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Unprecedented Direct Oxygen Atom Transfer from Hypervalent Oxido-λ^3-iodanes to α,*β*-Unsaturated Carbonyl Compounds: Synthesis of α,*β*-Epoxy Carbonyl Compounds

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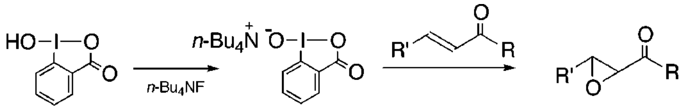
ABSTRACT



Tetra-*n*-butylammonium oxido-λ^3-iodane, prepared from 1-hydroxy-1,2-benziodoxol-3(1*H*)-one by reaction with tetra-*n*-butylammonium fluoride, directly undergoes oxygen atom transfer to α,*β*-unsaturated carbonyl compounds, yielding epoxides.

Hypervalent λ^3- and λ^5-organoiodanes are mild, selective, and environmentally friendly oxidizing reagents in organic synthesis.[1] λ^3-Aryliodanes with oxygen ligands such as iodosylbenzene, (diacetoxyiodo)benzene, and [hydroxy(tosyloxy)iodo]benzene oxidize α,*β*-unsaturated carbonyl compounds and afford a variety of rearranged and unrearranged products, depending on the reaction conditions and the structure of substrates: for instance, oxidation of chalcones with iodosylbenzene or its derivatives affords α-hydroxy-*β*-alkoxyacetals[2] under basic conditions, while rearranged *β*-ketoacetals[3] and *β*-alkoxyesters[4] are obtained under acidic conditions. All of these oxidations are believed to involve the electrophilic attack of the hypervalent iodine(III) on enolate anions or enols generated in situ from the α,*β*-unsaturated ketones via Michael addition, followed by reductive elimination of iodobenzene. There have been no preceding examples that involve nucleophilic attack of λ^3-organoiodanes on α,*β*-unsaturated carbonyl compounds.[5] We report herein the oxidation of α,*β*-unsaturated carbonyl compounds to the corresponding epoxides using a new λ^3-iodane, tetra-*n*-butylammonium oxido-λ^3-iodane **2** (Scheme 1). The reaction probably involves a nucleophilic attack of the oxyanion of **2** attached to the hypervalent iodine(III) on the electron-deficient olefins.

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[1] For reviews of organoiodanes, see: (a) Koser, G. F. *The Chemistry of Functional Groups, Supplement D*; Wiley: New York, 1983; Chapter 18. (b) Ochiai, M.; Nagao, Y. *J. Synth. Org. Chem., Jpn*. **1986**, *44*, 660. (c) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res*. **1986**, *19*, 244. (d) Merkushev, E. B. *Russ. Chem. Rev*. **1987**, *56*, 826. (e) Ochiai, M. *Rev. Heteroat. Chem*. **1989**, *2*, 92. (f) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (g) Stang, P. J. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 274. (h) Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem*. **1992**, *3*, 113. (i) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VHC Publishers: New York, 1992. (j) Koser, G. F. *The Chemistry of Functional Groups, Supplement D2*; Wiley: New York, 1995; Chapter 21. (k) Kitamura, T. *J. Synth. Org. Chem., Jpn*. **1995**, *53*, 893. (l) Stang, P. J.; Zhdankin, V. V. *Chem. Rev*. **1996**, *96*, 1123. (m) Muraki, T.; Togo, H.; Yokoyama, M. *Rev. Heteroat. Chem*. **1997**, *17*, 213. (n) Zhdankin, V. V.; Stang, P. J. *Chemistry of Hypervalent Compounds*; Wiley: New York, 1999; Chapter 11. (o) Ochiai, M. *Chemistry of Hypervalent Compounds*; Wiley: New York, 1999; Chapter 12.

[2] (a) Moriarty, R. M.; Prakash, O.; Freeman, W. A. *J. Chem. Soc., Chem. Commun*. **1984**, 927. (b) Tamura, Y.; Yakura, T.; Terashi, H.; Haruta, J.; Kita, Y. *Chem. Pharm. Bull*. **1987**, *35*, 570.

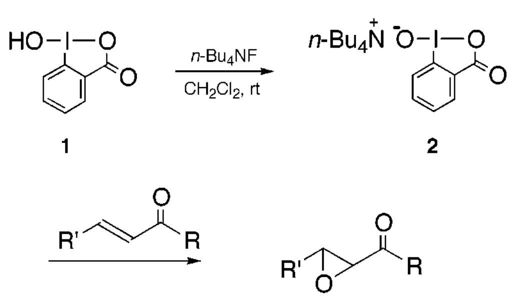
[3] Moriarty, R. M.; Khosrowshahi, J. S.; Prakash, O. *Tetrahedron Lett*. **1985**, *26*, 2961.

