OXIDATION OF AMINES WITH HYPERVALENT *TERT*-BUTYLPEROXYIODANES: SYNTHESIS OF IMINES AND *TERT*-BUTYLPEROXYAMINO ACETALS¶

Masahito Ochiai,* Daisuke Kajishima, and Takuya Sueda

Faculty of Pharmaceutical Sciences, University of Tokushima,
1-78 Shomachi, Tokushima 770, Japan

Abstract - Reaction of secondary amines with 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one (**2**) undergoes dehydrogenation to afford imines in the presence of K_2CO_3, while oxidation of tertiary amines without base produces *tert*-butylperoxyamino acetals.

Organoiodanes undergo oxidation of amines to give a variety of products depending on the type of amine.[1] Oxidation of primary aromatic amines with (diacetoxyiodo)benzene or [bis(trifluoroacetoxy)-iodo]benzene results in formation of *trans*-azo compounds *via* oxidative coupling.[2] Primary aliphatic amines on oxidation with iodosylbenzene give nitriles, while primary cycloalkylamines and cyclic secondary amines in the presence of water afford cyclic ketones and lactams, respectively, *via* intermediate formation of the corresponding imines.[3a] In the absence of water, iodosylbenzene oxidation of cyclic *sec*-amines affords the imines:[3b,c] for instance, oxidation of pyrrolidine in dichloromethane at room temperature gave quantitatively a mixture of 1-pyrroline and its cyclic trimer in a ratio 93:7. The elegant synthesis of discorhabdin C reported by Kita and coworkers involves an intramolecular oxidative spiro cyclization of silylated phenols with aminoquinone functionalities by [bis(trifluoroacetoxy)iodo]benzene.[4] Oxidations of tertiary amines with organoiodanes are limited. Magnus and coworkers have reported an interesting oxidation of tertiary amines with a combination of iodosylbenzene-trimethylsilylazide, which undergoes *N*-alkyl azidonation of *N*,*N*-dialkylarylamines.[5]

Recently, we reported the synthesis and characterization of the stable crystalline (alkylperoxy)iodane, 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one (**2**) *via* the Lewis acid-catalyzed ligand exchange of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one with *tert*-butyl hydroperoxide in chloroform.[6] The peroxyiodane (**2**) oxidizes benzyl and allyl ethers to the esters even at room temperature in the presence of alkali metal carbonates.[7] Because this reaction is compatible with other protecting groups such as MOM, THP, and TBDMS ethers, and acetoxy groups, and because esters are readily hydrolyzed under basic conditions, this method provides a convenient and effective alternative to the usual reductive deprotection of benzyl and

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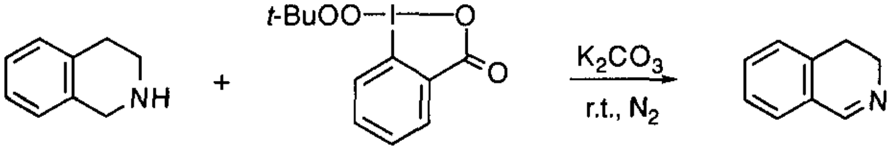
¶ This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

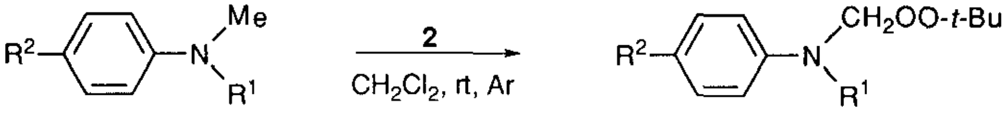
allyl ethers. We report here the oxidation of secondary and tertiary amines with the alkylperoxyiodane (**2**), which proceeds at room temperature yielding imines and *tert*-butylperoxyamino acetals, respectively.



