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A novel synthesis of α-hydroxy- and α,α′-dihydroxyketone from α-iodo and α,α′-diiodo ketone using photoirradiation

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Abstract—A novel reaction of α-iodo ketone (α-iodocycloalkanone, α-iodo-β-alkoxy ester, and α-iodoacyclicketone) with irradiation under a high-pressure mercury lamp gave the corresponding α-hydroxyketone in good yields. In the case of α,α′-diiodo ketone, α,α′-dihydroxyketone which little has been reported until now was obtained. This reaction affords a new, clean and convenient synthetic method for α-hydroxy- and α,α′-dihydroxyketone.

α-Hydroxyketones are usually prepared by one of the following methods: α-hydroxylation by treatment of their enolate forms with a molybdenum peroxide reagent in THF–hexane at −70°C,[1] transformation of the enamine derivatives of ketones to α-hydroxy derivatives by molecular oxygen,[2] and α-hydroxylation of silyl enol ethers with *m*-chloroperbenzoic acid,[3] or with certain other oxidizing agents.[4]

It is known that there has been considerable interest in the development of direct methods for the synthesis of α-hydroxyketones using nontoxic hypervalent iodine reagents, which involve the following methods: reaction of ketone with iodobenzene diacetate in the presence of potassium hydroxide in methanol and then hydrolysis of the dimethylacetals;[5] oxidation of enol silyl ether of acetophenone using the system iodosobenzene/boron trifluoride etherate/water in methylene chloride at −40°C;[6] and reaction of ketones with [bis(trifluoroacetoxy)] iodobenzene and trifluoroacetic acid in acetonitrile–water under acidic conditions.[7]

During the course of our studies, we investigated a novel self-coupling reaction of cyclic ketones with a high-pressure mercury lamp to give the corresponding pinacol-type compound in good yields.[8] α-Iodocycloalkanones are important as intermediates in organic synthesis, which were synthesized by our laboratory by a new method.[9] These iodo ketones are unstable and sensitive to light. We thus tried to obtain useful products from these iodo compounds. In this series, we have already shown that the photo-dehydroiodination from α-iodocycloalkanones in hexane affords α,β-unsaturated ketones as major products, accompanied by photoreduced products as by-products. In the hexane containing a small amount of water, the substituted product 2-hydroxycycloalkanone was also obtained.[10] In our previous paper, we found that photo-cleavage of the carbon–carbon bond of α-iodocycloalkanones giving ω,ω-dialkoxyalkanoic esters in alcohol gives α-hydroxyketone as intermediates.[11] In order to increase the yield of α-hydroxyketone, we undertook a closer inquiry into the reaction conditions. Herein, we report that the irradiation of α-iodoalkanones **1**–**12**, **22**–**25** in solvents containing a small amount of air gave the α-hydroxyketones **1d**–**12d**, **22d**–**25d** under a high-pressure mercury lamp. The reaction of α-iodo- and α,α′-diiodo ketone using photoirradiation in alcohols, hexane, and acetone, etc., in the presence of air afforded the corresponding α-hydroxy- and α,α′-dihydroxyketone in good yield (Scheme 1).

The irradiation of α-iodo ketones (**1**–**12**) in a solvent at room temperature under air atmosphere with a 400 W mercury lamp for 10–12 h gave the corresponding α-hydroxyketone (**1d**–**12d**) in good yields. These results are summarized in Table 1.

