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Iodomethane Oxidation by Dimethyldioxirane: A New Route to Hypoiodous Acid and Iodohydrines

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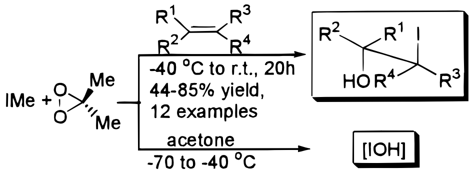
ABSTRACT



The oxidation of iodomethane with dimethyldioxirane allows the generation of stable neutral solutions of hypoiodous acid in the absence of any trapping agent for iodide anion. Hypoiodous acid is trapped in situ by addition to representative olefins to give iodohydrines in good yields. The stereochemical study of the products shows the *anti*-stereospecific nature of the iodohydroxylation reaction.

The oxidation of alkyl iodides[1,2] occurs with the formation of iodoso compounds. Polyvalent iodine derivatives with alkyl substituents at iodine are generally highly unstable and can exist only as short-lived reactive intermediates in the oxidation of alkyl iodides with peracids. These compounds, despite their lack of stability, have found several synthetic applications.[2] In the course of our continuing work on the reactivity of functional groups toward dioxiranes,[3] we determined to study the oxidation of alkyl iodides with dimethyldioxirane (DMDO) (**2**) with the aim, at first, of obtaining iodoso compounds under mild conditions that could be stable compounds in the reaction medium. Recently, Minisci et al.,[4] in a search for evidence of radical intermediates in oxidations with DMDO, reported the formation of 2-iodocyclohexanol in the DMDO oxidation of cyclohexyl iodide. This reaction illustrates the expected chemistry of secondary alkyl iodoso compounds,[1,2] i.e., the intramolecular elimination of hypoiodous acid, which then adds to the olefin generated in the elimination step. Iodohydrines are interesting synthetic intermediates whose preparation has been the subject of several recent reports.[5] In contrast with their homologous chloro- and bromohydrines, they cannot be prepared by the direct reaction of olefins with water solutions of the halogen, since the iodide anion generated in this

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(1) (a) Macdonald, T. L.; Narasimhan, N.; Burka, L. T. *J. Am. Chem. Soc.* **1980**, *102*, 7760. (b) Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 822. (c) Cambie, R. C.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Chem. Commun.* **1978**, 919. (d) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888. (e) Ogata, Y.; Aoki, K. *J. Org. Chem.* **1969**, *34*, 3974, 3978.

(2) (a) Kim, S.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 7163. (b) Lee, J.; Oh, J.; Jin, S.; Choi, J.; Atwood, J. L.; Cha, J. K. *J. Org. Chem.* **1994**, *59*, 6955. (c) Knapp, S.; Naughton, A. B. J.; Dhar, T. G. M. *Tetrahedron Lett.* **1992**, *33*, 1025. (d) Guivisdalsky, P. N.; Bittman, R. *J. Org. Chem.* **1989**, *54*, 4637. (e) Sicinski, R. R.; Szczepek, W. J. *Tetrahedron Lett.* **1987**, *28*, 5729. (f) Eaton, P. E.; Cunkle, G. T. *Tetrahedron Lett.* **1986**, *27*, 6055. (g) Zefirov, N. S.; Zhdankin, V. V.; Makhon'kova, G. V.; Dan'kov, Y. V.; Koz'min, A. S. *J. Org. Chem.* **1985**, *50*, 1872. (h) Yamamoto, S.; Itani, H.; Tsuji, T.; Nagata, W. *J. Am. Chem. Soc.* **1983**, *105*, 2908. (i) Davidson, R. L.; Kropp, P. J. *J. Org. Chem.* **1982**, *47*, 1904. (j) Greenhouse, R.; Muchowski, J. M. *Can. J. Chem.* **1981**, *59*, 1025. (k) Beeley, N. R. A.; Sutherlan, J. K. *J. Chem. Soc., Chem. Commun.* **1977**, 321.

(3) (a) Asensio, G.; Castellano, G.; Mello, R.; González-Nuñez, M. E. *J. Org. Chem.* **1996**, *61*, 5564. (b) Asensio, G.; Mello, R.; González-Nuñez, M. E.; Castellano, G.; Corral, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 217. (c) Asensio, G.; Mello, R.; González-Nuñez, M. E. *Tetrahedron Lett.* **1996**, *37*, 2299. (d) Asensio, G.; Mello, R.; Boix-Bernardini, C.; González-Nuñez, M. E.; Castellano, G. *J. Org. Chem.* **1995**, *60*, 3692. (e) Asensio, G.; González-Nuñez, M. E.; Boix-Bernardini, C.; Mello, R.; Adam, W. *J. Am. Chem Soc.* **1993**, *115*, 7250.

