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Radical Oxidation of Amides and Related Compounds with Hypervalent *tert*-Butylperoxyiodanes: Synthesis of Imides and *tert*-Butylperoxyamide Acetals

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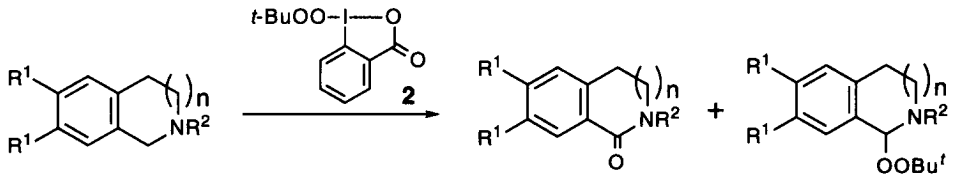
Abstract

tert-Butylperoxyiodane undergoes oxidation of the methylene groups α to the nitrogen atom of amides (or carbamates) yielding imides or *tert*-butylperoxyamide acetals, depending on the reaction conditions. A proposed mechanism involves generation of carbon-centered radicals α to the nitrogen atom.

Keywords: hypervalent elements; oxidation; amide; carbamates

In contrast to the methods available for oxidation of amines, the procedures for amide oxidation are very limited because of their inertness toward electrophilic oxidants [1]. Amides containing methylene groups adjacent to the nitrogen atoms are oxidized to imides by ruthenium tetroxide, which is usually generated *in situ* from ruthenium dioxide and sodium periodate [2]. Another method for the oxidation of amides involves the combination of a hydroperoxide or a peroxy acid and a catalytic amount of Mn(II) [3], Fe(II) [4], or Ru(II) [5]. Electrochemical anodic oxidation of amides and carbamates is a useful alternative [6]. We report herein the oxidation of amides and carbamates with 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one (**2**), which was synthesized *via* the Lewis acid-catalyzed ligand exchange of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one with *tert*-butyl hydroperoxide [7].



1 **3** **4**

a; n = 1, R^1 = H, R^2 = Ac, **b**; n = 1, R^1 = MeO, R^2 = Ac, **c**, n = 1, R^1 = H, R^2 = Boc
d; n = 1, R^1 = MeO, R^2 = Boc, **e**; n = 1, R^1 = H, R^2 = Ts, **f**; n = 1, R^1 = MeO, R^2 = Ts
g; n = 0, R^1 = H, R^2 = Ts, **h**; n = 0, R^1 = H, R^2 = Ac

Scheme 1

0040-4039/99/$ - see front matter
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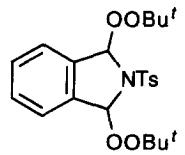
Oxidation of *N*-acetyl-1,2,3,4-tetrahydroisoquinolines **1a,b** with the *tert*-butylperoxyiodane **2** in the presence of K_2CO_3 in benzene at room temperature under dinitrogen rubber balloon takes place at the benzylic methylene group α to the nitrogen atom to give the imides **3a,b** as a major product, along with formation of a considerable amount of the *tert*-butylperoxyamide acetals **4a,b** [5,8] (Table 1, Entries 1 and 2). Without a base, the reaction becomes sluggish. These product profiles are highly sensitive to the presence of molecular dioxygen: when the reaction was carried out under dioxygen rubber balloon, the reaction went to completion within 3 h, and the only product detected was found to be the imides **3a,b** in more than 80% yields (Entries 5 and 6). Since atmospheric dioxygen gradually penetrates into a rubber balloon, these results clearly show that the presence of dioxygen is required for facile oxidation of **1a,b** to the imide by the peroxyiodane **2**. Similar effects of molecular dioxygen were observed in the oxidation of the carbamates **1c,d**. Under dioxygen, sulfonamides **1f,g** and *N*-acylated acyclic amines **5b,c** afforded the corresponding lactams **3f,g** and imides **6b,c** [2f]. Very interestingly, in the presence of a 10-fold excess of **1a** relative to **2**, the prolonged reactions (3 day) under dioxygen balloons afforded more than stoichiometric amounts of the imide **3a** (*ca.* 800%) and the lactam (*ca.* 150%), 1,2,3,4-tetrahydroisoquinolin-1-one, probably produced by the hydrolysis of the imide **3a**.

