ORGANIC LETTERS
2010
Vol. 12, No. 9
2128−2131

An Unprecedented Method for the Generation of *tert*-Butylperoxy Radical Using DIB/TBHP Protocol: Solvent Effect and Application on Allylic Oxidation

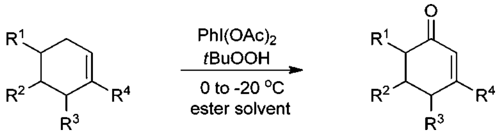
Yi Zhao and Ying-Yeung Yeung*

*Department of Chemistry, National University of Singapore, 3 Science Drive 3,
Singapore 117543*

chmyyy@nus.edu.sg

Received March 17, 2010

ABSTRACT



***tert*-Butylperoxy radical was generated with $PhI(OAc)_2$ and *t*BuOOH. Ester solvent was found to be critical and the protocol was applied in the allylic oxidation of various olefinic substrates, which gave the corresponding α,*β*-unsaturated enones in good yield and regioselectivity.**

Allylic oxidation of olefins is an important and useful organic transformation. The corresponding α,*β*-unsaturated enone products are commonly known as pharmacophores and building blocks in many organic syntheses.[1] In particular, allylic oxidation of Δ^5-steroids to Δ^5-en-7-ones is of interest because Δ^5-en-7-ones show excellent results in the prevention and treatment of cancer and can inhibit the biosynthesis of sterol.[2] Several metallic based allylic oxidations were documented, which generally encountered problems such as long reaction time, limited scope, low functional group tolerance, low regioselectivity, high cost, and/or difficult catalyst preparation.[3]

In contrast, sporadic studies were reported on the nonmetallic based generation of *tert*-butylperoxy radical **3** and application on allylic oxidation.[5] In 1968, Milas et al. reported the ligand exchange between diacetoxyiodobenzene (DIB) (**1**) and *tert*-butyl hydroperoxide (TBHP) to give bis(*tert*-butylperoxy)iodobenzene (**2**), which readily underwent elimination to yield **4** and decomposed through a **4** → **5** → **6** sequence accompanied by the evolution of molecular oxygen at −75 °C (Scheme 1, eq 1).[4] An interesting strategy using a fixed apical ligand to provide a stable *tert*-butylp-

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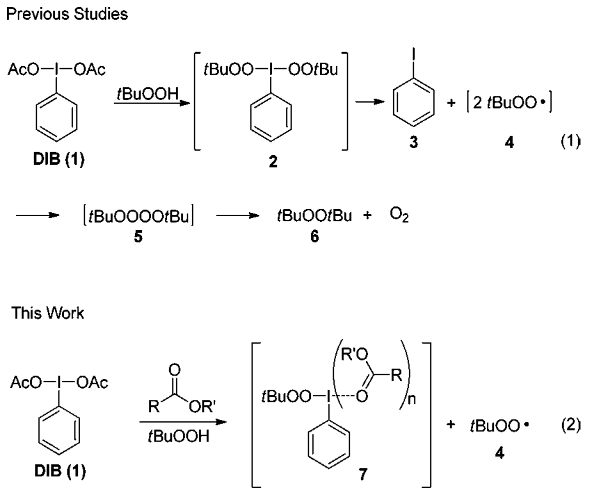
(1) Page, P. C. B.; McCarthy, T. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 7, pp 83−149.

(2) (a) Cheng, K. P.; Nagana, H.; Bang, L.; Ourisson, G. *J. Chem. Res. (S)* **1977**, 217. (b) Nagana, H.; Poyser, J. P.; Cheng, K. P.; Bang, L.; Ourisson, G. *J. Chem. Res. (S)* **1977**, 218. (c) For a review see: Parish, E. J.; Kizito, S. A.; Qiu, Z. *Lipids* **2004**, 801. (d) Arsenou, E. S.; Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S. *Mini Rev. Med. Chem.* **2003**, *3*, 557. (e) Smith, L. *Lipids* **1996**, *31*, 453. (f) Peng, S.-K.; Morin, R. J. In *The Biological Effects of Cholesterol Oxides*; CRC Press, Boca Raton, FL, 1992. (g) Salvador, J. A. R.; Silvestre, S. M.; Moreira, V. M. *Curr. Org. Chem.* **2006**, *10*, 2227–2257.