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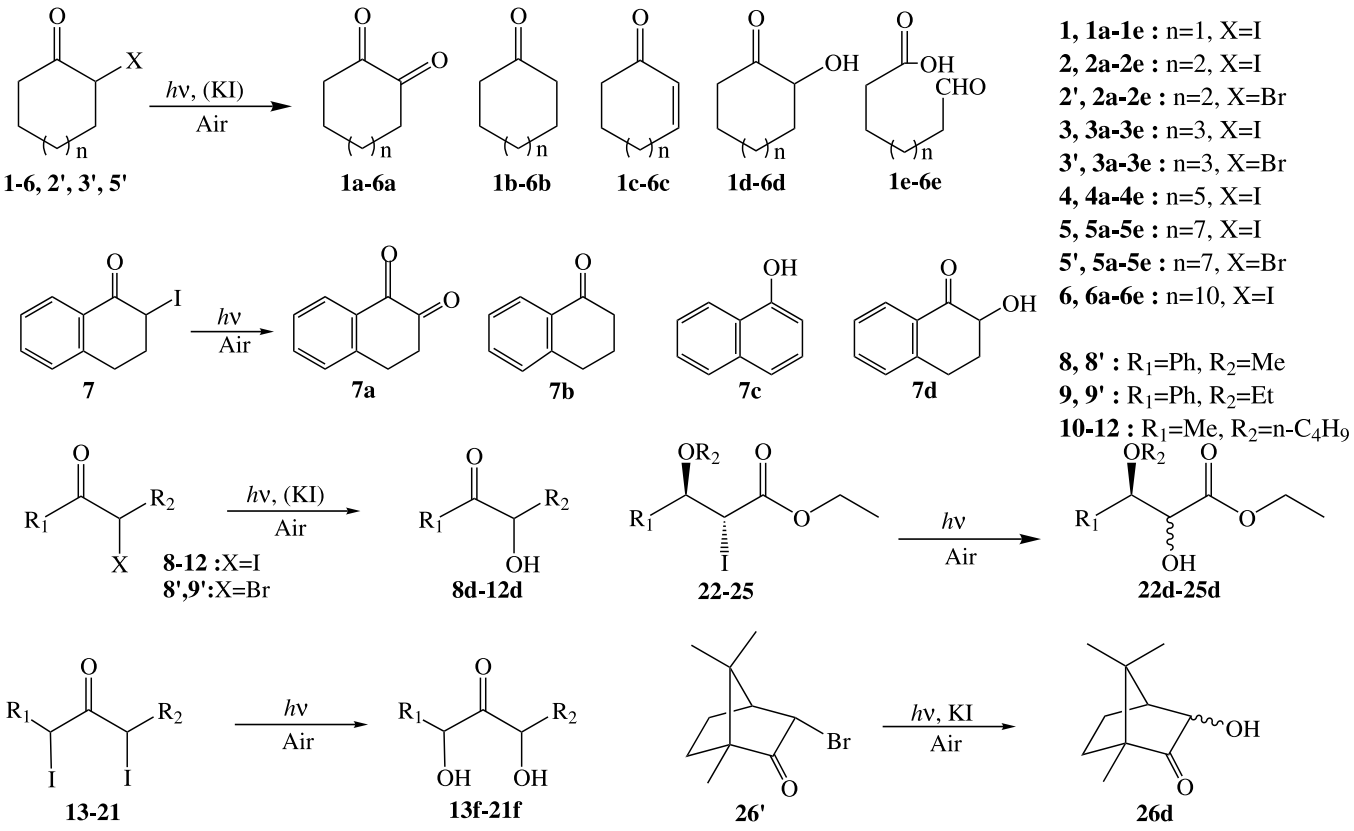


Scheme 1.