However, when the oxidation of **1a** was carried out in a degassed argon sealed tube (in the absence of dioxygen), the yield of the imide **3a** decreased substantially, and a large amount of the *tert*-butylperoxyamide acetal **4a** (63-74%) was produced (Entries 15-17). Use of dichloromethane as a solvent gave a higher yield of the acetal than that in benzene. All of the amide **1b**, the carbamates **1c,d**, and the sulfonamides **1e,f** produced the *tert*-butylperoxy acetals **4** in more than 98% selectivity under argon. In the oxidation of the sulfonamide **1g** with **2** (2.5 equiv.), 1,3-bis(*tert*-butylperoxy)amide **7** was obtained in 68% yield.



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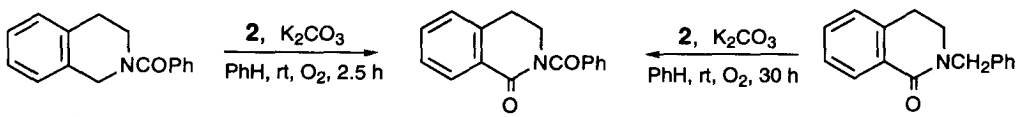
Oxidation of the endocyclic methylene groups α to nitrogen will be faster than that of exocyclic ones (Scheme 2); thus, the amide **8** afforded, after 2.5 h at room temperature under molecular dioxygen, the imide **9** in 73% yield, while prolonged treatment (30 h) of the lactam **10** recovered a large amount of the lactam and gave the imide **9** in 7% yield. The difference in reactivity of these benzylic methylene groups will be attributable to a difference in conformational freedom; the endocyclic methylene groups with limited conformational freedom are oxidized more easily than the exocyclic methylene groups [2c,d].



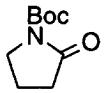
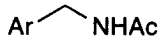
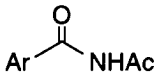
8 **9** **10**

Scheme 2

Effective inhibition of the oxidation of **1a,d** under argon was observed on addition of galvinoxyl (Entries 18 and 23), which is an efficient radical scavenger for both oxygen- and carbon-centered radicals [9,10]. These results probably suggest the involvement of a radical species in the oxidation.

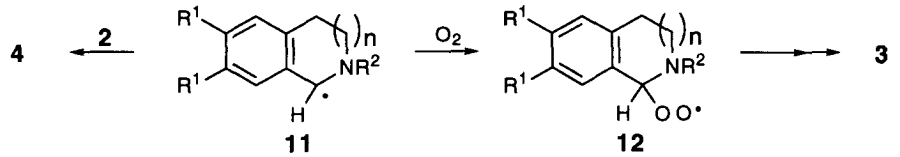
Table 1

Oxidation of Amides **1** with Hypervalent *tert*-Butylperoxyiodane **2**

Entry	Substrate	**2** (equiv)	Additive (equiv)	Solvent	Conditions[a] Temp(℃),Time(h)	Yield[b]/% **3** or **6**	**4**
1	**1a**	1.1	K_2CO_3 (10)	PhH	25, 24, N_2	**3a** (55)	**4a** (19)
2	**1b**	1.1	K_2CO_3 (10)	PhH	25, 8, N_2	**3b** (45)	**4b** (21)
3	**1c**	1.1	K_2CO_3 (10)	PhH	25, 8, N_2	**3c** (53)	**4c** (15)
4	**1d**	1.1	K_2CO_3 (10)	PhH	25, 7, N_2	**3d** (57)	**4d** (28)
5	**1a**	1.2	K_2CO_3 (10)	PhH	25, 3, O_2	**3a** (82)	
6	**1b**	1.2	K_2CO_3 (10)	PhH	25, 2.5, O_2	**3b** (87)	
7	**1c**	1.2	K_2CO_3 (10)	PhH	25, 4, O_2	**3c** (66)	
8	**1d**	1.2	K_2CO_3 (10)	PhH	25, 7, O_2	**3d** (63)	**4d** (6)
9	**1f**	1.2	K_2CO_3 (10)	PhH	25, 27, O_2	**3f** (59)	**4f** (3)
10	**1g**	1.2	K_2CO_3 (10)	PhH	25, 27, O_2	**3g** (78)	
11	**1h**	1.2	K_2CO_3 (10)	PhH	25, 5, O_2	**3h** (76)	
							
