

Iodination of Organic Substrates with Halide Salts and H₂O₂ Using an Organotelluride Catalyst

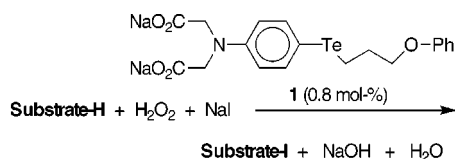
Donald E. Higgs, Marina I. Nelen, and Michael R. Detty*

Department of Chemistry, Division of Medicinal Chemistry, State University of New York at Buffalo, Buffalo, New York 14260

mdetty@acsu.buffalo.edu

Received November 1, 2000

ABSTRACT



Organotelluride **1** is a water-soluble catalyst for the oxidation of iodide with hydrogen peroxide in pH 6 phosphate buffer. In two-phase systems, organic substrates are efficiently iodinated using 0.8 mol % of catalyst. Water-soluble substrates are iodinated without an organic cosolvent.

The halogenation of organic substrates is an important reaction for the preparation of specialty, pharmaceutical, and agricultural chemicals. The general method used to halogenate organic substrates has been the use of bromine, chlorine, or iodine. However, halogenation reactions have associated environmental hazards with respect to transport, handling, and storage of chlorine, bromine, and iodine.¹ Halide salts are safer commodities and can be oxidized to the corresponding positive halogen/hypohalous acid by a variety of methods. One method is the oxidation of chloride, bromide, or iodide with H₂O₂, a powerful and environmentally friendly oxidant.² Although the oxidation of these halides with H₂O₂ is thermodynamically favored, it is kinetically slow.³ At lower pH, the oxidation is accelerated and the hypohalous acids generated from hydrochloric or hydrobromic acid and H₂O₂ have been used for the successful halogenation of a

variety of organic substrates although acid-sensitive functionality will not tolerate the reaction conditions.⁴

Nature has evolved the haloperoxidase enzymes to perform biological halogenations at neutral pH with the available H₂O₂ and halide salts found in seawater.⁵ In recent years, chemists have sought catalysts to activate H₂O₂ and other peroxides (such as *tert*-butyl hydroperoxide) to mimic the function of the haloperoxidases and to provide environmentally friendly means for the halogenation of organic substrates.⁶ We have been interested in the activation of H₂O₂ using organotellurium compounds as catalysts and have successfully performed halogenation reactions in the presence

(1) Clark, J. H.; Ross, J. C.; Macquarrie, D. J.; Barlow, S. J.; Bastock, T. W. *Chem. Commun.* **1997**, 1203–1204.

(2) Jones, C. W. *Applications of Hydrogen Peroxide and Derivatives*; "RSC Clean Technology Monographs"; Clark, J. H., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1999.

(3) (a) Leulier, A. *Bull. Soc. Chim. Fr.* **1924**, 35, 1325–1330. (b) Mohammed, A.; Liebhafsky, H. A. *J. Am. Chem. Soc.* **1934**, 56, 1680–1685.

(4) (a) Lubbecke, P.; Boldt, P. *Angew. Chem.* **1976**, 88, 641–643. (b) Keegstra, M. A.; Brandsma, L. *Synthesis* **1988**, 890–891.

(5) (a) Wever, R.; Kreen, M. B. E. In *Vanadium in Biological Systems*; Chasteen, N. D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1990; pp 81–97. (b) Butler, A. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1992; pp 425–445. (c) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, 93, 1937–1944.

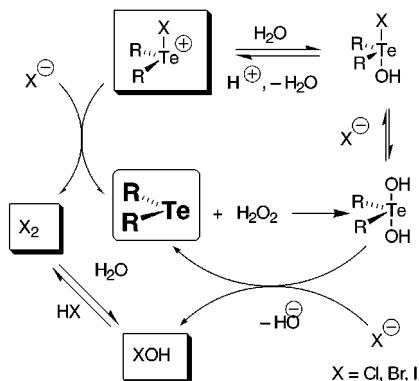
(6) (a) Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1994**, 35, 7429–7432. (b) Dinesh, C. U.; Kumar, R.; Pandey, B.; Kumar, P. *Chem. Commun.* **1995**, 611–612. (c) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, 39, 6349–6350. (d) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, 2, 247–249.

