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Efficient Radical Oxygenation of α-Iodocarboxylic Acid Derivatives

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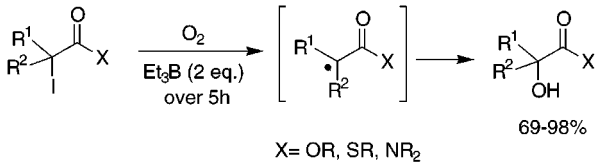
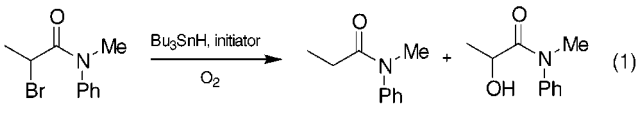
ABSTRACT



Treatment of α-iodocarboxylic acid derivatives with 2 equiv of triethylborane under oxygen atmosphere gives the corresponding α-hydroxy acid derivatives. This method is based on an iodine atom transfer from the ethyl radical, generated by the reaction of triethylborane and oxygen, with the α-iodocarbonyl compound. It offers several advantages over classical ionic substitution reactions: no elimination product is observed, tertiary iodides are efficiently converted to alcohols, and finally, this one-step procedure is working with substrates sensitive to nucleophiles.

Radical reactions have been widely used for the formation of carbon−hydrogen and carbon−carbon bonds.[1] For instance, the deoxygenation of alcohols (Barton−McCombie reaction) belongs to the classical methods of organic synthesis.[2] The reverse process, i.e., the formation of carbon−oxygen bonds via a radical process, is also known but is not widely applied for simple hydroxylation reactions. In this paper, we report an efficient radical oxygenation procedure to convert iodides to alcohols by using molecular oxygen as a radical trap.[3−5] This method is based on an iodine atom transfer and does not require the use of organotin derivatives.

During the investigation of radical reactions at low temperature, we have observed hydroxylation products when triethylborane−oxygen[6] was used as the radical initiator for simple reduction of bromides. A typical example is shown in eq 1.[7] When AIBN was used for the initiation of the same reaction, neither the hydroxylation product **3** nor the reduction product **2** was observed under saturated oxygen atmosphere; in fact, the chain reaction was inhibited by the oxygen and starting bromide **1** was recovered unchanged.



1

Initiator	**2**	**3**
Et_3B	22%	33%
AIBN, hν	starting material recovered	

On the basis of these preliminary results, the triethylborane-mediated hydroxylation procedure was optimized. Good to excellent yields were obtained when a 1 M solution of the α-iodo acid derivative in CH_2Cl_2 was saturated with oxygen and Et_3B was added dropwise over 5 h at −50 °C

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(1) For general review on radical reactions, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1986. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715−777. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1991. (d) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Synthesis*; Wiley: Chichester: 1995. (e) Chatgilialoglu, C.; Renaud, P. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester: 1999; pp 501−538.

(2) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. For reviews, see ref 1c and: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609−2645. See also: Jang, D. O.; Cho, D. H.; Barton, D. H. R. *Synlett* **1998**, 39−40 and references therein.

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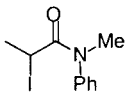
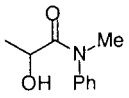
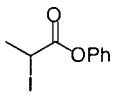
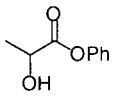
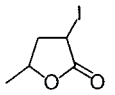
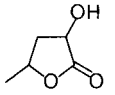
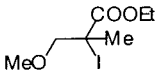
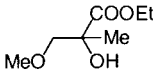
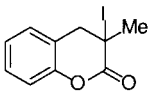
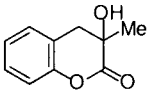
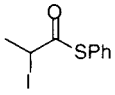
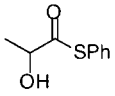
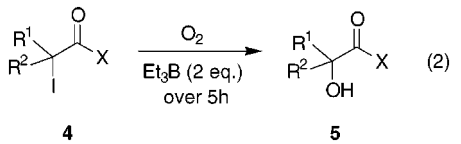
Table 1. Radical Hydroxylation of Iodides **4** According to Eq 2.

entry	iodide	product	% yield[a]
1	 **4a**	 **5a**	70
2	 **4b**	 **5b**	82
3	 **4c**	 **5c**	88[b]
4	 **4d**	 **5d**	81
5	 **4e**	 **5e**	82
6	 **4f**	 **5f**	69

[a] General procedure: The iodide (0.5 mmol) was placed in two-necked flask under an oxygen atmosphere. After introduction of CH_2Cl_2 (0.5 mL), the solution was cooled at −50 °C, and a 1 M solution of Et_3B in 1,2-dichloroethane (1 mL, 1 mmol) was added over 5 h using a syringe pump. The needle used for the addtion of Et_3B was placed into the reaction mixture to avoid oxidation of Et_3B before the reaction took place. At the end of the addition, MeOH (0.5 mL) was added followed by Me_2S (0.2 mL). After being stirred for 15 min, the solution was filtered through silica gel (Et_2O). The filtrate was concentrated, and the crude alcohol was purified by flash chromatography. [b] 1:1 mixture of diastereomers

(eq 2). Different α-iodo acid derivatives were investigated and results are summarized in Table 1.