12	**5a**	2.0	K_2CO_3 (10)	PhH	25, 40, O_2	**6a** (74)	
							
13	Ar = C_6H_5 **5b**	2.0	K_2CO_3 (10)	PhH	25, 26, O_2	**6b** (52)	
14	Ar = *p*-$MeOC_6H_4$ **5c**	2.0	K_2CO_3 (10)	PhH	25, 48, O_2	**6c** (65)	
15	**1a**	1.0		CH_2Cl_2	25, 73, Ar	**3a** (5)	**4a** (63)
16	**1a**	2.0		CH_2Cl_2	25, 70, Ar	**3a** (6)	**4a** (74)
17	**1a**	2.0	K_2CO_3 (2)	CH_2Cl_2	25, 72, Ar	**3a** (20)	**4a** (73)
18	**1a**	2.0	galvinoxyl (2)	CH_2Cl_2	25, 72, Ar		**4a** (15)[c]
19	**1a**	2.0	TEMPO (2)	CH_2Cl_2	25, 72, Ar		**4a** (90)
20	**1b**	2.0		CH_2Cl_2	25, 23, Ar		**4b** (68)
21	**1c**	2.0		CH_2Cl_2	25, 48, Ar	**3c** (2)	**4c** (79)
22	**1d**	2.0		CH_2Cl_2	25, 48, Ar		**4d** (91)
23	**1d**	2.0	galvinoxyl (2)	CH_2Cl_2	25, 48, Ar		**4d** (18)[d]
24	**1d**	2.0	TEMPO (2)	CH_2Cl_2	25, 48, Ar		**4d** (100)
25	**1e**	2.5		PhH	45, 24, Ar		**4d** (75)
26	**1f**	2.0		CH_2Cl_2	25, 48, Ar		**4f** (65)
27	**1g**	2.5		PhH	25, 96, Ar		**4g** (0)[e]

a) N_2: under dinitrogen rubber balloon. O_2: under dioxygen rubber balloon. Ar: in a degassed argon sealed tube. b) Isolated yields. c) **1a** (75%) was recovered unchanged. d) **1d** (72%) was recovered unchanged. e) 1,3-Bis(*tert*-butylperoxy)amide **7** was obtained in 68% yield.

The peroxyiodane **2** decomposes at room temperature *via* homolytic bond cleavage of the weak iodine(III)-peroxy bond generating the [9-I-2] iodanyl radical and *tert*-butylperoxy radical [7c]. These radicals would be responsible for the oxidation of amides **1**, and generate benzylic carbon-centered radicals **11** stabilized with the α nitrogen atom (Scheme 3). Nucleophilic attack of the benzylic radicals **11** to the iodine(III)-peroxy bond of **2** gives the *tert*-butylperoxyamide acetal **4** with concomitant regeneration of the [9-I-2] iodanyl radical. In the presence of molecular dioxygen, the alternative coupling between the α benzylic radicals **11** with dioxygen would compete and generate the peroxy radical **12** [11], which, in turn, decomposes to the imide **3** [1b]. Since a large amount of the imide **3a** (*ca.* 800%) was formed in the presence of dioxygen, it seems reasonable to assume that hydrogen abstraction of the amides **1** by this peroxy radical **12** generating the α benzylic radical **11** and a hydroperoxide, which was observed in autoxidation, plays an important role in this oxidation. The *tert*-butylperoxyamide acetal **4** does not seem to be an intermediate for the oxidation of the amide **1** to the imide **3** with **2**, because the acetal **4a** was recovered unchanged on treatment with **2** (1.2 equiv.) under dioxygen (K_2CO_3/PhH/25 °C/3 h).



Scheme 3

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