[4] Singh, O. V.; Garg, C. P.; Kapoor, R. P. *Synthesis* **1990**, 1025.

[5] Oxidation of tetracyanoethylene with iodosylbenzene affords tetracyanoethylene oxide. This reaction probably involves a nucleophilic attack of the oxygen atom of iodosylbenzene to the electron-deficient olefin. See: Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc*. **1981**, *103*, 686.

10.1021/ol006129v CCC: $19.00

Scheme 1

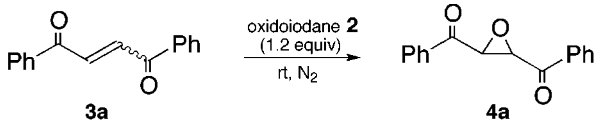


Epoxidation of olefins with iodosylarenes or their derivatives generally requires transition metal catalysts coordinated to porphyrins, which has been studied in detail as a model of cytochrome P-450 oxidation.[1i,6] In most cases, iodosylarenes act as efficient oxygen donors toward the coordinated metals to generate the reactive metal−oxo species. Direct oxygen atom transfer from λ^3-organoiodanes to simple or activated olefins yielding the corresponding epoxides has been shown to be a difficult process.[1i] Attempts to use iodosylbenzene as the synthetic equivalent of the hydroperoxide anion in the epoxidation of conjugated enones have been reported;[5] however, the reaction of α,β-unsaturated ketones with (diacetoxyiodo)benzene/HO^- afforded α-diketones instead of α,β-epoxy ketones.[7]

Synthesis of the oxygen transfer agent, tetra-*n*-butylammonium oxido-λ^3-iodane **2**, is very simple: when a THF solution of tetra-*n*-butylammonium fluoride (1 M, 0.4 mL, 0.4 mmol) was added to a stirred suspension of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) (106 mg, 0.4 mmol) in dichloromethane (5 mL) at room temperature under nitrogen, the reaction mixture immediately turned to a colorless clear solution. After stirring the solution for 30 min, evaporation of solvents gave oxidoiodane **2** as a solid of high purity (by ^{1}H NMR). Recrystallization from AcOEt/CH$_2$Cl$_2$/hexane gave iodane **2** (162 mg, 80%) as colorless crystals.[8,9] The facile formation of salt **2** is probably due to the high acidity of the apical OH group of *o*-iodosylbenzoic acid **1** with $pK_a = 7.25$.[9c] The bicyclic structure of **2** was confirmed by the carbonyl absorption band (1616 cm^{-1}) in its IR spectrum.[9a,10] Iodane **2** is stable to atmospheric moisture and easily soluble in common organic solvents.

Attempted oxygen atom transfers to electron-deficient conjugated enones were carried out without isolation of the tetra-*n*-butylammonium oxido-λ^3-iodane **2**: thus, exposure of (*E*)-1,2-dibenzoylethylene (**3a**) to the crude oxidoiodane **2** (1.2 equiv), prepared as described above and dissolved in a variety of solvents, at room temperature under nitrogen resulted in oxygen atom transfer and afforded the epoxide **4** as a mixture of stereoisomers (Table 1). In less polar solvents such as dichloromethane and benzene, the oxygen transfer reaction is slow and epoxide **4** was obtained in moderate yields (50−60%) (Table 1, entries 1 and 2). No epoxidation was observed when the reaction was carried out in the protic solvent methanol. Increased solvation to the oxygen atom of oxido-λ^3-iodane **2** via hydrogen bonding results in decreased nucleophilicity of iodane **2**, and therefore unsaturated diketone **3a** was recovered as a mixture of stereoisomers. Dipolar aprotic solvents including DMF, DMSO, MeCN, DMI, HMPA, and THF gave good yields (73−85%) of *trans* epoxide **4a** with more than 80% stereoselectivity (Table 1, entries 3−8).

