Aerobic Photooxidation of Benzylamide in the Presence of Catalytic Iodine

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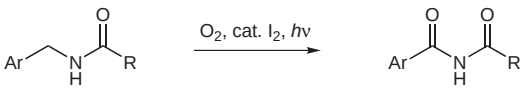
Received 16 December 2007

Abstract: Benzylamides were found to be oxidized to the corresponding imides in the presence of molecular oxygen and catalytic iodine under photoirradiation.

Key words: aerobic, amide, imide, iodine, photooxidations

Oxidation is the foundation of synthetic chemistry, and has been the subject of study by many researchers.[1] Especially, molecular oxygen has recently received much attention in the field of synthetic organic chemistry, since it is photosynthesized by plants and is an effective oxidant of larger atom efficiency than that of other oxidants.[2] With this background in mind, we have studied the oxidation with molecular oxygen, and recently reported aerobic photooxidation of benzyl and allylic alcohols to the corresponding aldehydes in the presence of catalytic amount of iodine.[3] In the course of our further study of this reaction, we also found that benzylamides were oxidized to the corresponding imides successfully under the similar conditions (Scheme 1). Imides have not only been used as the starting materials for preparation of N-containing heterocycles,[4] but also have been focused on from the viewpoint of biological activity.[5] In general the preparation of imides involves acylation of amides with anhydrides,[6] acyl chlorides,[5,7] or ketene,[8] and, with α,α,α-trichloromethyl carbonyl compounds[9] and enol esters;[10] however, these methods involve some problems, such as low yield or high environmental impact of the solvents used or waste produced. On the other hand, our method is interesting in keeping with the notion of Green chemistry due to nonuse of heavy metals, waste reduction, use of molecular oxygen, inexpensive acquisition of reagents, and environmentally low-impact solvent. In this Letter, we report our study of scope and limitations of this aerobic photooxidation of benzylamides to the corresponding imides in the presence of catalytic iodine.

Table 1 shows the results of aerobic oxidation of *N*-benzylacetamide (**1**) under external irradiation of 500 W Xenon lamp.[11] Among the solvents and iodo sources examined, ethyl acetate and iodine were found to afford



Scheme 1

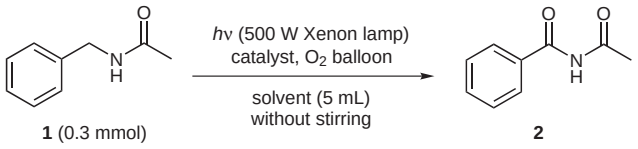
SYNLETT 2008, No. 5, pp 0675–0678
Advanced online publication: 26.02.2008
DOI: 10.1055/s-2008-1032097; Art ID: U12507ST

N-acetylbenzamide (**2**) most efficiently (entries 1−6 and 17−23). Since, surprisingly, the yield of **2** when conducting without stirring was almost as same as that under stirring condition, the following reactions were exclusively conducted without stirring (entries 6 and 7). Product **2** was obtained in moderate yield when using 400 W Hg lamp or fluorescent lamp (entries 8 and 9). The yield of **2** was slightly increased and benzoic acid was also obtained in low yield as byproduct when the reaction time was extended up to 48 hours (entry 11). Although 1 mol% of iodine was required to give **2** in good yield, an excess amount of iodine inhibited this oxidation (entries 6, 12, and 13). The fact that **2** was not obtained or was obtained only in low yield without either the addition of iodine or irradiation or molecular oxygen shows the necessity of all conditions for this reaction (entries 14−16). On the other hand, benzoic acid was obtained as a main product when using bromine instead of iodine (entry 24). The reason is not yet clear; however, we believe the ability of hydrogen abstraction by a bromo radical is stronger than that by a iodo radical.

