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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1997–2001

Regioselective 1,2-hydroxy and methoxy iodination of alkenes by molecular iodine and aqueous hydrogen peroxide

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Received 8 December 2005; revised 28 December 2005; accepted 13 January 2006
Available online 3 February 2006

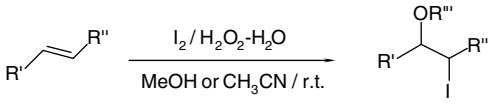
Abstract—Treatment of an alkene with iodine and aqueous hydrogen peroxide (30%) in acetonitrile gives the corresponding hydroxy-iodoalkane regioselectively in high yield. On the other hand the same reaction in methanol gives methoxyiodoalkanes in excellent yield.

The halofunctionalization of olefins such as 1,2-alkoxy, hydroxy, and acetoxy halogenations are important reactions in organic synthesis.[1] In particular, iodinated compounds are useful intermediates in carbon–carbon bond forming reactions and iodine–metal exchange reactions.[2] 1,2-Alkoxyiodoalkanes are the key intermediates for olefin inversion.[3] Vicinal halohydrins serve as intermediates in the synthesis of halogenated marine natural products.[4] In addition to this, iodinated compounds possess biological activity.[5] Several approaches toward the synthesis of iodohydrin and iodoalkoxy compounds from olefins are known. Among these the use of alkyl hypoiodides,[6] bis(pyridine)iodine(I) tetrafluoroborate,[7] hypoiodous acid,[8] the use of iodine in the presence of $Cu(OAc)_2$,[9] $AgNO_3$,[10] HgO,[11] $CuO{\cdot}HBF_4$,[12] $Ce(SO_3CF_3)_4$,[13] can be mentioned. Recently, Tingoli and co-workers have used molecular iodine and phenyliodine-(III) bis(trifluoroacetate) for iodohydroxylation.[14] It is evident from the above literature procedures that most methods use either metal salts as a promoter or as oxidizing agent or some of the methods require dry reaction conditions or expensive reagents and end up with low yields.

Aqueous solutions of hydrogen peroxide are convenient, safe, and environmentally favorable oxidants, and their utility are well exploited.[15] In this letter we describe the use of 30% aqueous hydrogen peroxide and molecular iodine as a hydroxy and methoxy iodination reagent without any additive.

When a mixture of molecular iodine, aqueous 30% hydrogen peroxide, and styrene in acetonitrile was stirred at room temperature, only 1-hydroxy-2-iodo-1-phenylethane was obtained in 94% yield[16] (Scheme 1). When the same reaction was carried out in the absence of hydrogen peroxide only 10% of the product was formed after 4 days. The reaction was generalized through entries 1–15 (Table 1). When the same reaction was performed in methanol, 2-iodo-1-methoxy-1-phenylethane was obtained in high yields (Table 2).

It was observed that a variety of cyclic and acyclic olefins could be converted to the corresponding methoxy- and hydroxy-iodoalkanes with good to excellent yields (see Tables 1 and 2). The reactions proceed rapidly with terminal and substituted olefins. However, olefins with an electron withdrawing group, such as methyl cinnamate, remain unaffected. Sterically hindered olefins (substrate **4a**) also react smoothly. Most importantly the reaction is regioselective. Only Markovnikov's addition product was obtained. Iodomethoxylation of norbornene gives the rearranged product



where R' = R'' = H, alkyl, aryl; R''' = H, Me

Scheme 1.

Keywords: Regioselective; Iodohydroxylation; Iodomethoxylation; Iodine; Hydrogen peroxide; Aqueous.
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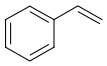
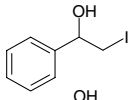
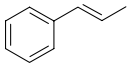
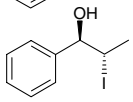
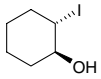
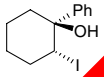
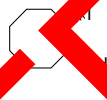
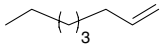
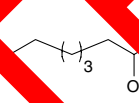
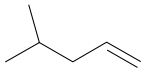
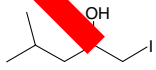
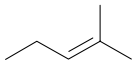
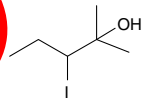
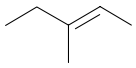
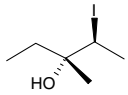
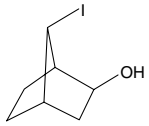
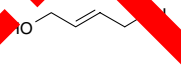
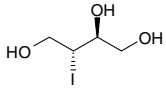
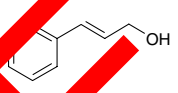
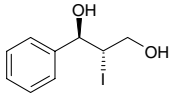
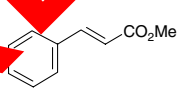
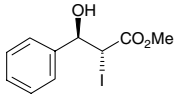
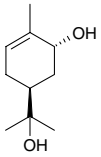
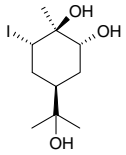
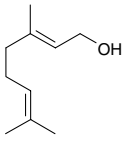
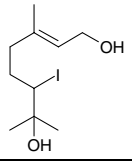
doi:10.1016/j.tetlet.2006.01.064