Table 1. Photochemical reaction of α-iodo ketone in the presence of air

Run	Substrate	*n*	Solvent	Base (mol. equiv.)	Time (h)	Product (%)[a]					
						a	**b**	**c**	**d**	**e**	
1	**1**	1	Me_2CO	Et_3N (1)	10	10	4	t	49	0	
2	**2**	2	Me_2CO	Et_3N (1)	10	41	t	t	56	0	
3	**2'**[b]	2	MeOH	Et_3N (1)	12	t	4	t	42	0	
4	**3**	3	Me_2CO	Et_3N (1)	10	35	t	t	60	0	
5	**3'**[b]	3	MeOH	Et_3N (1)	12	t	3	t	35	0	
6	**4**	5	Me_2CO	Et_3N (1)	10	24	t	t	70	0	
7	**5**	7	Me_2CO	Et_3N (1)	10	t	t	t	95	0	
8	**5'**[b]	7	MeOH	Et_3N (1)	12	t	3	7	47	0	
9	**6**	10	Me_2CO	Et_3N (1)	10	t	t	t	95	0	
10	**7**		Me_2CO	Et_3N (1)	12	t	5	15	70	0	
11	**8**		Me_2CO	Et_3N (2)	10	t	t	t	81	0	
12	**8'**[b]		Me_2CO	Et_3N (2)	12	t	t	t	30	0	
13	**9**		Me_2CO	Et_3N (2)	10	t	t	t	87	0	
14	**9'**[b]		Me_2CO	Et_3N (2)	12	t	t	t	31	0	
15	**10**		Me_2CO	Et_3N (2)	10	t	t	t	89[c]	0	
16	**11**		Me_2CO	Et_3N (2)	10	t	t	t	92[c]	0	
17	**12**		Me_2CO	Et_3N (2)	10	t	t	t	94[c]	0	
18	**26'**		MeOH	Et_3N (1)	48	t	t	t	85	0	(*exo*:*endo* = 40:60)[c]
19	**26'**		MeOH	Et_3N (2)	12	t	t	t	62	0	(*exo*:*endo* = 40:60)[c]
20	**26'**		EtOH	Et_3N (2)	24	t	t	t	52	0	(*exo*:*endo* = 33:67)[c]
21	**26'**		Me_2CO	Et_3N (2)	72	t	t	t	86	0	(*exo*:*endo* = 43:57)[c]
22	**26'**		MeCN	Et_3N (2)	68	t	t	t	85	0	(*exo*:*endo* = 43:57)[c]

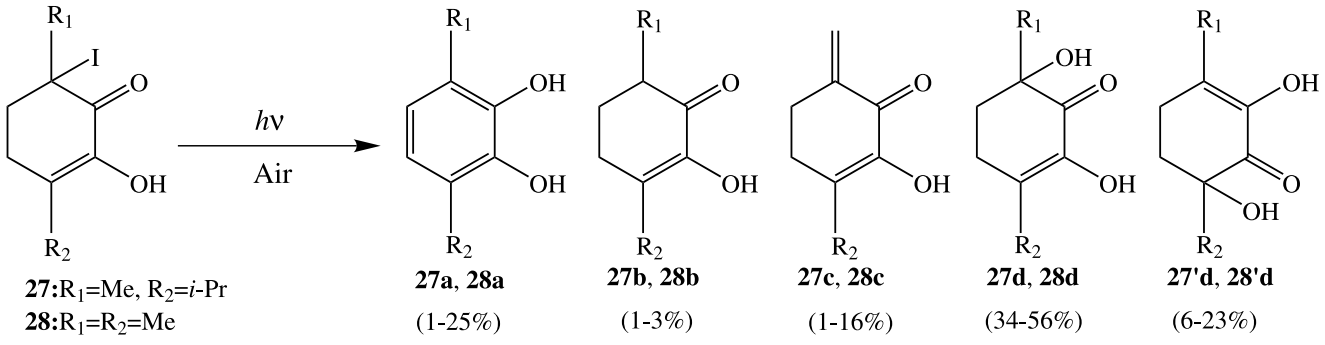
Reaction conditions: Substrate (0.1 mmol) in solvent (10 ml) was irradiated by a high pressure mercury lamp (400W) under air.
[a] Yields were determined by GLC.
[b] KI (0.1 mmol) was used.
[c] Product ratio was determined from the peak area ratio of the NMR spectrum. t = trace.