1a **2** **3a**

Methods for oxidation of amines to imines[8] involve diphenylselenium bis(trifluoroacetate),[9a] di-*tert*-butyliminoxyl radical,[9b] Swern oxidation,[9c] manganese dioxide,[9d] and Fremy's salt.[9e] Recently, an efficient transition-metal catalyzed dehydrogenation of *sec*-amines with *tert*-butyl hydroperoxide into imines was reported by Murahashi[10a] and Nishinaga.[10b] Table 1 summarizes the results of oxidation of a variety of *sec*-amines (**1**) with the *tert*-butylperoxyiodane (**2**). Exposure of tetrahydroisoquinoline (**1a**) to **2** (1.1 equiv) in the presence of excess amounts of K_2CO_3 in dichloromethane at room temperature for 18 h afforded 3,4-dihydroisoquinoline (**3a**) in 83% yield. Use of benzene as a solvent increased the rate of the dehydrogenation. The use of K_2CO_3 as a base is not crucial, but increases both the rate of oxidation and the yield of **3a**; without K_2CO_3, even after 120 h at room temperature in benzene, a considerable amount of **1a** (13%) was recovered unchanged. Furthermore, this reaction led to formation of a mixture of products consisting of the imine (**3a**; 36%), 1,2,3,4-tetrahydroisoquinolin-1-one[11] (11%), and isoquinoline (7%) (Compare Table 1, entries 2 and 3). A similar rate enhancement by the use of alkali metal carbonates was observed in the benzylic oxidation of benzyl ethers to the esters with **2**.[7] Formation of a small amount of isoquinoline always accompanies oxidation of tetrahydroisoquinolines (**1a**) and (**1b**). When 2.5 equivalents of the peroxyiodane (**2**) were used in the oxidation of **1b** in benzene (room temperature, 13 h), 6,7-dimethoxyisoquinoline was obtained as a major product in 43% yield.

Benzyl-*tert*-butylamine (**1c**) was dehydrogenated to *N*-benzylidene-*tert*-butylamine (**3c**) in 61% yield. Benzylamines (**1d-i**) similarly afforded the corresponding imines in good yields (Table 1, entries 9-14). Presence of an electron-withdrawing aryl group at nitrogen of **1d-h** and a cyano group at benzylic position of **1h** causes the reaction rate to slow down. L-Proline methyl ester (**1j**) was converted to methyl pyrrolinecarboxylate (**3j**) in 72% yield, being a key intermediate for the synthesis of (-)-detoxinine,[12] while indoline (**1k**) gives indole (**3k**) *via* the double bond shift to aromatize.[3b]

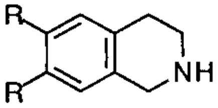
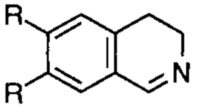
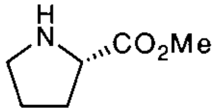
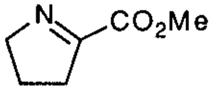
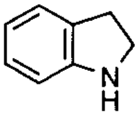
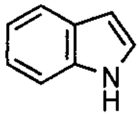


4a-d **5a-d**

a; R^1 = Me, R^2 = H, **b**; R^1 = Me, R^2 = Br, **c**; R^1, R^2 = Me, **d**; R^1 = Et, R^2 = H

Having established that secondary amines are dehydrogenated to imines with the alkylperoxyiodane (**2**)

Table 1. Oxidation of *sec*-Amines (**1**) with *tert*-Butylperoxyiodane (**2**)[a]

entry	*sec*-Amine **1**	**2**	Additive	Solvent	Reaction	Product	
		(equiv)	(equiv)		Time (h)	**3**	Yield[b]/%
							
1	**1a** (R = H)	1.1		CH_2Cl_2	18	**3a**	83
2	**1a**	1.1		PhH	6	**3a**	73[c]
3	**1a**	1.1		PhH[d]	120	**3a**	36[c,e]
4	**1a**	1.1		PhH[f]	6	**3a**	75[c]
5	**1a**	1.1	TEMPO (1.1)	PhH	3	**3a**	63[c]
6	**1b** (R = MeO)	1.1		CH_2Cl_2	8	**3b**	75[g]
7	**1b**	1.1		PhH	3.5	**3b**	76[g]
	PhR^1CHNHR^2					$PhR^1C{=}NR^2$	
8	**1c** (R^1 = H, R^2 = *t*-Bu)	1.1		PhH	5	**3c**	(61)[h]
9	**1d** (R^1 = H, R^2 = Ph)	1.3		PhH	25	**3d**	(84)
10	**1e** (R^1 = H, R^2 = *p*-MePh)	1.1		PhH	16	**3e**	(74)
11	**1f** (R^1 = H, R^2 = *p*-MeOPh)	1.1		PhH	17	**3f**	(80)
12	**1g** (R^1 = H, R^2 = *p*-ClPh)	1.1		PhH	21	**3g**	(78)
13	**1h** (R^1 = CN, R^2 = Ph)	2		PhH	34	**3h**	56
14	**1i** (R^1 = H, R^2 = CH_2Ph)	1.3		PhH	6	**3i**	(68)
							