Table 1. Oxygen Atom Transfer from Oxidoiodane **2** to Unsaturated Diketone **3a**[a]



entry	**3a**	solvent	time (h)	**4a** (% yield[b])	ratio[c]
1	(*E*)-**3a**	benzene	5	58	70:30[d]
2	(*E*)-**3a**	CH$_2$Cl$_2$	5	64	75:25[d]
3	(*E*)-**3a**	THF	2	83	89:11
4	(*E*)-**3a**	MeCN	5	77	74:26
5	(*E*)-**3a**	DMF	1	85	81:19
6	(*E*)-**3a**	DMSO	5	82	78:22
7	(*E*)-**3a**	HMPA	1	73	94:6
8	(*E*)-**3a**	DMI[e]	1	83	84:16
9	(*E*)-**3a**	MeOH	20	0	*d*
10	(*E*)-**3a**	DMF[f]	1	42	83:17
11	(*E*)-**3a**	DMF[g]	14	3	87:13[d]
12	(*Z*)-**3a**	DMF	3	78	83:17

[a] The reaction was carried out using 1.2 equiv of tetra-*n*-butylammonium oxido-λ^3-iodane **2** at room temperature under nitrogen. [b] Isolated yields. [c] Ratio of *trans*-**4a**:*cis*-**4a**. [d] A large amount of **3a** was recovered as a mixture of stereoisomers. [e] DMI: 1,3-dimethyl-2-imidazolidinone. [f] NaH was used as a base instead of *n*-Bu$_4$NF. [g] Oxido-λ^5-iodane **6** was used instead of oxido-λ^3-iodane **2**.

(*Z*)-Isomer **3a** also afforded an 83:17 mixture of *trans*- and *cis*-**4a** in the reaction with oxidoiodane **2** in DMF (Table 1, entry 12). Facile base-catalyzed isomerization of diketone **3a** under these conditions seems to be responsible for

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(6) (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (b) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.

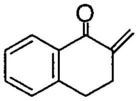
(7) Reaction of (diacetoxyiodo)benzene with hydroxide anion produces iodosylbenzene. See: Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1963**, *43*, 60.

(8) **Tetra-*n*-butylammonium 1-oxido-1,2-benziodoxol-3(1*H*)-one** (**2**): mp 128−129 °C; IR (KBr) 2961, 1616, 1592, 1348, 752, 668 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.11 (dd, $J = 7.5$, 1.3 Hz, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 7.64 (ddd, $J = 7.8$, 7.6, 1.3 Hz, 1H), 7.47 (dd, $J = 7.6$, 7.5 Hz, 1H), 3.26 (m, 8H), 1.63 (quint, $J = 7.4$ Hz, 8H), 1.44 (sext, $J = 7.4$ Hz, 8H), 0.99 (t, $J = 7.4$ Hz, 12H); ^{13}C NMR (CDCl$_3$) δ 169.0, 134.0, 132.0, 130.4, 128.5, 124.7, 121.1, 58.7, 23.9, 19.7, 13.6; FAB MS *m/z* negative 263 [(M − *n*-Bu$_4$N)$^+$], positive 242 (*n*-Bu$_4$N)$^+$. Anal. Calcd for C$_{23}$H$_{40}$INO$_3$: C, 54.65; H, 7.98; N, 2.77. Found: C, 54.26; H, 7.95; N, 2.75.

(9) For syntheses of sodium, calcium, and ammonium 2-iodosylbenzoates, which show low solubility toward common organic solvents, see: (a) Baker, G. P.; Mann, F. G.; Sheppard, N.; Tetlow, A. J. *J. Chem. Soc.* **1965**, 3721. (b) Siebert, H.; Handrich, M. *Z. Anorg. Allg. Chem.* **1976**, *426*, 173. (c) Moss, R. A.; Alwis, K. W.; Bizzigotti, G. O. *J. Am. Chem. Soc.* **1983**, *105*, 681. (d) Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Blair, J. T.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 250.

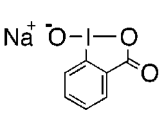
(10) For X-ray structure analysis of sodium 2-iodosylbenzoates, see: Katritzky, A. R.; Savage, G. P.; Palenik, G. J.; Qian, K.; Zhang, Z. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1657.