As can be seen from Table 1, it was found that the reaction containing triethylamine (molar equivalent) gives preferentially the α-hydroxyketone. Thus, in order to discuss the reactivity of the α-iodocyclicketone, it was compared with that of the bromo derivatives. The reaction of α-bromo ketone did not give α-hydroxyketone. So, the following experiment was attempted. The reaction of α-bromo ketone with KI gave the corresponding α-hydroxyketone (runs 3, 5, 8, 12, and 14). On the basis of these results, it was found that in the case of the bromo ketone with KI, the yields of α-hydroxy ketone are lower. However, in the case of nonoccurrence of α-iodination, i.e., α-iodocamphor, this reaction can not be applied to the synthesis of α-hydroxycamphor. In order to overcome this problem, we tried the reaction of α-bromocamphor (**26′**) with KI. As can be seen from Table 1 (runs 18–22), it was found that α-hydroxycamphor was obtained in good yields. We further developed the reaction conditions to decrease the reduced ketone and ω-formyl alkanoic acid. These results are summarized in Table 2. As can be seen from Table 2, it was found that amines of *i*-Pr_2NH, Et_3N, and *n*-Pr_3N are effective. Moreover, in the case of absence of triethylamine, α-hydroxyketone was not obtained, and ω-formylcarboxylic acid was formed.

Table 2. Effects of some amines for photochemical reaction of α-iodo ketone

Run	Substrate	*n*	Base (mol. equiv.)	Time (h)	Product (%)[a]				
					a	**b**	**c**	**d**	**e**
1	**5**	7	*i*-Pr_2NH (1)	10	t	4	t	95	0
2	**5**	7	Et_3N (1)	10	t	t	t	95	0
3	**5**	7	*n*-Pr_3N (1)	10	t	2	t	95	0
4	**5**	7	Et_2NH (1)	43	t	4	t	90	0
5	**5**	7	$PhNMe_2$ (1)	50	10	4	t	85	0
6	**5**	7	C_5H_5N (1)	10	16	13	t	17	45
7	**5**	7	C_5H_5N (10)	10	16	10	t	24	43
8	**5**	7	C_5H_5N (50)	15	11	11	t	43	30
9	**5**	7	C_4H_5NH (1)	40	9	6	t	30	46
10	**5**	7	C_4H_5NH (10)	40	7	22	t	37	0
11	**5**	7	*t*-BuOK (1)	10	t	58	t	33	0
12	**5**	7	NaOH (1)	20	t	93	t	2	0
13	**5**	7	NH_3 (1)	20	4	5	t	90	0
14	**5**	7	Et_3N (1)	10	t	t	t	95	0
15	**5**	7	Et_3N (1)	15	3	t	2	68	0
16	**5**	7	Et_3N (1)	15	9	t	7	63	0
17	**5**	7	Et_3N (1)	25	t	t	t	83	0
18	**5**	7	Et_3N (1)	62	2	t	t	87	0
19	**5**	7	Et_3N (1)	17	t	t	t	90	0
20	**5**	7	Et_3N (1)	17	t	7	t	77	0
21	**5**	7	Et_3N (1)	18	12	t	t	77	0
22	**5′**	7	Et_3N (1)	12	t	3	7	47	0
23	**5**	7	0	10	3	50	t	5	42
24	**5**	7	0	10	8	t	6	5	41
25	**5**	7	0	10	4	3	15	9	45
26	**5**	7	0	10	5	2	9	2	52
27	**5**	7	0	10	4	t	8	13	53
28	**5**	7	0	10	5	t	2	8	28
29	**5**	7	0	10	17	t	3	3	59
30	**5**	7	0	10	13	t	2	12	70

Reaction conditions: Substrate (0.1 mmol) in acetone (10 ml) was irradiated by a high pressure mercury lamp (400 W) under air.
[a] Yields were determined by GLC. t = trace.



Scheme 2.

Thus, this reaction affords hydroxydiosphenol[12,13] in buchu oil from the leaves of *Barosma betulina* Bartl. (mountain buchu) (Scheme 2).