(7) (a) Detty, M. R.; Gibson, S. L. *J. Am. Chem. Soc.* **1990**, 112, 4086–4088. (b) Detty, M. R.; Gibson, S. L. *Organometallics* **1992**, 11, 2147–2155. (c) Detty, M. R.; Friedman, A. E.; Oseroff, A. *J. Org. Chem.* **1994**, 59, 8245–8250. (d) Detty, M. R.; Zhou, F.; Friedman, A. E. *J. Am. Chem. Soc.* **1996**, 118, 313–318.

of H_2O_2 and halide salts.⁷ While these reactions have demonstrated proof of principle, the positive halogen species were trapped in the presence of a large excess of substrate, limiting the synthetic utility of these earlier studies.

The activation of H_2O_2 with organotellurides is a multistep process involving oxidative addition, ligand exchange, and reductive elimination.^{7c,d} The active halogenating species in the telluride-catalyzed reactions may either be the free halogen/hypohalous acid or a halotelluronium salt intermediate as illustrated in Scheme 1.⁸ The rate-limiting step in these

Scheme 1. Possible Halogenating Agents from the Oxidation of Halide Salts with Organotelluride Catalysts



reactions appears to be the rate of reductive elimination or cleavage of the halogen–tellurium bond.^{7d,8} The most effective catalysts have some water solubility,^{7d} and the most active halogen transfer agents have a chelating heteroatom as a ligand to the oxidized tellurium center (see Figure 1a).⁹

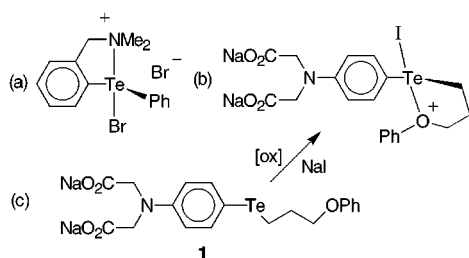


Figure 1. (a and b) Chelating ligands that activate halo ligand on tellurium. (c) Catalyst 1.

The chelating ligand prevents the addition of a second halide to the oxidized tellurium atom while the positive charge activates the halo ligand to nucleophilic attack.⁹

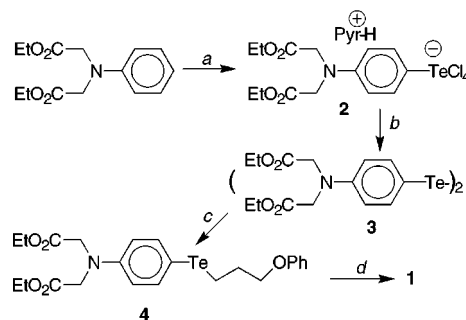
(8) (a) Leonard, K. A.; Zhou, F.; Detty, M. R. *Organometallics* **1996**, *15*, 4285–4292. (b) Butcher, T. S.; Zhou, F.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 169–176. (c) Butcher, T. S.; Detty, M. R. *J. Org. Chem.* **1999**, *64*, 5677–5681.

(9) (a) Detty, M. R.; Friedman, A. E.; McMillan, M. *Organometallics* **1995**, *14*, 1442–1449. (b) Detty, M. R.; Williams, A. J.; Hewitt, J. M.; McMillan, M. *Organometallics* **1995**, *14*, 5258–5262.

We report highly efficient iodination reactions employing the organotelluride catalyst **1** (Figure 1b) for the oxidation of iodide with H_2O_2 . The catalyst **1** was designed to provide water solubility and to optimize both oxidation with H_2O_2 and reductive elimination or halogen transfer. We anticipated that the amino substituent of **1** would add electron density to the telluride, which would facilitate oxidation with H_2O_2 . The oxygen atom of the phenoxypropyl group would chelate the oxidized tellurium center by donating an electron pair (via a five-membered ring, Figure 1b) to block addition of iodide to form the I–Te–I array and to activate nucleophilic attack at the iodo ligand. The catalyst **1** is readily oxidized by hydrogen peroxide with a second-order rate constant of $(3.93 \pm 0.08) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ in pH 6 phosphate buffer and is an effective iodination catalyst at 0.8 mol % of substrate (see Supporting Information for experimental details). As a biscarboxylate salt, **1** is water-soluble and remains in solution at pH 6, where the iodination reactions were run. The near-neutral pH of these reactions is tolerated by most acid-sensitive organic functionality. Furthermore, the reactions can be run without an organic cosolvent if the substrates have some aqueous solubility.