4 **5** (2)

α-Iodoamides, -esters, -thioesters, and -lactones are hydroxylated in 69−88% yield. The use of 2 equiv of Et_3B is necessary to reach high yields. Traces of hydroperoxides are occasionally isolated; therefore, a preventive reductive treatment with dimethyl sulfide is done before workup. Interestingly, the reaction gives good yields with tertiary iodides (entries 4 and 5) as well as with substrates sensitive to nucleophiles such as the thioester **4f** (entry 6) and the oxazolidinone **16** reported in eq 4. However, this procedure is not suitable for the hydroxylation of α-bromocarboxylic acid derivatives; see the discussion of the mechanism (vide infra) for an explanation.

Two possible mechanisms for the transformation are depicted in Figure 1. Reaction of triethylborane with oxygen gives ethyl radicals, which abstract the iodine atom[8] from the radical precursor **4** to furnish an enolate radical **6**. Reaction of this radical with oxygen gives the peroxyl radical **7**. In the first mechanism (**A**), **7** reacts with Et_3B to furnish **8** and to propagate the chain by formation of an ethyl radical. The peroxyborane **8** is reduced with the second equivalent

(3) For conversion of halides to alcohols with oxygen in the presence of tin derivatives, see: Nakamura, E.; Inubishi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980−8982. Nakamura, E.; Imanishi, Y.; Machii, D. *J. Org. Chem.* **1994**, *59*, 8178−8186. Nakamura, E.; Sato, K.; Imanishi, Y. *Synlett* **1995**, 525−526. Sawamura, M.; Kawaguchi, Y.; Sato, K.; Nakamura, E. *Chem. Lett.* **1997**, 705−706. Moutel, S.; Prandi, J. *Tetrahedron Lett.* **1994**, *35*, 8163−8166. Mayer, S.; Prandi, J. *Tetrahedron Lett.* **1996**, *37*, 3117−3120. Takahashi, T.; Tomida, S.; Doi, T. *Synlett* **1999**, 644−646. Yoshida, M.; Ohkoshi, M.; Aoki, N.; Ohnuma, Y.; Iyoda, M. *Tetrahedron Lett.* **1999**, *40*, 5731−5734. Kittaka, A.; Tsubaki, Y.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Nucleosides Nucleotides* **1996**, *15*, 97−107. A related process with tetraphenyldistibine: Barrett, G. M.; Melcher, L. M. *J. Am. Chem. Soc.* **1991**, *113*, 8177−8178. Organocobalt compounds react with oxygen via a radical mechanism: Okamoto, T.; Oka, S. *J. Org. Chem.* **1984**, *49*, 1589−1594. Bhandal, H.; Pattenden, G.; Russell, J. J. *Tetrahedron Lett.* **1986**, *27*, 2299−2302. Patel, V. F.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1451−1454. Patel, V. F.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2703−2708. Mayer, S.; Prandi, J.; Bamhaoud, T.; Bakkas, S.; Guillou, O. *Tetrahedron* **1998**, *54*, 8753−8770. Punniyamurthy, T.; Bhatia, B.; Iqbal, J. *J. Org. Chem.* **1994**, *59*, 850−853. Alkylmercuric halides react with oxygen in the presence of $NaBH_4$: Hill, C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870−876. For reactions of radicals with oxygen under oxidative conditions, see: Yoshida, J.; Nakatani, S.; Sakaguchi, K.; Isoe, S. *J. Org. Chem.* **1989**, *54*, 3383−3389. Colombo, M. I.; Signorella, S.; Mischne, M. P.; Gonzales-Sierra, M.; Ruveda, E. A. *Tetrahedron* **1990**, *46*, 4149−4154. Nguyen, V.; Nishino, H.; Kurosawa, K. *Heterocycles* **1998**, *48*, 465−480. Ohshima, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 8509−8512. Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089−6092. Nair, V.; Nair, L. G.; Mathew, J. *Tetrahedron Lett.* **1998**, *39*, 2801−2804. Boto, A.; Freire, R.; Hernandez, R.; Suarez, E.; Rodriguez, M. S. *J. Org. Chem.* **1997**, *62*, 2975−2981. Reaction of radicals with oxygen is a key step in lipid autoxidation; for a review, see: Porter, N. A. *Acc. Chem. Res.* **1986**, *19*, 262−268. For related synthetic applications, see: Beckwith, A. L. J.; Wagner, R. D. *J. Chem. Soc., Chem. Commun.* **1980**, 485−486. Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1994**, *35*, 539−542. Feldman, K. S. *Synlett* **1995**, 217−225. Bachi, M. D.; Korshin, E. *Synlett* **1998**, 122−124. For miscellaneous reactions of radicals with oxygen, see: Fukunishi, K.; Shimode, M.; Hisamune, R.; Akita, M.; Kuwabara, M.; Yamanaka, H.; Nomura, M. *Chem. Lett.* **1991**, 337−340. Barton, D. H. R.; Gero, S. D.; Holliday, P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 6751−6756.