Moreover, it is interesting that in the case of α,α′-diiodo ketones, α,α′-dihydroxyketones were obtained in good yields. The reaction of α,α′-diiodo ketones (**13**–**21**) and α-iodo-β-alkoxy esters (**22**–**25**) in acetone gave the corresponding α,α′-dihydroxyketones (**13f**–**21f**) and α-hydroxy-β-alkoxy esters (**22d**–**25d**) in good yield. These results are summarized in Table 3.

From these results, it is considered that the reaction proceeds by two pathways (Fig. 1); in the absence of

Table 3. Photochemical reaction of α-iodo-β-alkoxy ester and α,α′-diiodo ketone

Run	Substrate	R_1	R_2	Time (h)	Product (%)
1	**13** (*cis*/*trans* = 95/5)	Me	Me	5	**13f** (47, *cis*/*trans* = 50/50)[a,b]
2	**14** (*cis*/*trans* = 90/10)	Et	Et	6	**14f** (58, *cis*/*trans* = 50/50)[a,b]
3	**15** (*cis*/*trans* = 75/25)	n-C_3H_7	n-C_3H_7	6	**15f** (65, *cis*/*trans* = 50/50)[a,b]
4	**16** (*cis*/*trans* = 62/38)	n-C_4H_9	n-C_4H_9	6	**16f** (73, *cis*/*trans* = 50/50)[a,b]
5	**17** (*cis*/*trans* = 54/46)	Me	n-C_7H_{15}	5	**17f** (70, *cis*/*trans* = 50/50)[a,b]
6	**18**	H_2	n-C_3H_7	3	**18f** (t)
7	**19**	H_2	n-C_4H_9	3	**19f** (t)
8	**20**	CH_2-$(CH_2)_2$-CH_2		5	**20f** (82, *cis*/*trans* = 87/13)[a,b]
9	**21**	CH_2-$(CH_2)_7$-CH_2		5	**21f** (54, *cis*/*trans* = 90/10)[a,b]
10	**22**	Me	Me	10	**22d** (65, *syn*/*anti* = 81/19)[a,b]
11	**23**	Me	Et	10	**23d** (62, *syn*/*anti* = 80/20)[a,b]
12	**24**	Ph	Me	8	**24d** (72, *syn*/*anti* = 84/16)[a,b]
13	**25**	Ph	Et	8	**25d** (75, *syn*/*anti* = 81/10)[a,b]

Reaction conditions: Substrate (0.1 mmol) in solvent (10 ml) was irradiated by a high pressure mercury lamp (400W) under air.
[a] Yields were determined by GLC.
[b] KI (0.1 mmol) was used.