(4) (a) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Zhao, L. *J. Org. Chem.* **1998**, *63*, 254. (b) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Serri, A. *Tetrahedron Lett.* **1995**, *36*, 6945.

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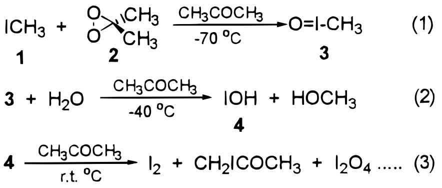
process itself reacts with iodine or the intermediate iodonium ion to give the I_3^- anion or iodine, respectively. For this reason, all known methods for the generation of electrophilic iodine species require the presence of a trapping agent for iodide anion, whether by precipitation with mercury(II) salts[5l] or oxidation with Fe(III),[5d] Cu(II),[5f] or Ce(IV)[5e] salts, CrO_3/pyridine,[5b] and others.[5]

In this Letter, we report the DMDO (**2**) oxidation of iodomethane (**1**) to iodosomethane (**3**) and its further decomposition in solution to hypoiodous acid (**4**) which is trapped by addition to representative olefins (**5**) to give iodohydrines (**6**) in good yields.

The oxidation was performed by mixing acetone solutions of DMDO and iodomethane at −70 °C. Under these conditions, a pale yellow precipitate thought to be iodosomethane was formed. Unfortunately, this precipitate, although stable in suspension at −70 °C, is very difficult to handle, and decomposed in all attempts at isolation for spectroscopic characterization. Upon raising the temperature of the suspension to −40 °C, the yellow solid gave rise first to a deep-orange solution and finally, when allowed to warm to room temperature, to a yellow solution, a new precipitate and 1-iodopropanone, as determined by GC-MS analysis. The final pH of the solution was neutral or slightly acidic. The UV spectrum of the latter yellow solution was identical to that of a solution of iodine in acetone. The latter solid was isolated and exhibited oxidant behavior toward an acid solution of potassium iodide but was unstable, decomposed to give iodine, and could not be further characterized.

These observations can be explained by considering an initial oxygen transfer process from DMDO to iodomethane to generate iodosomethane, which is stable and insoluble in acetone at −70 °C (Scheme 1, eq 1), becomes soluble at −40 °C, and undergoes nucleophilic substitution by water in the medium to give hypoiodous acid, which was present in the deep-orange solution (eq 2) and responsible for the α-iodination of acetone (eq 3). In fact, some synthetic applications of hypervalent iodine derivatives[6] are based on the leaving group ability of the hypervalent iodine moiety. On the other hand, hypoiodous acid has been reported to be an unstable species which undergoes dismutation to iodine and oxygen under acidic conditions.[7] In addition, iodoso derivatives show a clear tendency to form polymeric materials in which each iodine atom is coordinated to two oxygen atoms. An example of these structures is amorphous iodosobenzene.[8] All of these processes would account for the yellow iodine solution and the solid with oxidizing properties obtained in the last step of the oxidation of iodomethane described above (eq 3). Dismutation of hypoiodous acid to iodide and iodate ions can be disregarded under our conditions, provided that it only takes place in basic medium.

Scheme 1



To determine unequivocally that hypoiodous acid can be readily generated in a synthetically useful form by DMDO oxidation of sacrificial iodomethane, we performed the in situ trapping of **4** with a series of representative alkenes **5**, which afforded the expected iodohydrines **6**[9] (see Scheme 2). This process represents the first practical example of the preparation of hypoiodous acid from an iodine source other than molecular iodine and its application to the synthesis of iodohydrines by direct electrophilic addition to C═C double bonds. The electrophilic character of the iodination process was ascertained by measuring the corresponding rate constants in competition experiments between styrene and *para*-substituted styrenes. The ρ value found for the reaction (−5.65) shows that the reagent is highly sensitive to the effects of substituents. The regioselectivity of the iodohydroxylation shows that the hydroxy group is bonded to the carbon atom which better supports the positive charge density in the iodonium intermediate (**I**), with the only exception being the reaction with allylbenzene (**5d**) in which the iodonium ring opens in part due to nucleophilic attack of the less hindered terminus (see Scheme 2). Epoxidation of the alkene by iodosomethane was not observed in any of the cases.