(3) Examples for metal-based allylic oxidation: Cr-based: (a) Muzart, J. *Chem. Rev.* **1992**, *92*, 113–140. (b) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal., A: Chem.* **2006**, *250*, 70. Cu-based: (c) Salvador, J. A. R.; Sá e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1997**, *38*, 119–122. (d) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407. Co-based: (e) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, *6*, 33–34. (f) Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett.* **2003**, *44*, 4283–4286. Fe-based: (g) Barton, D. R. H.; Le Gloahec, V. N. *Tetrahedron* **1998**, *54*, 15457–15468. Pd-based: (h) Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233. (i) Yu, J. Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415–1417. Rh-based: (j) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623. (k) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167–5170. (l) Choi, H.; Doyle, M. P. *Org. Lett.* **2007**, *9*, 5349–5352. (m) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730–738. (n) McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317–4319. Mn-based: (o) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151. Sodium chlorite: (p) Silvestre, S. M.; Salvador, J. A. R. *Tetrahedron* **2007**, *63*, 2439. Bi-based: (q) Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005**, *46*, 2581.

10.1021/ol100603q

Scheme 1. Comparison of Previous Studies and Present Work



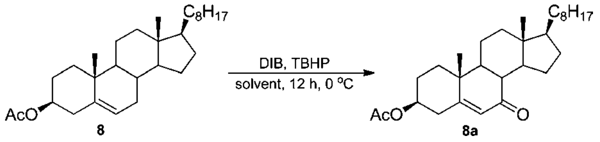
eroxy iodane was reported.[5a] Alternatively,we describe herein the first solvent-assisted nonmetallic based generation of reactive and controllable *tert*-butylperoxy radical **4** using DIB/TBHP protocol as well as the application on allylic oxidation (Scheme 1, eq 2).

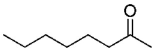
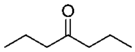
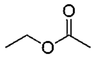
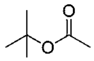
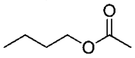
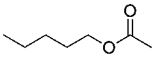
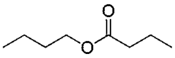
Initially, a DIB/TBHP (1:3) mixture was used in the allylic oxidation of cholesteryl acetate (**8**) at 0 °C. Various solvents were studied and it was found that the reaction performed exceptionally smooth in ethyl acetate, resulting in the formation of 3β-acetoxycholest-5-ene-7-one (**8a**) in 46% yield (Table 1, entry 7). Further examination of bulkier ester solvents showed that *n*-butyl butanoate was superior to the others (Table 1, entry 11). A comparison of similarly bulky solvents indicated the electron-rich ester unit is important to the reaction (Table 1, entries 5 and 10).

The effect of additive was also investigated. The significance of additive in various allylic oxidations was well documented. In our studies, K_2CO_3 (0.5 equiv) was also found to be effective. Moreover, acetate salts including NaOAc, KOAc, and $Mg(OAc)_2{\cdot}4H_2O$ could promote the allylic oxidation.[6]

Having identified the appropriate solvent and potential additives, the other parameters were varied systematically to achieve the optimum conditions,[6] which were then applied on the allylic oxidation of various Δ^5-steroids.[7] The reactions proceeded smoothly with excellent regioselectivities and good yields, resulting in the formation of the corresponding Δ^5-en-7-ones (Table 2). For example, allylic oxidation of cholesteryl acetate (**8**) commonly required 24−48 h to achieve acceptable yield,[2,3] while the reaction was completed in 5 h with 82% yield when using the DIB/TBHP protocol (Table 2, entry 1).