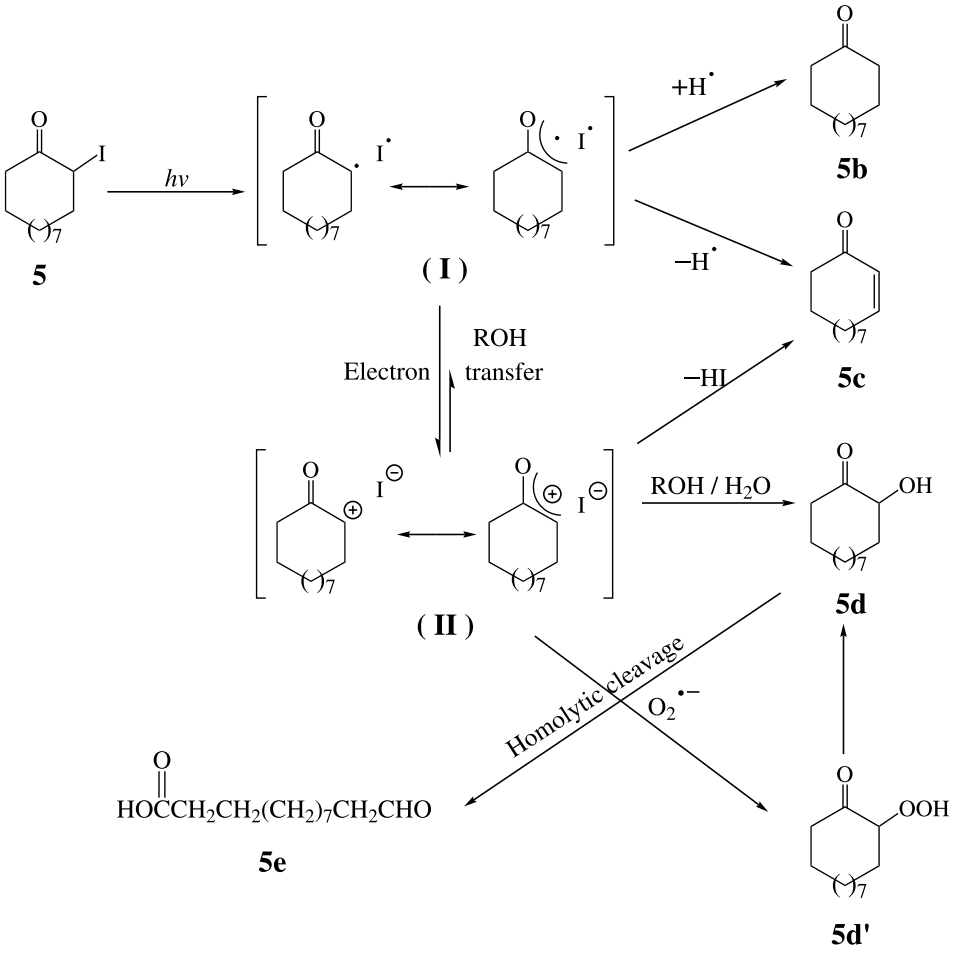


Figure 1. Pathway from α-iodocyclododecanone into α-hydroxyketone.

air, hydroxyl ion attacks at C_2 preferentially and 2-hydroxyketone (**5d**) forms, and in the presence of air, O_2 radical attacks at C_2 and 2-hydroperoxyketone (**5′d**) forms.

In conclusion, this method is very clean, simple, and convenient for the synthesis of α-hydroxyketones. It is particularly noteworthy that this reaction affords a new synthetic method for α-hydroxyketones and α,α′-dihydroxyketones. Moreover, it is interesting that for the first time, we have succeeded in establishing a convenient synthesis of α,α′-dihydroxyketone which has little reported until now.

Typical procedures: **irradiation of 2-iodocyclododecanone (5) by high pressure mercury lamp (400 W) under air in acetone**. A mixture of α-iodo ketone (**5**) (0.10 mmol) and triethylamine (0.10 mmol) in acetone (10 ml) was irradiated by a high pressure mercury lamp in the presence of air for 10 h. After the irradiation was completed, the mixture was concentrated, poured into water, and extracted with diethyl ether (30 ml). The ethereal solution was washed with a saturated solution of sodium thiosulfate (2×2.0 ml), saturated aq. NaCl (2×2.0 ml) and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ether (3:1) gave 2-hydroxycyclododecanone (**5d**) as a pale-yellow oil (19 mg, 95%). **2-Hydroxycyclododecanone** (**5d**): Pale-yellow oil; IR (NaCl) 3418 and 1714 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta = 4.23$ (brs, 1H), 3.94 (brs, 1H), 3.01 (m, 1H), 2.05–2.31 (m, 2H), 1.48–1.68 (m, 1H), 1.05–1.45 (m, 15H) and 0.73–0.91 (m, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 214.5$, 76.8, 35.2, 30.0, 26.1, 24.9, 22.6, 22.5, 21.9, 21.6, 18.8 and 15.6; MS (EI) m/z 198 (M^+), 180, 162, 149, 133, 111, 95, 82 and 55; MS (CI) m/z 199 ($[M+1]^+$).

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