Table 1. Hydroxy iodination of olefins by iodine and aqueous hydrogen peroxide in acetonitrile

Sl. No.	Substrate (**a**)	Time/h	Product (**b**)	Yield/%[a]
1		5.5		94
2		18		91
3		4		86
4		7		88
5		6		90
6		3		78
7		5		87
8		4		89
9		7		80
10		[illegible]		78
11		13		87
12		10		92
13		24		0
14		11		70
15		7		74[b]

[a] Yield refers to isolated yield. The compounds were characterized by ^{1}H, ^{13}C NMR, IR spectroscopy, and comparison with the literature.
[b] 2,6-Diodo-3,7-dihydroxy-3,7-dimethyloct-1-ol was obtained (5%).

Table 2. Methoxy iodination of olefins by iodine and aqueous hydrogen peroxide in methanol

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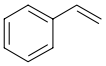
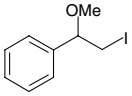
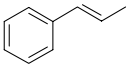
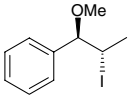
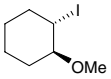
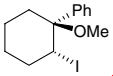
1		5		96
2		16		93
3		3		92
4		8		
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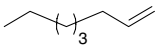
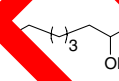
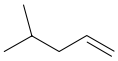
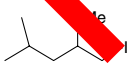
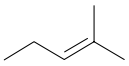
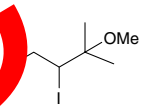
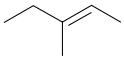
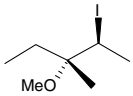
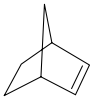
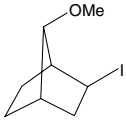
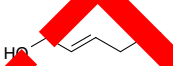
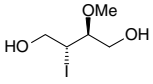
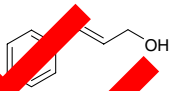
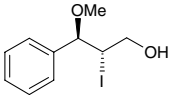
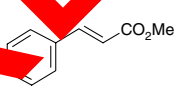
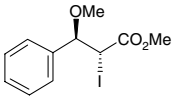
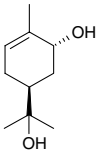
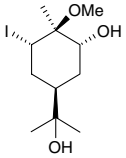
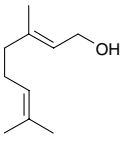
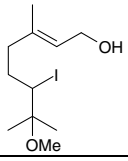
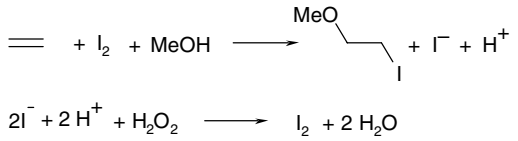
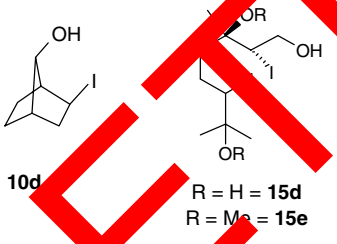
6		3.5		81
7		4		83
8		6		84
9		7		80
10		5		87
11		12		90
12		9		91
13		24		0
14		9		72
15		6		74[b]

[a] Yield refers to isolated yield. The compounds were characterized by ^{1}H, ^{13}C NMR, IR spectroscopy, and comparison with the literature.
[b] 2,6-Diodo-3,7-dimethoxy-3,7-dimethyloct-1-ol was obtained (5%).



Scheme 2.

2-*exo*-iodo-7-*syn*-methoxybicyclo-[2.2.1]heptane, **10c**[17] in 87% yield along with 2-*exo*-hydroxy-7-*syn*-iodobicyclo[2.2.1]heptane, **10b** in 7% yield. On the other hand iodohydroxylation of **10a** gives 2-*exo*-hydroxy-7-*syn*-iodobicyclo[2.2.1]heptane, **10b** as the major product (78%) and its isomer 2-*exo*-iodo-7-*syn*-hydroxybicyclo[2.2.1]heptane, **10d** as a minor product (10%).[18] Geraniol gives the 6,7-addition products, **15b** and **15c**, as the major products (74%) with minor 2,3- and 6,7-addition products (5%). Interestingly, when the same reaction was carried out in the presence of glacial acetic acid, instead of the acetylated products iodohydrins were obtained. It was also observed that no hydrolyzed product was formed under these reaction conditions. This can be attributed to the reactions shown in Scheme 2. The product is formed by nucleophilic attack of the methanol or water on the iodonium ion formed from the reaction of the olefin and iodine, releasing iodide and hydrogen ion. The iodide thus formed is reoxidized to molecular iodine by hydrogen peroxide in the presence of hydrogen ion and the water consuming the hydrogen iodide formed in the reaction. As a result the reaction medium becomes neutral and there is no chance of acid hydrolysis of the iodo compounds. It is important to note that only water is formed as a byproduct.



In conclusion, an efficient method for methoxy and hydroxy iodination of olefins using molecular iodine and hydrogen peroxide under mild conditions has been developed. This protocol may be extended for the synthesis of other alkoxyiodoalkanes.