Table 2. Epoxidation of α,β-Unsaturated Carbonyl Compounds **3** with Oxidoiodane **2** at 50 °C

entry	olefin		iodane **2** (equiv)	solvent	conditions[a] time (h)	epoxide	% yield[b]
1	2-cyclohexenone	**3b**	1.2	DMF	20	**4b**	9[c]
2	(*E*)-PhCOCH=CHMe	**3c**	1.2	DMF	7	*trans*-**4c**	45[d]
3	(*E*)-PhCOCH=CHMe	**3c**	2.5	DMF	3	*trans*-**4c**	66
4	(*E*)-PhCOCH=CHPh	**3d**	2.5	DMF	24	*trans*-**4d**	34[e]
5		**3e**	2.5	DMF	12	**4e**	63
6	$(PhCO)_2C=CHPh$	**3f**	2.5	DMF	2	**4f**	73
7	$(PhCO)_2C=CHPh$	**3f**	1.2	HMPA	12	**4f**	60
8	$(MeCO)_2C=CHPh$	**3g**	1.2	DMF	2	**4g**	72
9	$(EtO_2C)_2C=CHPh$	**3h**	2.5	DMF	24	**4h**	51

[a] The reaction was carried out under nitrogen. [b] Isolated yields. [c] **3b** (39%) was recovered unchanged. [d] **3c** (20%) was recovered unchanged. [e] **3d** (37%) was recovered unchanged.

extensive stereoconvergence in the epoxidation;[11] in fact, the diketones (*E*)- and (*Z*)-**3a** rapidly isomerize to the equilibrium mixture (*E*:*Z* = 70−76:24−30) even under less basic conditions using tetra-*n*-butylammonium acetate (DMF/rt/3 h).



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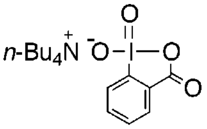

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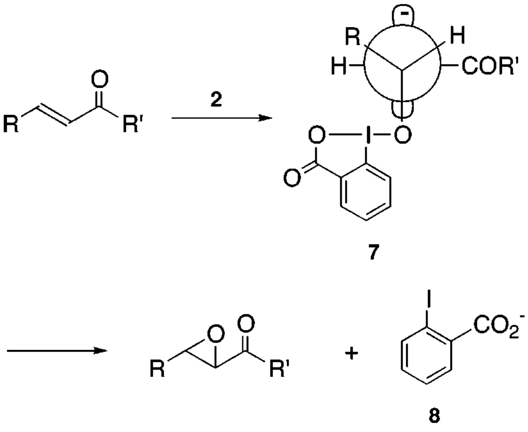
Sodium oxido-λ^3-iodane **5**, an effective catalyst for the hydrolysis of esters and phosphates in aqueous micellar cetyltrimethylammonium chloride solutions at pH 8,[9c,12] also cause epoxidation of (*E*)-**3a** in DMF at room temperature, albeit in low yield (Table 1, entry 10). On the other hand, reactivity of tetra-*n*-butylammonium oxido-λ^5-iodane **6**[13] for the oxygen atom transfer appears to be low and a large amount of the unsaturated diketone **3a** was recovered (Table 1, entry 11). This is probably due to the decreased nucleophilicity of the anionic oxygen atom of **6** directly bonded to the more electronegative pentavalent iodine.[12]

Table 2 summarizes the results of the epoxidation of electron-deficient olefins at 50 °C. Nucleophilicity of oxidoiodane **2** seems to be moderate,[14] because the reaction of 2-cyclohexenone **3b** returned a large amount of the olefin and afforded α,β-epoxy ketone **4b** in only 9% yield. Sterically less hindered **3e** and highly electron deficient olefins **3f**−**h** afforded a reasonable yield of epoxides **4e**−**h**. Exclusive retention of stereochemistry of olefins was observed in the epoxidation of **3c**,**d**, in which no isomerization of olefins takes place under these conditions.

The epoxidation of α,β-unsaturated carbonyl compounds probably involves Michael-type addition of oxidoiodane **2** and produces enolate anion **7** (Scheme 2). The leaving ability of the λ^3-iodanyl group of **7** is high,[15] and therefore, intramolecular cyclization of **7** with reductive elimination of *o*-iodobenzoate anion **8** gives the epoxide with retention of stereochemistry.

Scheme 2



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[11] The recovered diketone **3a** in this epoxidation always consists of a mixture of (*E*)- and (*Z*)-isomers.

[12] Moss, R. A.; Alwis, K. W.; Shin, J. *J. Am. Chem. Soc.* **1984**, *106*, 2651.

[13] Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

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(14) The oxido anion of λ^3-iodane **2** exhibits a modest α-effect. (a) Moss, R. A.; Swarup, S.; Ganguli, S. *J. Chem. Soc., Chem. Commun*. **1987**, 860. (b) Colthurst, M. J.; Kanagasooriam, A. J.; Wong, M. S.; Contini, C.; Williams, A. *Can. J. Chem.* **1998**, *76*, 678.

(15) The λ^3-phenyliodanyl group shows a very high leaving group ability and is called a hyperleaving group. See ref 1o.