Table 2 shows the results for oxidation of a variety of benzylamides under the reaction conditions mentioned above. *N*-Benzylacetamide (**1**), *N*-(4-methoxybenzyl)acetamide (**3**), and *N*-(4-methylbenzyl)acetamide (**5**), which possess an electron-donating group at aromatic nucleus, afforded the corresponding imides (**2**, **4**, **6**) in good yield (entries 1−3). On the other hand, *N*-(4-chlorobenzyl)acetamide (**7**) was less reactive than **1** (entry 4). *N*-(2-Methylbenzyl)acetamide (**9**) gave *N*-acetyl-2-methylbenzamide (**10**) only in moderate yield due to the steric hindrance of methyl group at *ortho* position (entry 5). Regarding the amide group, an electron-donating group accelerated and an electron-withdrawing group retarded this oxidation. (entries 6−8). Unfortunately, *N*-(1-naphthyl)acetamide (**17**) gave the corresponding product **18** only in 36% yield, and *N*-dodecylacetamide (**19**), an aliphatic amide, was intact under these conditions (entries 9 and 10).

Scheme 2 shows a plausible path of this oxidation, which is postulated by considering the necessity of continuous irradiation, a catalytic amount of iodine and molecular oxygen in this reaction. Amide initially reacts with iodo radical, generated by irradiation with 500 W Xenon lamp, to give benzyl radical species **20**. The resulting radical species **20** traps molecular oxygen to afford peroxyradical **21**, which is subsequently transformed to hydroperoxide **22** by abstraction of hydrogen atom from hydrogen iodide or solvent. Imide is formed from **22** through aza-hemiacetal species **23** and hypoiodide **24**. Iodine is regenerated by

Table 1 Study of Reaction Conditions for Aerobic Photooxidation of Amide



1 (0.3 mmol) **2**

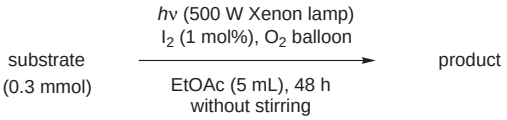
Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[a]
1	I_2 (1.0)	Acetone	36	48
2	I_2 (1.0)	MeCN	36	51
3	I_2 (1.0)	Hexane	36	18
4	I_2 (1.0)	MeOH	36	0
5	I_2 (1.0)	CH_2Cl_2	36	0
6	I_2 (1.0)	EtOAc	36	67
7	I_2 (1.0)	EtOAc	36	66[b]
8	I_2 (1.0)	EtOAc	36	43[c]
9	I_2 (1.0)	EtOAc	36	33[d]
10	I_2 (1.0)	EtOAc	24	58
11	I_2 (0.5)	EtOAc	48	71
12	I_2 (5.0)	EtOAc	36	56
13	I_2 (–)	EtOAc	36	63
14	I_2 (1.0)	EtOAc	48	0
15	I_2 (1.0)	EtOAc	48	0[e]
16	I_2 (1.0)	EtOAc	48	Trace[f]
17	CI_4 (1.0)	EtOAc	36	60
18	NIS (1.0)	EtOAc	36	55
19	LiI (1.0)	EtOAc	36	40
20	NaI (1.0)	EtOAc	36	42
21	KI (1.0)	EtOAc	36	12
22	CsI (1.0)	EtOAc	36	23
23	CaI_2 (1.0)	EtOAc	36	62
24	Br_2 (1.0)	EtOAc	36	26[g]

