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Tetrahedronfuranylation of alcohols catalyzed by alkylperoxy-λ^3-iodane and carbon tetrachloride

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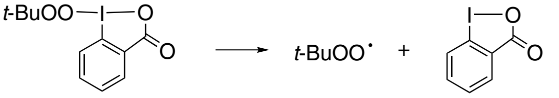
Abstract—Reaction of primary and secondary alcohols with tetrahydrofuran and a catalytic amount of 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one in the presence of carbon tetrachloride at 50 °C provides an efficient method for protecting the hydroxy group as 2-tetrahydrofuranyl ethers.

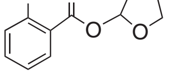
Commercially available crystalline 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one **1**, which is stable in the solid state but gradually decomposes in solution at ambient temperature to generate *tert*-butylperoxy radical and [9-I-2] iodanyl radical **2** through homolytic cleavage of the hypervalent iodine(III)-peroxy bond (Eq. 1),[1] serves as a versatile oxidizing agent.[2] Oxidation of benzyl and allyl ethers with the *tert*-butylperoxy-λ^3-iodane **1** in the presence of alkali metal carbonates affords the corresponding esters via the intermediacy of benzylic and allylic radicals.[1] Cyclic acetals generate α-oxy carbon-centered radicals and undergo oxidative ring cleavage to give hydroxy esters through the formation of *tert*-butylperoxy *ortho*-esters.[3] Sulfides, secondary and tertiary amines, and amides are readily oxidized to sulfoxides, imines, *tert*-butylperoxyamino acetals, and imides (or *tert*-butylperoxyamide acetals), respectively.[4] 4-Substituted phenols are readily transformed to 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-ones in good yields.[5] We report herein a new method for protection of alcohols as 2-tetrahydrofuranyl ethers by using the *tert*-butylperoxy-λ^3-iodane **1** in THF. Addition of carbon tetrachloride not only suppressed a competing side reaction but also decreased the amounts of the λ^3-iodane **1** required in the reaction.



(1)

1 **2**

When a THF solution of the peroxy-λ^3-iodane **1** was heated at 50 °C for 10 h under argon, acid-labile 2-tetrahydrofuranyl *o*-iodobenzoate **3** was produced in a 45% yield along with the formation of a large amount of *o*-iodobenzoic acid **5** (55%). These product profiles indicate that the reaction involves not only reduction of the trivalent iodine in **1** to iodide but also oxidation of the solvent THF. It seems reasonable to assume that the reaction of *o*-iodobenzoic acid **5** generated in situ with THF-derived cationic species (See below, Eq. 3) is responsible for the formation of 2-tetrahydrofuranyl *o*-iodobenzoate **3**. With these considerations in mind, we envisioned that, if the decomposition of the peroxy-λ^3-iodane **1** in THF is carried out in the presence of an alcohol, tetrahydrofuranylation of the hydroxy group would take place in preference to that of less nucleophilic *o*-iodobenzoic acid **5** yielding the ester **3**.[6]



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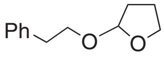

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In fact, exposure of 2-phenylethanol to a stoichiometric amount of the peroxy-λ^3-iodane **1** in THF at 50 °C for 10 h resulted in the formation of 2-tetrahydrofuranyl ether **4** in 41% yield; the reaction, however, competes with the esterification that produces the labile ester **3** (16%, Table 1, entry 1). Use of 2 equiv of **1** increased the yield of **4** up to 73%. As shown in Table 1, good yields of THF ethers were obtained in the reactions with primary

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Keywords: Protection; Hypervalent; Iodine; Iodane; Alcohol; Radical.

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Table 1. Tetrahydrofuranylation of alcohols with peroxy-λ^3-iodane **1**[a]

Entry	Alcohol	Product [yield (%)]	
		THF ether[b]	**3**[c]
1	$PhCH_2CH_2OH$[d]	41	16
2	$PhCH_2CH_2OH$	73	17
3	n-$C_8H_{17}OH$	63	27
4	$EtOCH_2CH_2OH$	52	29
5	$BrCH_2CH_2OH$	54	18
6	c-$C_6H_{11}OH$	30	55
7	$PhCH_2CHMeOH$	30	60
8	$PhCH_2CMe_2OH$	—	51

[a] Unless otherwise noted, tetrahydrofuranylation of an alcohol [0.1 M] was carried using peroxy-λ^3-iodane **1** (2 equiv) at 50 °C for 10 h in THF under argon.