Table 1. Allylic Oxidation of Cholesteryl Acetate (**8**) in Different Solvents



entry[a]	solvent	yield[b] (%)
1	CH_2Cl_2	37
2	MeCN	15
3	Benzene	36
4	Toluene	20
5		43
6		40
7		46
8		54
9		53
10		64
11		***66***

[a] Reactions were carried out with substrate (0.5 mmol), DIB (0.5 mmol), and TBHP (1.5 mmol) in solvent (0.13 M). [b] Isolated yield.

Other than Δ^5-steroids, a number of simple olefins and benzylic substrates were also subjected to the studies. The scope of the DIB/TBHP allylic oxidation process was indicated by the 14 examples listed in Table 3. The reactions proceeded smoothly even at −20 °C and similar regioselectivities were observed in which oxidation occurred at the less hindered allylic carbon. Electron-deficient olefins are commonly known as being inactive toward allylic oxidation. Surprisingly, the DIB/TBHP protocol could promote the formation of enones **23a**−**26a** from the corresponding alkenes (Table 3, entries 8−11). In general it is noteworthy that the reaction protocol is highly compatible with various protecting groups (OAc, OBz, silyl, acetal), functional groups (ketone, nitro, cyano), and rigid ring (four-membered ring).

Toward the understanding of the mechanism, we believed bis(*tert*-butylperoxy)iodobenzene (**2**) was generated as reported by the literature.[4] It is important to notice that large numbers of gas bubbles were evolved instantly and gave iodobenzene when the allylic oxidations were performed in nonester solvents, which indicated a significant number of *tert*-butylperoxy radicals **4** were decomposed due to the

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(4) Milas, N. A.; Plesnicar, B. *J. Am. Chem. Soc.* **1968**, *90*, 4450–4453.

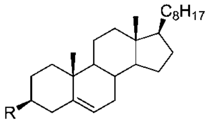
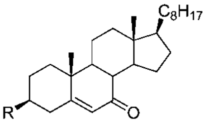
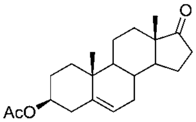
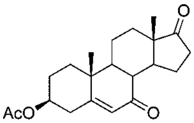
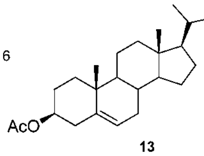
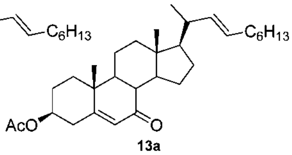
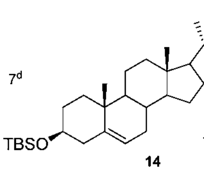
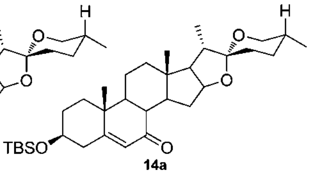
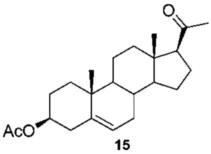
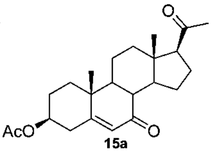
(5) (a) Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716–7730. (b) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2008**, *73*, 7365–7368.

(6) For details, please see the Supporting Information.

(7) Representative procedure: To a solution of cholesterol acetate (**8**) (214 mg, 0.5 mmol) in *n*-butyl butanoate (1 mL) was added diacetoxyiodobenzene (**1**) (312 mg, 1.5 mmol) and $Mg(OAc)_2{\cdot}4H_2O$ (124 mg, 1.0 mmol) at 0 °C. The resulting suspension was vigorously stirred and a solution of *tert*-butyl hydroperoxide (6.0 M in decane, 333 μL, 2.0 mmol) was added dropwise over 30 min. The solution was further stirred for 4.5 h at 0 °C and filtered. The filtrate was chromatographed on silica gel eluted with *n*-hexanes/EtOAc (10:1) to yield 3β-acetoxycholest-5-ene-7-one (**8a**) as a white solid (181 mg, 82%).