Acknowledgments

The authors are grateful to Council of Scientific and Industrial Research (CSIR), New Delhi, for the financial assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.064.

References and notes

1. (a) House, H. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: Menlo Park, CA, 1972; p 432; (b) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992, p 815T.W; (c) Eisch, J. J.; Liu, Z. R.; Ma, X.; Zheng, G. X. *J. Org. Chem.* **1992**, *57*, 5140; (d) Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1988**, *29*, 5197; (e) Konopelski, J. P.; Boehler, M. A.; Tarasow, T. M. *J. Org. Chem.* **1989**, *54*, 4966; (f) Gibson, K. H.; Saxton, J. E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2776; (g) Wilson, C. V. *Org. React.* **1957**, *9*, 332.
2. (a) Sasson, Y. Formation of Ca...on–Hal...n Bonds (Cl, Br, I). In *The Chemistry of Fu...tional Groups, Supplement D2: The Chemistry of Halides, Pseudo Halides and Azides, Part 2*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1995; pp 535–620; (b) Diederich, ... Stang, ... J. *Metal-Catalysed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998; (c) Tang, X.; Althammer, A.; Knochel, P. *Org. ... 2004*, *6*, 1665.
3. Maeda, K...shinoku... H.; Osh...a, K. *J. Org. Chem.* **1996**, *61*, ...70.
4. (a) Bo...ni, ... Righi, G. *Synthesis* **1994**, 204; (b) Fenical, W. In *Marin... Natural Products*; Scheuer, P. J., Ed.; Academic: New ...rk, 1980; Vol. 2, p 174; (c) Faulkner, D. J. *Nat. Prod. Re...* **1984**, 25.
5. ... Sovak, M. *Radiocontrast Agents. Handbook of Experimental Pharmacology*; Springer: Berlin, 1993.
6. Glover, S. ...A.; Gossen, A. *Tetrahedron Lett.* **1980**, *21*, 2005.
7. ... Barluenga, J.; Gonzalez, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319; (b) Cambie, R. C.; Noall, W. I.; Potter, G. J.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 226.
8. Asensio, G.; Andreu, C.; Boix-Bernardini, C.; Mello, R.; Gonzalez-Nunez, M. E. *Org. Lett.* **1999**, *1*, 2125.
9. Georgoulis, C.; Valery, J. M. *Synthesis* **1978**, 402.
10. (a) Wilson, C. V. *Org. React.* **1957**, *9*, 332; (b) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.
11. (a) Bougault, J. *C.R. Acad. Sci.* **1900**, *130*, 1766; (b) Bougault, J. *C.R. Acad. Sci.* **1900**, *131*, 528.
12. Barluenga, J.; Rodriguez, M. A.; Campos, P. J.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1987**, 1491.
13. Iranpoor, N.; Shekarriz, M. *Tetrahedron* **2000**, *56*, 5209.
14. Corso, A. R. D.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2001**, *42*, 7245.
15. (a) Clark, J.; Macquarrie, D. *Handbook of Green Chemistry & Technology*; Blackwell Science: London, 2002; (b) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977; (c) Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457.
16. Typical experimental procedure for the synthesis of an alkoxyiodoalkane: A mixture of styrene (400 mg, 3.8 mmol), acetonitrile (4 ml), iodine (533 mg, 2.1 mmol) was stirred at room temperature and to this mixture was added 30% hydrogen peroxide (0.64 ml, 5.7 mmol) and the mixture allowed to stir for 5 h. The reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the acetonitrile was removed under vacuum. The residue was extracted with ethyl acetate and the organic layer was washed with a solution of sodium thiosulfate, dried (Na_2SO_4), and evaporated to get the crude product. Finally, the product was purified by column chromatography to give 958 mg (96%) of the pure product. The compound was characterized by spectroscopic methods.[19] ^1H NMR (400 MHz, $CDCl_3$): δ 2.52 (br s, 1H, –OH), 3.39 (m, 1H, –CH–), 3.48

(m, 1H, –CH–), 4.82 (dd, $J = 8.0$ and 2.8 Hz, 1H, –CH–), 7.34 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.32, 73.91, 125.56, 128.13, 128.46, 140.91; IR: 3401, 3027, 2919, 1455, 1178, 1061, 707 cm^{-1}. Similarly for the synthesis of methoxy iodinated compounds methanol was used instead of acetonitrile.

17. The structure of the compound **10b** was determined by comparison the literature. For its isomer see: (a) Schauble, J. H.; Trauffer, E. A.; Despande, P. P.; Evans, R. D. *Synthesis* **2005**, 1333; (b) Davidson, R. I.; Kropp, P. J. *J. Org. Chem.* **1982**, *47*, 1904.
18. The structures of the compounds **10c** and **10d** were determined by comparison see: (a) Gerteisen, T. J.; Kleinfelter, D. C. *J. Org. Chem.* **1971**, *36*, 3255; (b) Cambie, R. C.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 845, and Ref. 8.
19. Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709.