Biscarboxylate salt **1** was prepared from 4-*N,N*-bis(carboethoxymethyl)aniline as shown in Scheme 2. The

Scheme 2^a



^a Key: (a) TeCl_4 or SeCl_4 , pyridine, EtOAc, 0 °C to r.t.; (b) 10% NaHSO_3 , toluene; (c) NaBH_4 , EtOH, $\text{Br}(\text{CH}_2)_3\text{OPh}$; (d) 4 eq NaOH , aq EtOH

addition of TeCl_4 to 4-*N,N*-bis(carboethoxymethyl)aniline followed the procedure of Engman and Persson¹⁰ except that 1 equiv of pyridine was added to give pyridinium salt **2** as an isolable intermediate,¹¹ which was then reduced with sodium bisulfite to give the ditelluride **3**. Ditelluride **3** was isolated as the major product in a 2:1 mixture with the corresponding monotelluride (85% isolated yield of the mixture). We were not able to separate the ditelluride from the monotelluride in this mixture. Ditelluride **3** was reduced with NaBH_4 to the corresponding sodium aryltelluroate, which reacted with 1-bromo-3-phenoxypropane to give the

(10) Engman, L.; Persson, J. *Organometallics* **1993**, *12*, 1068–1072.

(11) (a) Logan, M. E.; Decann, C. A.; Oenick, M. D. B.; Snodgrass, G. L.; Snoke, R. E. Eur. Pat. Appl., 30 pp. CODEN: EP 747704 A2 961211. Application: EP 96-304211 960606. *Chem. Abstr.* **1997**, *126*, 57086. (b) Logan, M. E. (SUNY College at Brockport), private communication.

bisester **4** in 74% isolated yield. Compound **4** was saponified with 4 equiv of sodium hydroxide in aqueous EtOH to give **1** in >95% isolated yields.¹²

The **1**-catalyzed iodinations of organic substrates with NaI and H₂O₂ are summarized in Table 1 and used the following

Table 1. Iodination of Organic Substrates with NaI, Hydrogen Peroxide, and 0.8 mol % of Organotelluride Catalyst **1**^a

Subst-H + NaI + H ₂ O ₂		0.8 mol-% 1 pH-6 buffer		Subst-I + NaOH + H ₂ O	
entry	substrate	product	% isolated yield	equivalents subst: H ₂ O ₂ : NaI	rxn time
(1)			94 92	1:1.7:1.1 1.1 equiv I ₂	1 h 1 h
(2)			93 90	1:5:4 2.5 equiv I ₂	2 h 2 h
(3)			40 45	1:1.7:1 1.1 equiv I ₂	2 h 2 h
(4)			58 65	1:3.4:2.2 2.5 equiv I ₂	3 h 3 h
(5)			94 95	1:5:3.6 2.5 equiv I ₂	5 h 5 h
(6)			88 74	1:5:3.6 2.5 equiv I ₂	5 h 5 h
(7)			76 58	1:5:4 2.5 equiv I ₂	5 h 5 h
(8) ^b			88 75	1:1.7:1.1 1.1 equiv I ₂	1 h 1 h

^a Two phase mixture of 2.5 mmol substrate in 25 mL of ether and 50 mL pH-6 phosphate buffer. ^b Substrate in 50 mL of pH-6 phosphate buffer.

general procedure. The substrate (2.5 mmol) and **1** (10.3 mg, 0.020 mmol) were dissolved in a stirred mixture of 25 mL of ether and 50 mL of pH 6 phosphate buffer at ambient temperature. Sodium iodide as a 2 M solution (2.75–5.0 mL) and 2 M H₂O₂ (2.1–6.3 mL) were added independently in small aliquots via syringe every 5 min over a 45-min interval in the stoichiometry described in Table 1. The reaction mixtures were stirred until reaction was complete (1–5 h) as monitored by ¹H NMR. The organic phase was separated and the aqueous layer extracted with two additional aliquots of ether. The combined ether extracts were washed with brine and then 3% sodium bisulfite, dried over MgSO₄, and concentrated. The crude product was purified via chromatography on SiO₂ or recrystallization for crystalline products. Isolated yields of purified products are compiled in Table


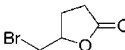
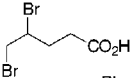
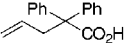
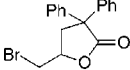
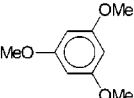
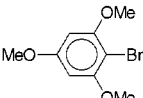
1.¹² For entry 8, the sodium salt of 4-pentenoic acid was iodinated without an organic cosolvent and 5-iodo-γ-valerolactone was isolated in a yield nearly identical to the two-phase procedure of entry 1. In the absence of catalyst, less than 10% conversion of substrate was observed after 24 h for all substrates in Table 1.