Table 2. Allylic Oxidation of Δ^5-Steroids **8−15**

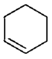
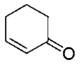
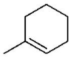
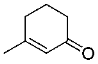
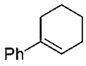
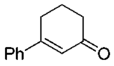
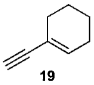
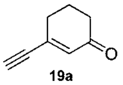
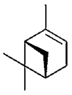
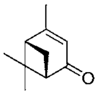
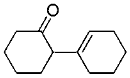
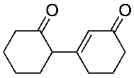
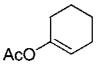
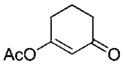
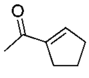
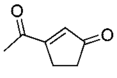
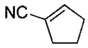
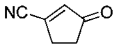
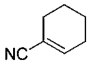
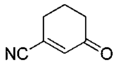
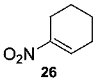
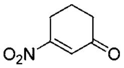
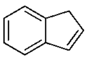
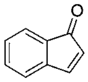
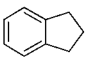
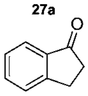
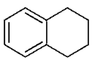
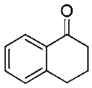
$$\text{Substrates } \mathbf{8\text{-}15} \xrightarrow[n\text{PrCO}_2n\text{Bu, 0 }^\circ\text{C}]{\text{DIB, TBHP, K}_2\text{CO}_3\text{ or Mg(OAc)}_2\cdot 4\text{H}_2\text{O}} \text{Products } \mathbf{8a\text{-}15a}$$

entry[a,b]	substrate	product	time (h), yield[c] (%)
1	 **8** R = OAc	 **8a** R = OAc	5, 82
2[d]	**9** R = OTBS	**9a** R = OTBS	6, 76
3	**10** R = OBz	**10a** R = OBz	6, 78
4	**11** R = Cl	**11a** R = Cl	6, 85
5	 **12**	 **12a**	6, 75
6	 **13**	 **13a**	8, 65
7[d]	 **14**	 **14a**	8, 60
8	 **15**	 **15a**	8, 81

[a] Reactions were carried out with substrate (0.5 mmol), DIB (1.5 mmol), TBHP (2.0 mmol), and K_2CO_3 or $Mg(OAc)_2$•$4H_2O$ in nPrCO$_2n$Bu (0.4 M). [b] $Mg(OAc)_2$•$4H_2O$ (1.0 mmol) was used as the additive in entries 1−3, while K_2CO_3 (0.25 mmol) was used in entries 4−8. [c] Isolated yield. [d] nPrCO$_2n$Bu/n-hexanes (1:1) was used due to the solubility issue.

Table 3. Allylic Oxidation of Substrates **16−29**

$$\text{Substrates } \mathbf{16\text{-}29} \xrightarrow[n\text{PrCO}_2n\text{Bu, -20 }^\circ\text{C}]{\text{DIB, TBHP, K}_2\text{CO}_3} \text{Products } \mathbf{16a\text{-}29a}$$

entry[a]	substrate	product	time (h), yield[b] (%)
1	 **16**	 **16a**	12, 56[c]
2	 **17**	 **17a**	8, 73
3	 **18**	 **18a**	7, 83
4	 **19**	 **19a**	7, 67
5	 **20**	 **20a**	8, 63
6	 **21**	 **21a**	12, 59
7	 **22**	 **22a**	8, 73
8	 **23**	 **23a**	18, 79
9	 **24**	 **24a**	18, 76
10	 **25**	 **25a**	18, 81
11	 **26**	 **26a**	18, 84
12	 **27**	 **27a**	9, 78
13	 **28**	 **28a**	9, 71
14	 **29**	 **29a**	9, 80