15	**1j**	1.1		PhH	12	**3j**	72
							
16	**1k**	1.2		PhH[f]	12	**3k**	69

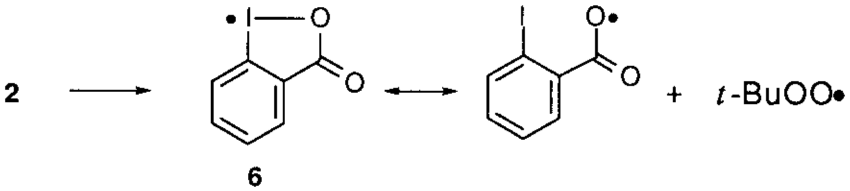
[a] Unless otherwise noted, reactions were carried out in the presence of 10 equivalents of K_2CO_3 at room temperature under nitrogen. [b] Isolated yields. Parentheses are GC or ^1H NMR yields. [c] Isoquinoline was obtained in 2-8% yields. [d] Without a base (K_2CO_3). [e] 1,2,3,4-Tetrahydroisoquinolin-1-one was obtained in 11% yield. **1a** (13%) was recovered. [f] Under oxygen. [g] 6,7-Dimethoxyisoquinoline was obtained in 5-6% yields. [h] Benzaldehyde (13%) was detected.

Table 2. Oxidation of *tert*-Amines (**4**) with *tert*-Butylperoxyiodane (**2**)[a]

entry	**4**	**2** (equiv)	Additive (equiv)	Time (h)	**5**	Yield[b]/%
1	**4a**	1		17	**5a**	76
2	**4a**	1	K_2CO_3 (10)	30	**5a**	35[c]
3	**4a**	1	galvinoxyl (1)	17	**5a**	10[d]
4	**4a**	3		24	**5a**	55[e]
5	**4b**	1		7	**5b**	67
6	**4c**	1		4	**5c**	46
7	**4d**	1.2		13	**5d**	47

[a] Reactions were carried out in CH_2Cl_2 at room temperature under argon. [b] Yields were determined by ^1H NMR. [c] *N*-Formyl-*N*-methylaniline was obtained in 22% yield. [d] **4a** (57%) was recovered. [e] *N*,*N*-Bis(*tert*-butylperoxymethyl)aniline (**5e**) was obtained in 14% yield.

under mild conditions, we further examined the fate of tertiary amines with the oxidant (**2**). In marked contrast, the *tert*-butylperoxy group of **2** was transferred to the methyl group on the oxidation of tertiary *N*-methylanilines (**4**) (Table 2). Reaction of *N*,*N*-dimethylaniline (**4a**) with an equivalent amount of the peroxyiodane (**2**) in dichloromethane at room temperature under argon resulted in the formation of unstable *N*-methyl-*N*-(*tert*-butylperoxymethyl)aniline (**5a**) in 76% yield (NMR).[13,14] No formation of the corresponding *N*-oxide was detected. Use of K_2CO_3 as an additive resulted in decomposition of the (*tert*-butylperoxymethyl)aniline (**5a**) to some extent yielding *N*-formyl-*N*-methylaniline (22%), probably *via* the base-induced β-elimination (Table 2, entry 2).[15] An excess amount (3 equiv) of **2** led to the further oxidation of **5a** yielding *N*,*N*-bis(*tert*-butylperoxymethyl)aniline (**5e**) in 14% yield (Table 2, entry 4). Substituted *N*,*N*-dimethylanilines (**4b**) and (**4c**) similarly afforded the peroxyamino acetals (**5b**; 67%) and (**5c**; 46%), respectively. High regioselectivity was observed for reaction of *N*-methyl-*N*-ethylaniline (**4d**) with the peroxyiodane (**2**), which resulted in preferential oxidation of the methyl group of **4d** affording the *N*-(*tert*-butylperoxymethyl)aniline (**5d**) in 47% yield. Similar selectivity for oxidation of *N*-methyl over other alkyl groups was reported in the anodic oxidation of tertiary amines in methanol[16] and in the ruthenium-catalyzed oxidation with *tert*-butyl hydroperoxide.[14] The *N*-methyl-*N*-(*tert*-butylperoxymethyl)anilines (**5**) have been shown to be a useful precursor for generation of iminium ions[14] and for the synthesis of a variety of substituted tetrahydroquinolines.[16,17]



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Radical nature of the oxidation of tertiary amines was substantiated by the inhibition of the reaction with the added radical scavenger galvinoxyl (Table 2, entry 3). The alkylperoxyiodane (**2**) has been shown to decompose in dichloromethane at 30 °C with a half-life of 7.4 h, *via* homolytic bond cleavage of the weak iodine(III)-peroxy bond generating the [9-I-2] iodanyl radical (**6**) and *tert*-butylperoxy radical.[7] These radicals are probably responsible for the oxidation of tertiary amines with **2**. Detailed mechanistic studies are in progress.

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