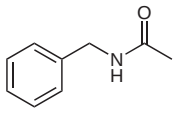
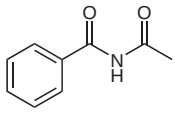
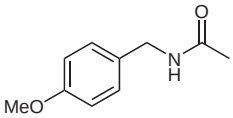
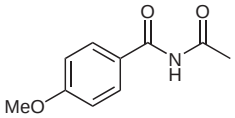
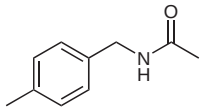
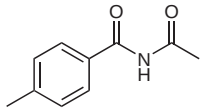
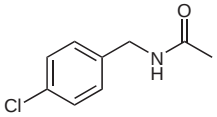
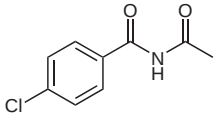
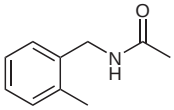
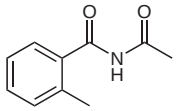
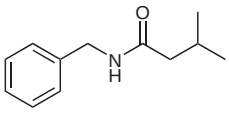
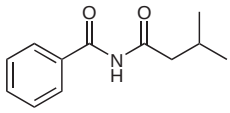
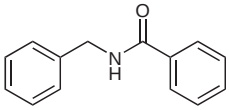
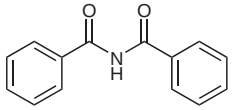
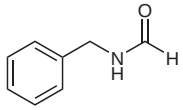
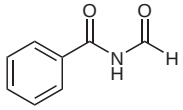
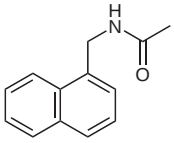
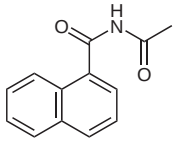
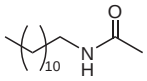
[a] All yields were for pure, isolated products.
[b] The reaction was carried out under stirring conditions.
[c] The reaction was carried out under irradiation of 400 W Hg lamp.
[d] The reaction was carried out under irradiation of fluorescent lamp.
[e] The reaction was carried out in the dark.
[f] The reaction was carried out under Ar.
[g] Benzoic acid was obtained as main product.

aerobic photooxidation of hydrogen iodide or by reaction of hypoiodous acid with hydrogen iodide.[12]

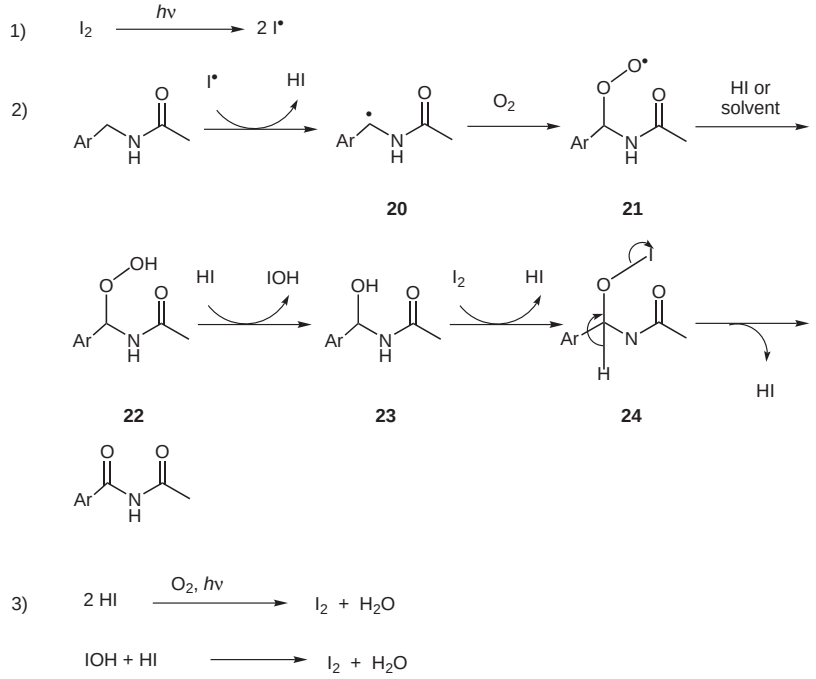
In conclusion, we have developed a novel and practical method for preparation of imides by aerobic photooxidation of amides in the presence of the catalytic amount of

Table 2 Aerobic Photooxidation of Benzylamides



Entry	Substrate	Product	Yield (%)[a]
1	 **1**	 **2**	71
2	 **3**	 **4**	70
3	 **5**	 **6**	70
4	 **7**	 **8**	61
5	 **9**	 **10**	51
6	 **11**	 **12**	68
7	 **13**	 **14**	55
8	 **15**	 **16**	42
9	 **17**	 **18**	36
10	 **19**	–	0

[a] All yields were for pure, isolated products.



Scheme 2 Plausible path of the aerobic photooxidation of amide

iodine. This oxidation is a facile and convenient method in the viewpoint of synthetic organic chemistry. Further studies directed toward the elucidation of scope, mechanism, and additional applications are progress in our laboratory.

