Highly Efficient and Clean Method for Direct α-Iodination of Aromatic Ketones

Guodong Yin,[a] Meng Gao,[a] Nengfang She,[a] Shengli Hu,[a] Anxin Wu,*[a] Yuanjiang Pan*[b]

[a] Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, Central China Normal University, Wuhan 430079, P. R. of China
E-mail: chwuax@mail.ccnu.edu.cn

[b] Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China
E-mail: panyuanjiang@zju.edu.cn

Received 13 June 2007; revised 17 July 2007

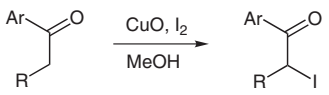
Abstract: Under neutral reaction conditions, aromatic ketones were transformed into the corresponding α-iodo ketones in high yields by the combination of copper(II) oxide and iodine. The reaction mechanism showed that copper(II) oxide played multiple roles through random self-sorting.

Key words: aromatic ketones, iodine, α-iodo ketones, multifunctional reagent, self-sorting

α-Iodo ketones are among the most versatile intermediates in organic synthesis and their high reactivity makes them available to react with a large number of nucleophiles to provide a variety of useful compounds.[1] In addition, many iodoorganic compounds are biologically active molecules, often used in medicine as drugs or diagnostic aids, such as radioactively labeled markers or contrasting agents, and therefore their related chemistry has attracted broad interest.[2] α-Iodo ketones are usually prepared from olefins,[3] ketones derivatives[4] (enol silyl ethers and acetates), or by halogen interchange of bromo compounds with sodium iodide.[5] Due to the difficulties in the synthesis and purification of enol silyl ethers and acetates, a number of methods for direct α-iodination of ketones with different iodonium-donating systems have been reported more recently. Examples are $KI/KIO_3/H_2SO_4$,[6] $NaI/H_2O_2/H_2SO_4$,[7] $I_2/HgCl_2$,[8] $I_2/AgNO_3$,[9] $I_2/Cu(OAc)_2/AcOH$[10] (the method was limited to aliphatic ketones and enol silyl ether), I_2/CAN,[11] I_2/N–F reagent,[12] $SeO_2/I_2/AcOH$,[13] and other systems.[14–18] However, most of these systems have drawbacks, such as cumbersome workup procedures, acidic reaction conditions (formation of the acid in situ), the use of expensive, complicated, or sensitive regents, and the generation of hazardous waste. Therefore, the development of an efficient, economic and environmentally friendly method is still desirable.

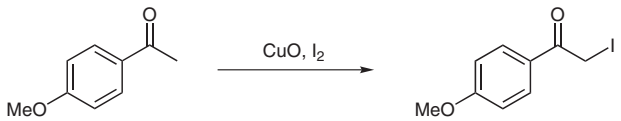
Herein we report an efficient method, based on our recent work,[19] for the synthesis of α-iodo ketones by reaction of the corresponding aromatic ketones with copper(II) oxide and iodine in methanol (Scheme 1). To the best of our knowledge, this is a previously unreported method for direct α-iodination of aromatic ketones. For the present study, *p*-methoxyacetophenone (**1a**) was chosen as a model substrate to find the optimal conditions (Table 1). Since Stavber and co-workers reported that the solvent played an important role in the direct iodination of alkyl aryl ketones, and that even the regiochemistry of the iodination process could be regulated merely by the solvent,[12d] we first investigated the effect of different solvents, as well as the reaction temperature, on the conversion of *p*-methoxyacetophenone (**1a**) into the corresponding α-iodo ketone **1b** (Table 1).

As shown by the data collected in Table 1, methanol was found to be a suitable solvent for performing the conversion (Table 1, entries 2 and 3), and this transformation was also attempted in other solvents such as ethanol, dichloromethane, tetrahydrofuran, acetonitrile, and



Scheme 1 Access to α-iodo ketones from the reaction of aromatic ketones with iodine and copper(II) oxide in methanol

Table 1 Effect of Solvent and Temperature on the Iodination of *p*-Methoxyacetophenone[a]



1a **1b**

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	MeOH	20	15	0
2	MeOH	40	10	94
3	MeOH	65	1	99
4	EtOH	78	2	91
5	CH_2Cl_2	40	8	0
6	THF	65	8	0
7	MeCN	81	8	0
8	benzene	80	8	0

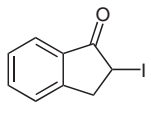
[a] Reagents and conditions: CuO (>98% powder, 1 equiv), I_2 (1 equiv).
[b] Isolated yield.