[b] GC yields.

[c] ^1H NMR yields based on iodane **1**.

[d] Iodane **1** (1 equiv) was used.

alcohols but not with secondary and tertiary alcohols. The protection of alcohols always competes with formation of the ester **3**.

The tetrahydrofuranylation of alcohols with the peroxy-λ^3-iodane **1** in THF probably involves the following sequences: (a) α-hydrogen atom abstraction of THF with *tert*-butylperoxy radical and/or the iodanyl radical **2** to give α-tetrahydrofuranyl radical **6** (Eq. 2),[7] (b) a single-electron transfer from α-THF radical **6** to the peroxy-λ^3-iodane **1** (or *tert*-butylperoxy radical and the iodanyl radical **2**), generating the oxonium ion **7** (Eq. 3).[8] Finally, nucleophilic attack of an alcohol on **7** produces the desired THF ethers, whereas the ester **3** is produced by the reaction of **7** with *o*-iodobenzoic acid **5**.

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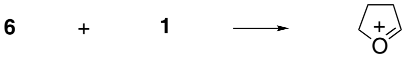
(2)



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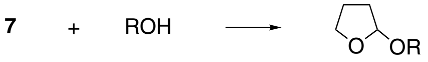
(3)



(4)

Our attention is focused on developing the method that not only affords high yields of THF ethers but also requires only a catalytic amount of the peroxy-λ^3-iodane **1**, which in turn makes it possible to suppress the competing side reaction that is, the ester formation by decreasing the amounts of *o*-iodobenzoic acid **5** generated in situ. Recently, Mioskowski and co-workers reported an efficient method for tetrahydrofuranylation of alcohols using a stoichiometric amount of carbon tetrachloride and $CrCl_2$, in which $CrCl_2$ undergoes single electron reduction of both carbon tetrachloride and trichloromethyl radical generated in situ.[9] We found that the use of carbon tetrachloride as an additive meets the above requirements (Table 2).

Use of 3–4 equiv of carbon tetrachloride in the presence of the peroxy-λ^3-iodane **1** (1 equiv) and potassium carbonate (1 equiv) afforded excellent yields of 2-tetrahydrofuranylated alcohol **4** (Table 2, entries 4 and 5). A comparable yield (93%) of **4** was obtained with the use of a catalytic amount of **1** (0.3 equiv) (Table 2, entry 6). The presence of molecular dioxygen completely inhibits the reaction, and instead a large amounts of γ-butyrolactone was produced under oxygen (Table 2, entry 9). Use of radical scavenger galvinoxyl as an additive also inhibits the reaction (Table 2, entry 7). These results indicate radical nature of the reaction. Carbon tetrabromide is also useful for protection of the alcohol and afforded the ether **4** in 70% yield, but with formation of a large amount of by-product, 2-(4-bromobutoxy)tetrahydrofuran. In marked contrast, carbon tetraiodide gave a complex mixture of products.

As shown in Table 3, the tetrahydrofuranylation using a catalytic amount of the peroxy-λ^3-iodane **1** and excess carbon tetrachloride proceeds smoothly for a variety of primary and secondary alcohols, but not for tertiary alcohols and phenol. Thus, selective protection of a primary alcohol, 2-phenylethanol, was successfully car-

Table 2. Tetrahydrofuranylation of 2-phenylethanol with peroxy-λ^3-iodane **1** in the presence of CX_4[a]

Entry	**1** (equiv)	K_2CO_3 (equiv)	CX_4 (equiv)	Product [yield (%)][b]
				4
1	1	—	CCl_4 (1)	30
2	1	1	CCl_4 (1)	55
3	1	1	CCl_4 (2)	84
4	1	1	CCl_4 (3)	93
5	1	1	CCl_4 (4)	89
6	0.3	1	CCl_4 (4)	93
7	0.3	1	CCl_4 (4)[c]	0
8	0.1	1	CCl_4 (4)	30
9	1	1	CCl_4 (1)[d]	0[e]
10	1	1	CBr_4 (3)	70[f]
11	1	1	CI_4 (3)	1

[a] Unless otherwise noted, tetrahydrofuranylation of 2-phenylethanol [0.1 M] was carried at 50 °C for 10 h in THF under argon.