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(11) A typical procedure follows: A dry EtOAc solution (5 mL) of the *N*-benzylacetamide (**1**, 0.3 mmol) and I_2 (0.003 mmol) in a pyrex test tube equipped with an O_2 balloon, was irradiated without stirring condition for 48 h with a 500 W Xenon lamp, which was set from the test tube in the distance of 45 cm. The reaction mixture was concentrated under reduced pressure, and the pure product was obtained by preparative TLC.

***N*-Acetyl-4-methoxybenzamide (4)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (s, 1 H), 7.85 (d, *J* = 9.0 Hz, 2 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 3.83 (s, 3 H), 2.56 (s, 3 H). IR (KBr): 3233, 1712, 1689, 1607, 1472, 1251, 854 cm^{-1}. HRMS (EI$^+$): *m/z* calcd for $C_{10}H_{11}NO_3$ [M$^+$]: 193.07390; found: 193.07484.

***N*-Acetyl-4-methylbenzamide (6)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 2.60 (s, 3 H), 2.42 (s, 3 H). IR (KBr): 3263, 1725, 1611, 1506, 1231 cm^{-1}. HRMS (EI$^+$): *m/z* calcd for $C_{10}H_{11}NO_2$ [M$^+$]: 177.07898; found: 177.07970.

***N*-Acetyl-4-chlorobenzamide (8)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (s, 1 H), 7.88 (d, *J* = 8.8 Hz, 2 H), 7.48 (d, *J* = 8.8 Hz, 2 H), 2.61 (s, 3 H). IR (KBr): 3263, 1710, 1689, 1592, 1468, 750 cm^{-1}. HRMS (EI$^+$): *m/z* calcd for $C_{10}H_{11}NO_3$ [M$^+$]: 197.02435; found: 197.02382.

***N*-(2-Methybenzyl)acetamide (9)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23−7.19 (m, 4 H), 5.56 (s, 1 H), 4.43 (d, *J* = 5.3 Hz, 2 H), 2.32 (s, 3 H), 2.01 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.7, 136.5, 135.8, 130.6, 128.7, 127.8, 126.2, 41.9, 23.1, 19.0. IR (KBr): 3293, 1637, 1547, 742 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.53; H, 8.14; N, 8.63.

***N*-Acetyl-2-methylbenzamide (10)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 7.41 (d, *J* = 5.3 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.24−7.22 (m, 2 H), 2.52 (s, 3 H), 2.44 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.9, 167.9, 137.4, 133.9, 131.7, 131.5, 126.9, 126.0, 23.4, 20.0. IR (KBr): 3248, 1727, 1506, 1221, 738 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.63; H, 6.26; N,7.90. Found: C, 67.63; H, 6.27; N, 7.75.

***N*-(1-Naphthylmethyl)acetamide (17)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.7 Hz, 1 H), 7.86 (d, *J* = 7.4 Hz, 1 H), 7.79 (t, *J* = 4.8 Hz, 1 H), 7.55−7.48 (m, 2 H), 7.40 (d, *J* = 4.8 Hz, 2 H), 5.87 (s, 1 H), 4.83 (d, *J* = 5.3 Hz, 2 H), 1.96 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.7, 133.8, 133.5, 131.4, 128.7, 128.6, 126.7, 126.6,

126.0, 125.3, 123.5, 41.8, 23.1. IR (KBr): 3301, 1638, 1553, 1290, 780, 606 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.47; H, 6.71; N, 6.96.

***N*-Acetyl-1-naphthalenecarboxamide (18)**

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 8.32 (d, *J* = 8.3 Hz, 1 H), 7.99 (d, *J* = 8.3 Hz, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 7.1 Hz, 1 H), 7.61–7.54 (m, 2 H), 7.48 (t, *J* = 7.3 Hz, 1 H), 2.64 (s, 3 H). IR (KBr): 3263, 1715, 1686, 1487, 1244, 779 cm^{-1}. HRMS (EI^+): *m*/*z* calcd for $C_{15}H_{13}NO_3$ [M^+]: 213.07898; found: 213.07983.

(12) In the presence of 1 equiv of galvinoxyl, no oxidation proceeded when **1** was used as starting material.