Regarding the stereochemistry of this process (see Figure 1), the iodohydroxylation of *trans*-3-nonene (**5c**) followed

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(5) (a) Cornforth, J. W.; Green, D. T. *J. Chem. Soc. C* **1970**, 846. (b) Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* **1983**, *39*, 1765. (c) Cambie, R. C.; Noall, W. I.; Potter, G. J.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 226. (d) deMattos, M. C. S.; Sanseverino, A. M. *J. Chem. Res., Synop.* **1994**, 440. (e) Horiuchi, C. A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T. *J. Chem. Res., Synop.* **1996**, 60. (f) Barluenga, J.; Rodríguez, M. A.; Campos, P. J.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1987**, 1491. (g) Georgoulis, C.; Valery, J. M. *Synthesis* **1978**, 402. (h) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342. (i) Jalai-Naini, M.; Lallemand, J. Y. *Tetrahedron Lett.* **1986**, *27*, 497. (j) Acton, E. M.; Ryan, K. J.; Tracy, M.; Arora, S. K. *Tetrahedron Lett.* **1986**, *27*, 4245. (k) Naz, N.; Al-Tel, T. H.; Al Abed, Y.; Voelter, W. *J. Org. Chem.* **1996**, *61*, 3250. (l) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1984**, *24*, 319.

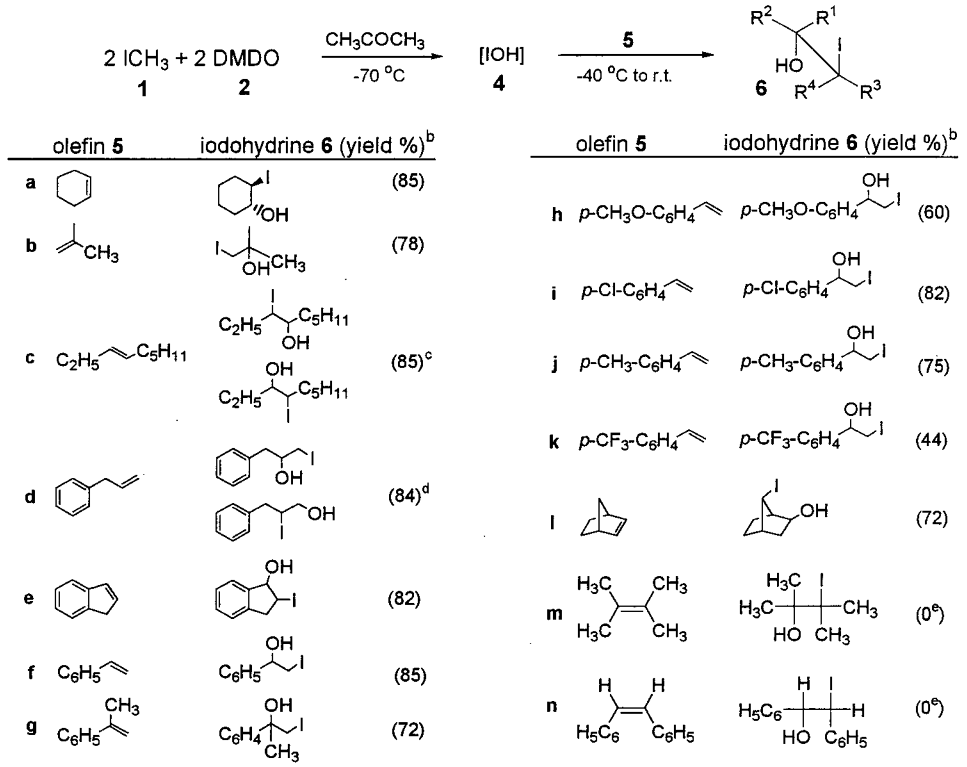
(6) (a) Ochiai, M. In *Chemistry of Hypervalent Compounds*; Kin-ya Akiba, Ed.; Wiley-VCH: Weinheim, 1999; pp 359−387. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (c) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274.

(7) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; John Wiley & Sons: New York, 1999.

(8) Carmalt, C. J.; Crossley, J. G.; Knight, J. G.; Lightfoot, P.; Martin, A.; Muldowney, M. P.; Norman, N. C.; Orpen, A. G. *J. Chem. Soc., Chem. Commun.* **1994**, 2367.