(4) Reaction of alkyl radicals with aminoxyl radicals such as TEMPO represents also an indirect way of radical oxygenation: Ollivier, C.; Chuard, R.; Renaud, P. *Synlett* **1999**, 807−809 and references therein.

(5) The rate constant for the reaction of radicals with oxygen have been measured. In all systems investigated, this rate is bigger than 10^9 M^{-1} s^{-1}: Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095−5099.

(6) Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692−700. Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547−2549.

(7) Guindon has observed a similar Et_3B−oxygen-initiated low-yielding radical hydroxylation process with tertiary α-iodoesters: Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528−12535.

(8) The rate constant of iodine atom transfer from ethyl iodoacetate to primary alkyl radicals is 2.6×10^7 M^{-1} s^{-1}: Curran, D. P.; Bosch, E.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826−1831. The rate constant of the corresponding bromine atom transfer ($2.7-7 \times 10^4$ M^{-1} s^{-1}) is too slow to compete with the direct reaction of ethyl radicals with oxygen. This explains the failure of the hydroxylation process with α-bromocarboxylic acid derivatives.

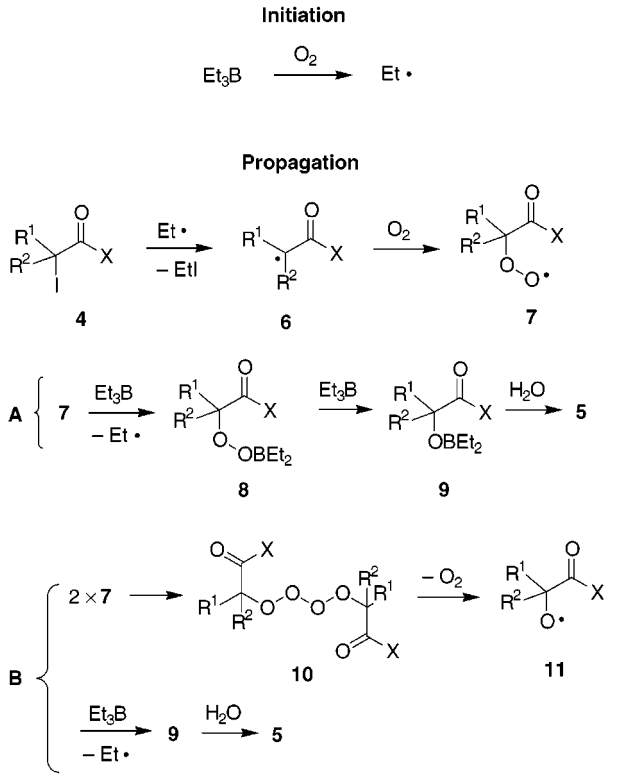
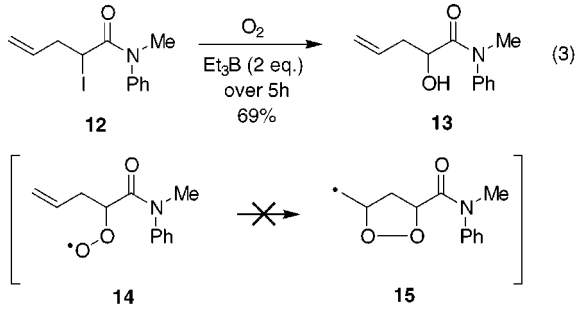