[a] Reactions were carried out with substrate (0.5 mmol), DIB (1.5 mmol), TBHP (2.0 mmol), and K_2CO_3 (0.25 mmol) in nPrCO$_2n$Bu (0.5 M). [b] Isolated yield. [c] Low yield due to the high volatility.

dimerization to di-*tert*-butyltetraoxide (**5**) (Scheme 1).[4] On the other hand, no gas bubble was observed during the reaction in *n*-butyl butanoate, leading us to hypothesize the extra stabilization effect of ester solvent to the hypervalent iodine(III) species. A set of simple experiments was carried out by stirring a suspension of DIB/TBHP in *n*-hexane, toluene, acetonitrile, or *n*-butyl butanoate in the absence of olefinic substrate at 0 °C. The time period of oxygen gas bubbles evolution was summerized in Table 4. Fast and vigorous evolution of oxygen in nonpolar solvents could be attributed to the rapid decomposition of **2** and hence coupling of *t*BuOO• **4**. On the other hand, σ-donor solvent, especially for *n*-butyl butanoate, gave a much better control in the generation of *t*BuOO• **4** which is reflected in the gentle and sustainable evolution of O_2. On the basis of this observation, we speculated a further displacement of a *t*BuOO• **4** by the ester solvent molecules, resulting in the formation of complex **7** (Scheme 1). This hypothesis was supported by a number of studies, which clearly demonstrated that electron-deficient hypervalent iodine(III) center could be stabilized by ligand coordination.[8,9] In our case, the bulky ester solvent coordination might serve as a protecting pocket that prevented rapid

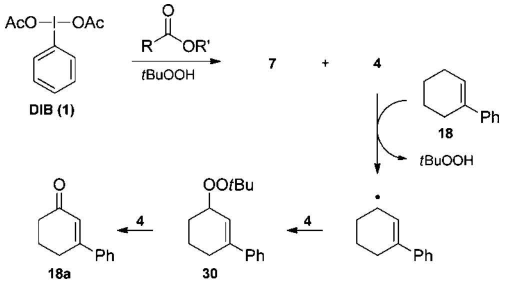
Table 4. Comparsion of O_2 Evolution by DIB/TBHP in Different Solvents

entry[a]	solvent	O_2 evolution time period (min)
1	*n*-hexanes	25
2	toluene	35
3	MeCN	50
4	*n*-butyl butanoate	110

[a] Reactions were carried out with DIB (0.1 mmol) and TBHP (0.13 mmol) in the solvent (0.1 M) at 0 °C.

reductive elimination/coupling of *tert*-butylperoxy radical (**2** → **4** → **5**). The reactive but controllable *t*BuOO• **4** would react with olefin to generate the allylic radical. Further coupling of *t*BuOO• **4** with the allylic radical yielded the peroxy ether (e.g., **30**), which was evidenced by the successful isolation of peroxy ether **30** when the reaction of 1-phenylcyclohexene (**18**) with DIB/TBHP was quenched at 0 °C.[6] Subjecting the intermediate **30** under standard allylic oxidation conditions gave the desired enone **18a**. Finally, the reaction was terminated immediately upon the addition of butylated hydroxytoluene (BHT), which further indicated the radical nature of the reaction. Overall, a proposed reaction mechanism is illustrated in Scheme 2.

Scheme 2. Proposed Mechanism of the Allylic Oxidation



In summary, a mild and efficient allylic oxidation with inexpensive and commercially available DIB/TBHP protocol has been developed. K_2CO_3 and $Mg(OAc)_2 \cdot 4H_2O$ were found to be important additives and ester solvent played a critical role in the reaction. In general good yields and excellent regioselectivies were observed for both simple and Δ^5-steroid olefinic substrates. Further investigations to clarify the mechanism and on other applications are underway.

Acknowledgment. We thank the National University of Singapore (Grant No. 143-000-384-133) for financial support.

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

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