[b] GC yields.

[c] Galvinoxyl (0.3 equiv) was used.

[d] Under oxygen.

[e] γ-Butyrolactone (190%, based on the iodane **1**) was obtained and 2-phenylethanol (84%) was recovered unchanged.

[f] 2-(4-Bromobutoxy)tetrahydrofuran (109%, based on the iodane **1**) was obtained.

Table 3. Tetrahydrofuranylation of alcohols with peroxy-λ^3-iodane **1** in the presence of CCl_4[a]

Entry	Alcohol	THF ether [yield (%)][b]
1	n-$C_8H_{17}OH$	93
2	$EtOCH_2CH_2OH$	94
3	$BrCH_2CH_2OH$[c]	94
4	$NCCH_2CH_2OH$	87
5	$PhCH_2OH$	77
6	c-$C_6H_{11}OH$[d]	98
7	$PhCH_2CHMeOH$[c]	63[e]
8	2-Cyclohexenol	30[e,f]
9	$PhCH_2CMe_2OH$[d]	0
10	PhOH[d]	5[e]
11	$PhCH_2CH_2OH$[d,g]	43[h]

[a] Unless otherwise noted, tetrahydrofuranylation of an alcohol [0.1 M] was carried using peroxy-λ^3-iodane **1** (0.3 equiv), K_2 CO_3 (1 equiv), and CCl_4 (4 equiv) at 50 °C for 10 h in THF under argon.

[b] GC yields.

[c] K_2CO_3 (5 equiv) was used.

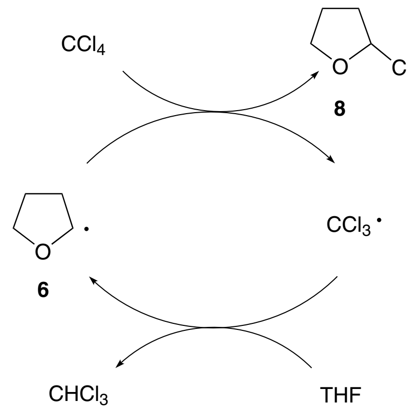
[d] Peroxy-λ^3-iodane **1** (1 equiv) was used.

[e] Isolated yields.

[f] Cyclohexenone (17%) was obtained.

[g] Instead of THF, tetrahydropyran was used.

[h] THP ether.



Scheme 1.

ried out in 87% yield in the presence of a tertiary alcohol, 1-phenyl-2-methyl-2-propanol (95% recovered). Ethoxy, bromo, and cyano groups are compatible with our conditions: however, competitive oxidation to a carbonyl compound was observed in the protection of an allylic alcohol (Table 3, entry 8). Instead of THF, use of tetrahydropyran resulted in a modest yield of tetrahydropyranyl ether (Table 3, entry 11).

The carbon tetrachloride-mediated protection of alcohols presumably involves the intervention of 2-chlorotetrahydrofuran **8** as a reactive intermediate, being generated by chlorine atom abstraction from CCl_4 with α-THF radical **6** (Scheme 1).[9] 2-Chlorotetrahydrofuran **8** undergoes a facile transfer of the tetrahydrofuranyl group to alcohols.[10] Trichloromethyl radical abstracts a hydrogen atom from THF to regenerate α-THF radical **6** with liberation of chloroform, which constitutes a radical chain reaction. Potassium carbonate traps the hydrogen chloride liberated during the transfer of the tetrahydrofuranyl group in **8** to alcohols. Hydrogen chloride probably promotes the decomposition of the peroxy-λ^3-iodane **1**[1b] as well as the products THF ethers (compare Table 2, entries 1 and 2). The observed large deuterium isotope effect ($k_H/k_D = 4.7$) in the protection of 1-octanol in THF-d_8 is compatible with the proposed mechanism.

2-Tetrahydrofuranyl ethers have been used as useful protecting groups for alcohols, because they are removed under weakly acidic conditions.[11] We have developed an efficient method for protecting hydroxy groups as 2-tetrahydrofuranyl ethers using the *tert*-butylperoxy-λ^3-iodane **1** in THF in the presence of carbon tetrachloride.

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