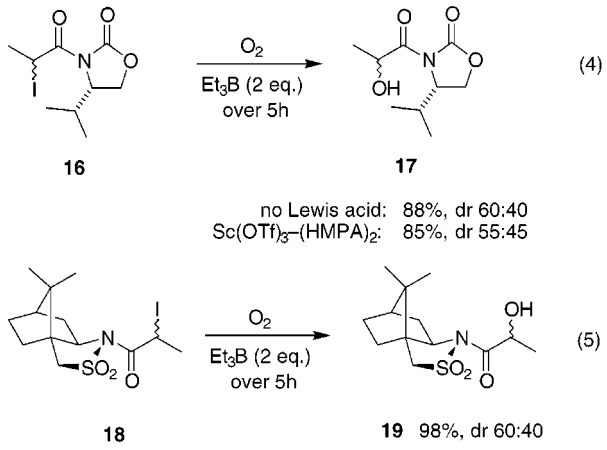
Figure 1. Proposed mechanisms for the hydroxylation process.

of Et_3B to give the borinate **9** and, after hydrolysis, the alcohol **5**. An alternative mechanism (**B**) going through dimerization of the peroxyl radical **7** is also presented (Figure 1, **B**).[9] Oxygen extrusion from the tetraoxidane **10** gives the alkoxyl radical **11** that reacts with Et_3B to give **9**. A third mechanism involving oxidation of a transient boron enolate was also envisaged but could be ruled out.[10]

An attempt to trap the peroxyl radical **14** via a 5-exo cyclization reaction (eq 3) failed. Indeed, oxygenation of **12** gave **13** as a single product in 69% yield. No product derived from the cyclized radical **15** was observed. This indicates that peroxyl radicals of type **7** have a short lifetime. This observation is more in agreement with mechanism **A** (Figure 1) where the peroxyl radical is rapidly trapped by triethylborane.



Finally, the stereochemical outcome of hydroxylation reaction was examined. The oxazolidinone derivative **16** was examined first (eq 4); this system gave a low diastereoselectivity even in the presence of scandium triflate, a Lewis acid known to be efficient in related reactions.[11] The Oppolzer camphor sultam derivative **18** was also tested (eq 5). This system gave **19** as a 60:40 mixture of diastereomers. This result contrasts with carbon−carbon bond forming reactions that have been reported for this substrate.[12] These low stereoselectivities are explained by the high reactivity of oxygen toward radicals and by the small steric bulk of oxygen.



In conclusion, we have shown that radical hydroxylation of α-iodocarboxylic acid derivatives is possible and high yielding when run with oxygen in the presence of 2 equiv of triethylborane. This method gives good yields of hydroxylated compounds, even when sterically hindered iodides, for instance, tertiary iodides, are employed. From a preparative point of view, this reaction offers several advantages over classical nucleophilic substitution reactions:[13] (1) It is a one-step procedure (nucleophilic substitution usually requires two steps: the substitution itself with a mild nucleophile such as an acetate and the deprotection of the desired hydroxy group). (2) Since no base is used in this process, no trace of *β*-elimination product is observed (nucleophilic substitutions involving α-iodocarbonyl compounds are usually accompanied by base-catalyzed elimination). (3) The reaction works with sensitive α-iodocarbonyl compounds such as thioesters without side reactions resulting from nucleophilic addition to the carbonyl moiety. At the moment, a limitation of the method is the low stereochemical control observed with

(9) Bell, E. R.; Raley, J. H.; Rust, F. F.; Seubold, F. H.; Vaughan, W. E. *Discussions Faraday Soc.* **1951**, *10*, 242−249. Neumann, B.; Müller, S. C.; Hauser, M. J. B.; Steinbock, O.; Simoyi, R. H.; Dalal, N. S. *J. Am. Chem. Soc.* **1995**, *117*, 6372−6373.

(10) The boron enolate prepared by treating (*S*)-4-isopropyl-3-propionyl-1,3-oxazolidin-2-one with Bu_2BOTf/Et(*i*-Pr)$_2$N gave, under the hydroxylation conditions (Et_3B/O_2), no trace of the expected hydroxylation product **17**.

(11) (a) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190−192. For a review on the use of Lewis acids in radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562−2579.

(12) Curran, D. P.; Shen, W.; Zhang, J.; Gieb, S. J.; Lin, C.-H. *Heterocycles* **1994**, *37*, 1773−1788.

(13) The nucleophilic substitution of α-iodocarbonyl compound by oxygenated nucleophiles is not commonly used. Better results are obtained with the corresponding bromides and chlorides.

chiral auxiliaries. Our efforts toward elucidation of the exact mechanism of this reaction as well as the incorporation of this process into radical cascade reactions will be reported in due course.

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Supporting Information Available: Experimental for the radical reactions and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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