxidation using the DIB/TBHP protocol. The reaction is mild, efficient, and site-specific. The experimental setup is extremely simple using inexpensive and commercially available materials. Future studies will be focused on studying the mechanistic and expanding the substrate scope.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.