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A New α-Iodination of Ketones Using Iodine-Cerium(IV) Ammonium Nitrate

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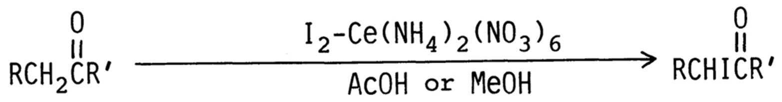
Direct α-iodination of some ketones using iodine-cerium(IV) ammonium nitrate in acetic acid or methanol, gave the corresponding α-iodoketone in high yield. In the case of 2-pentanone, 4-methyl-2-pentanone, 2-hexanone, and 2-heptanone in methanol, the regioselective products were obtained.

α-Iodoketones are important as synthetic intermediates. They are usually prepared by one of the following methods: the halogen interchange¹⁾ of bromo compounds with sodium iodide in acetone; the reaction of N-iodosuccinimide²⁾ or iodine chloride³⁾ with the enol acetates⁴⁾ and enol silyl ethers⁵⁾ with iodine-metal acetate; or the reaction of alkene with iodine-silver chromate,⁶⁾ iodine-pyridinium dichromate,⁷⁾ or bis(*sym*-collidine)iodine(I) tetrafluoroborate.⁸⁾ More recently, it was reported that the reaction of the carbonyl compounds with iodine-mercury(II) chloride gave α-iodoketones.⁹⁾ However, this method is not applicable to cyclic ketones. There has been only very little information on the direct α-iodination of ketones under acidic conditions. In connection with our studies, we have found that iodine-copper(II) acetate¹⁰⁾ in acetic acid is a useful reagent for the syntheses of some iodo compounds. In a previous paper,¹¹⁾ we reported a novel α-iodination of ketones using iodine-copper(II) acetate in acetic acid. The procedure suffers some deficiencies. The most of serious of these are the loss of iodine from the reaction as metallic iodide, and low regioselectivities with unsymmetrical ketones.

In the present paper, we would like to report that the α-iodination of ketones, with iodine-cerium(IV) ammonium nitrate in acetic acid or methanol gave the corresponding α-iodoketones in good yields.



$$\mathrm{RCH_2\overset{O}{\overset{\|}{C}}R'} \xrightarrow[\text{AcOH or MeOH}]{\mathrm{I_2\text{-}Ce(NH_4)_2(NO_3)_6}} \mathrm{RCHI\overset{O}{\overset{\|}{C}}R'}$$

A typical procedure is as follows. A mixture of 5α-cholestan-3-one (1) (200 mg, 0.517 mmol), iodine (0.259 mmol), and cerium(IV) ammonium nitrate (0.259 mmol) in acetic acid-water (20 ml, 9:1) was stirred at 50 °C for 8 h. The reaction mixture was poured into water and extracted with ether. The ethereal solution was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. Crystallization of the residue from ethanol gave needles of 13 (213 mg, 80%), mp 132-133 °C. These results are summarized in Table for the α-iodination of ketones. The NMR spectra of compounds 19, 20, and 21 showed a doublet at δ 4.55 with an equatorial character, a doublet (J=1.5 Hz) at δ 4.17 with long range planar W-type coupling, and a multiplet (W/2=6.0 Hz) at δ 4.42 with an equatorial character, respectively. These were also supported by the shift of C=O compared with that of parent ketone in the IR spectra. From these results, it is considered that the configurations of these iodoketones are axial.

As can be seen in the Table, the present iodination reaction proceeds well under more mild conditions in comparison with the method using copper(II) acetate. In the case of unsymmetrical ketones in methanol such as 2-pentanone, 4-methyl-2-pentanone, 2-hexanone, and 2-heptanone, preferentially, the more substituted position is iodinated. However, in the presence of water [methanol-water (9:1)], the mixed C_1- and C_3-iodination products were yielded. Thus, it is assumed that the cerium(IV) ion is coordinated to the oxygen of the carbonyl group, and then unsymmetrical ketone enolizes predominantly towards the C_3-position. It is known that in the presence of water, equilibrium constant for cerium(IV)-methanol complex is larger than the case of no water.12) Therefore, it is possible to consider that in the presence of water, the cerium(IV)-methanol complex is preferentially formed, and then the relationship between the carbonyl group and the cerium(IV) ion is diminished. Also, it is found that the iodine added is almost completely consumed, and two moles of α-iodoketone are formed from one mole of iodine. It is particularly noteworthy that this reaction may provide us with a new synthetic method for α-iodoketone, more convenient than the methods used heretofore.

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Table 1. α-Iodination of Ketones with Iodine-Cerium(IV) Ammonium Nitrate

Substrate	Product	Solvent	Temperature/°C/ Time/h	Yield/%	
1	2α-Iodo-5α-cholestan-3-one(13)	AcOH-H_2O	50 /8	80	
1	2α-Iodo-5α-cholestan-3-one(13)	MeOH	25 /12	85	
1	2α-Iodo-5α-cholestan-3-one(13)	MeCN	25 /60	85	
1	2α-Iodo-5α-cholestan-3-one(13)	CCl_4	25 /60	82	
2	4β-Iodo-5β-cholestan-3-one(14)	AcOH-H_2O	50 /2.5	60	
3	2α-Iodocholest-4-en-3-one(15)	AcOH-H_2O	50 /36	60	
4	2-Iodocyclohexanone(16)	AcOH	50 /2.5	84	
5	2-Iodocycloheptanone(17)	AcOH	50 /8	95	
6	2-Iodo-2-methylcyclohexanone(18)	AcOH	50 /13	85	
7	2-Iodo-3-methylcyclohexanone(19)	AcOH	50 /5	88	
8	2-Iodo-3,3,5-trimethylcyclohexanone(20) 6-Iodo- (21)	AcOH	50 /9	92	$43^{a)}$ $57^{a)}$
8	2-Iodo-3,3,5-trimethylcyclohexanone(20) 6-Iodo- (21)	MeOH	25 /17	90	$14^{a)}$ $86^{a)}$
9	1-Iodo-2-pentanone(22) 3-Iodo- (23)	MeOH	25 /15	80	$3^{a)}$ $97^{a)}$
10	1-Iodo-4-methyl-2-pentanone(24) 3-Iodo- (25)	MeOH	25 /15	75	$13^{a)}$ $87^{a)}$
11	1-Iodo-2-hexanone(26) 3-Iodo- (27)	AcOH	50 /10	99	$46^{a)}$ $54^{a)}$
11	1-Iodo-2-hexanone(26) 3-Iodo- (27)	AcOH-H_2O	50 /6	96	$43^{a)}$ $57^{a)}$
11	1-Iodo-2-hexanone(26) 3-Iodo- (27)	MeOH	25 /15	83	$4^{a)}$ $96^{a)}$
11	1-Iodo-2-hexanone(26) 3-Iodo- (27)	MeOH-H_2O	25 /30	70	$26^{a)}$ $74^{a)}$
12	1-Iodo-2-heptanone(28) 3-Iodo- (29)	AcOH	50 /14	89	$56^{a)}$ $44^{a)}$
12	1-Iodo-2-heptanone(28) 3-Iodo- (29)	MeOH	25 /20	62	$<1^{a)}$ $100^{a)}$

a) Removal of solvent from the dried solution gave the iodoketone as an unstable oil which was examined by NMR spectrum as soon as possible after preparation. The composition of reaction mixtures was determined from the peak area ratio of NMR spectrum.

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