The iodination of *N,N*-dimethylaniline (entry 6) and *N*-phenylmorpholine (entry 7) gave the 4-substituted products with >98% regioselectivity as determined by the ¹H NMR spectra of the crude product mixtures. The lactonizations of 4-pentenoic acid (entries 1 and 8), 2,2-diphenyl-4-pentenoic acid¹³ (entry 2), and 2-(1-cyclohexen-1-yl)acetic acid¹⁴ (entry 3) as well as the cyclization of 4-pentanol (entry 4) gave only products containing five-membered rings as determined by ¹H NMR. Unreacted 2-(1-cyclohexen-1-yl)acetic acid (35%) was recovered from entry 3. The iodination of 1,3,5-trimethoxybenzene (entry 5) gave 2–3% of the diiodo product as determined by the ¹H NMR spectrum of the crude product mixture.

As shown for each substrate entry of Table 1, the **1**-catalyzed iodinations with iodide and H₂O₂ gave results nearly identical to the use of elemental iodine in two-phase systems. Furthermore, neither the catalyzed iodination nor the direct iodination with iodine was effective with unactivated aromatic substrates (benzene, toluene) giving less than 10% iodination after 24 h with 5 equiv of H₂O₂ and 4 equiv of NaI in the catalyzed reaction and less than 10% iodination after 24 h with 2.5 equiv of iodine.

We are developing chlorination and bromination reactions using chalcogenide catalysts with halide salts and H₂O₂. In other systems, bromination reactions with organotelluride reagents have been less efficient than iodination reactions

Table 2. Bromination of Organic Substrates with Sodium Bromide, Hydrogen Peroxide, and 2.5 mol % of Organotelluride Catalyst **1**

Subst-H + NaBr + H ₂ O ₂		2.5 mol-% catalyst 1		
		pH-6 buffer		
		Subst-Br + NaOH + H ₂ O		
entry	substrate	products	% yield after 24 h	
(1) ^a		 + 	44 35	
(2) ^b			< 5	
(3) ^b			45	

^a 2.05 mmol substrate in 16.5 mL of 2.0 M NaBr, 3.0 M H₂O₂ in pH-6 phosphate buffer. ^b Two-phase with 20 mL of ether in addition to the reagents in (a).

(12) Experimental details and characterization of products are compiled in the Supporting Information.

(13) Arnold, R. T.; Lindsay, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 1048–1049.

(14) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611–3614.

with organotelluride reagents.^{8a} This is presumably due to the greater bond strength of the Te–Br bond relative to the bond strength of the Te–I bond. In stoichiometric reactions, selenium(IV) bromides were found to be better brominating agents than tellurium(IV) bromides presumably due to the weaker Se–Br bond strength, which facilitates bromine transfer.

Consistent with these earlier observations, the **1**-catalyzed brominations of organic substrates required higher concentrations of bromide, peroxide, and catalyst than the corresponding iodinations as well as longer reaction times. Several examples are listed in Table 2 using 2.5 mol % of **1** in pH 6 phosphate buffer with a 15-fold excess of H₂O₂ (3 M) and a 10-fold excess of NaBr (2 M). These reactions were stopped after 24 h. It should be noted that in the absence of catalyst less than 5% conversion of substrate to product occurred after 24 h. Although the sodium salt of 4-pentenoic acid was readily brominated under these reaction conditions, 2,2-diphenyl-4-pentenoic gave only trace amounts of products after 24 h. The bromination of 1,3,5-trimethoxybenzene gave only 45% conversion to 2-bromo-1,3,5-trimethoxybenzene after 24 h.

We are currently preparing the selenide analogue of **1** and related compounds as catalysts for brominations and chlorinations. Hopefully, the weaker selenium–halogen bonds in the oxidized catalyst will provide more efficient chlorination and bromination of organic substrates to complement the efficient iodinations that we have described here.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We also thank Dr. Margaret E. Logan (SUNY College at Brockport) for sharing her modified procedure for the addition of tellurium tetrachloride to electron-rich aromatic substrates.

Supporting Information Available: Detailed experimental procedures and characterization data for the preparation of catalyst **1**, compounds **2–4**, and the products of entries 1–8 of Table 1, experimental details for the oxidation of **1** with H₂O₂. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0068142