(9) **Preparation of Iodohydrines. Typical Experimental Procedure.** To a solution of iodomethane (**1**) (1.19 mmol, 0.75 mL) in acetone cooled to −70 °C was added an aliquot of a DMDO (**2**) acetone solution (1.13 mmol) with stirring. After a few seconds the formation of a white solid was observed. The mixture was allowed to stand for 1 h, and then the olefin **5** (0.56 mmol) in 2 mL of acetone was added at once. The resulting mixture was then allowed to warm slowly (20 h) to reach room temperature. The solvent was removed under vacuum and the residue redissolved in CH_2Cl_2 (20 mL). The solution was washed with aqueous $Na_2S_2O_3$ (1 N, 2 × 15 mL) and distilled water (1 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed under vacuum. GC-MS analysis of the reaction mixture showed in most cases the nearly total conversion of **5** into the expected iodohydrine **6** and the presence of variable amounts of 2-iodopropanone. Products were purified by column chromatography (silica, hexane:ethyl acetate 95:5).

Scheme 2. Synthesis of Iodohydrines (**6**) from Olefins (**5**) by Electrophilic Addition of IOH (**4**) Generated by Oxidation of Iodomethane (**1**) with DMDO (**2**)[a]



[a] Molar ratio iodomethane:DMDO:**5** 2:2:1. [b] Products were isolated by column chromatography. [c] 1:1 mixture of two regioisomers. [d] 65:35 mixture of two regioisomers. [e] Iodohydrine could not be isolated in this case.

by treatment with base (potassium carbonate, dichloromethane) yielded quantitatively a single (±)-*trans*-epoxide (**7c**) that was identified by comparison with the product obtained by direct *syn*-stereospecific epoxidation of **5c** with DMDO (**2**). This observation shows the *anti*-stereospecific nature of the iodohydroxylation reaction. This is also revealed in the stereospecific transformation of cyclohexene (**5a**) into (±)-*trans*-2-iodocyclohexanol (**6a**) under our conditions (see Scheme 2) and indicates the participation of cyclic iodonium ion intermediate **8a**. The addition of IOH (**4**) to norbornene (**5l**) took place with rearrangement of the intermediate cyclic iodonium ion intermediate **8l** to give **6l**. In this case, the presence of small amounts of 3-cyclohexencarbaldehyde (**9l**) was also observed. In general, steric congestion and an enhanced tendency for ionization of the C−I bond appear to decrease the stability of iodohydrines, and for this reason the reaction of IOH (**4**) with tetramethylethylene (**5m**) and *cis*-stilbene (**5n**) led exclusively to the formation of the corresponding epoxide (**7m**) and diphenylacetaldehyde (**9n**), respectively. This latter compound is most probably derived from a simple pinacol type rearrangement of the corresponding iodohydrine or, alternatively, by rearrangement of the epoxide **7n** formed by nucleophilic displacement of iodide ion by the *anti*-hydroxy group in the precursor iodohydrine **6n**.

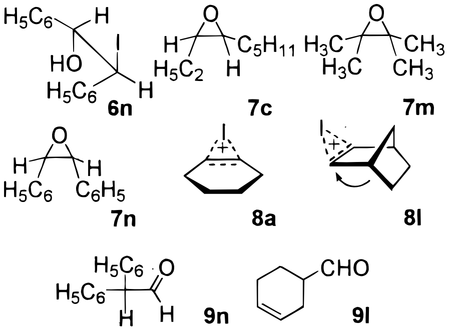


Figure 1.

The synthesis of iodohydrines described here represents a new strategy for these compounds with the added merit and novelty of generating stable IOH neutral solutions based on the quantitative and stoichiometric DMDO oxidation of sacrificial iodomethane to iodosomethane at low temperature, and hence without the involvement of any trapping reagent for iodide ion. The scope of this new and general synthesis of iodohydrines is somewhat limited by the inherent lack of stability of some of these compounds that undergo anchimerically assisted displacement of iodide ion by the neighboring hydroxy group to afford the epoxide. Work is in progress to identify new applications for the stable IOH solutions that are now available by this synthesis.

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Supporting Information Available: Experimental details for the preparation of IOH (**4**) and iodohydrines **6**, structural information, NMR and HRMS spectral data for compounds **6**. This material is available free of charge via the Internet at http:/pubs.acs.org

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