SYNTHESIS 2007, No. 20, pp 3113–3116
Advanced online publication: 11.09.2007
DOI: 10.1055/s-2007-983880; Art ID: F09407SS

benzene. When ethanol was used as the solvent, **1b** was also obtained, in 91% yield (Table 1, entry 4). However, it was interesting to find that in the aprotic solvents no reactions occurred after eight hours (Table 1, entries 5–8).[20] At room temperature (20 °C) in methanol, no reaction was observed either (Table 1, entry 1). If the reaction temperature was elevated to 40 °C or 65 °C, the conversion proceeded smoothly, although a longer reaction time was required in the former case (Table 1, entries 2 and 3). Under optimized conditions, treatment of *p*-methoxyacetophenone (**1a**) with 1.0 molar equivalent iodine and 1.0 molar equivalent finely powdered copper(II) oxide in methanol at reflux for one hour afforded the corresponding α-monoiodo ketone **1b** in 99% yield (Table 1, entry 3).

To assess the generality of the method and to evaluate the electronic influence of the aromatic ring substituents, the transformations of various other aromatic ketones **2a**–**18a** into the corresponding α-iodo ketones **2b**–**18b** were examined (Table 2). Acetophenone and its derivatives bearing electron-donating groups on the phenyl rings were readily transformed into the corresponding 1-aryl-substituted 2-iodoethanones in near-quantitative yields (Table 2, entries 1–5). Even substrates **6a** and **7a** containing a sensitive functional group (hydroxy) formed α-iodo ketones **6b** and **7b** in 91% and 84% yield, respectively (Table 2, entries 6 and 7). Substrates bearing electron-withdrawing groups on the phenyl rings (**8a**–**10a**) gave slightly lower yields, and needed longer reaction times (Table 2, entries 8–10).

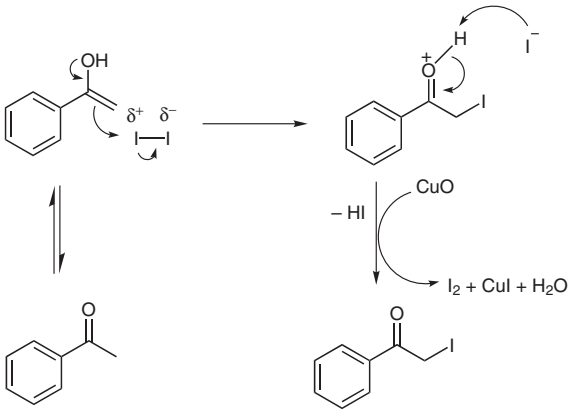
Table 2 Preparation of α-Iodo Ketones ArCOCH(R)I **1b**–**18b** by Reaction of Ketones $ArCOCH_2R$ with Copper(II) Oxide and Iodine in Refluxing MeOH

Entry	Ar	R	Product	Time (h)	Yield[a] (%)
1	PMP	H	**1b**	1	99
2	Ph	H	**2b**	1	96
3	Tol	H	**3b**	1	95
4	4-$EtOC_6H_4$	H	**4b**	1	87
5	1,3-benzodioxol-5-yl	H	**5b**	1	98 (75[12c])
6	4-HOC_6H_4	H	**6b**	2	91
7	3-HOC_6H_4	H	**7b**	2	84
8	4-PhC_6H_4	H	**8b**	3	83
9	4-ClC_6H_4	H	**9b**	5	83
10	4-BrC_6H_4	H	**10b**	6	87
11	4-$O_2NC_6H_4$	H	**11b**	12	53[b]
12	1-Naph	H	**12b**	3	92
13	2-Naph	H	**13b**	3	93
14	6-methoxy-2-naphthyl	H	**14b**	2	98
15	2-furyl	H	**15b**	1	93
16	2-thienyl	H	**16b**	1	91
17[c]			**17b**	1	85 (69,[13] 55[15b])
18	Ph	Ph	**18b**	4	18[d]

[a] Isolated yield.
[b] The dimethyl ketal product 4-$O_2NC_6H_4C(OMe)_2CH_2I$ (**11c**) was isolated in 40% yield.
[c] The drawn compound represents the product ArCOCH(R)I.
[d] The major product was PhCOCH(OMe)Ph (**18c**, 80%).

α-Iodo ketone **11b**, containing the strongly electron-withdrawing nitro group on the phenyl ring, was obtained in 53% yield along with the dimethyl ketal product **11c** in 40% yield (Table 2, entry 11). Much to our satisfaction, naphthyl and hetaryl methyl ketones also led to the corresponding products in excellent yields (Table 2, entries 12–16). The non-methyl ketone indan-1-one (**17a**) also gave the expected product **17b**, which was isolated in 85% yield (Table 2, entry 17). However, the expected α-iodo ketone product 2-iodo-1,2-diphenylethanone (**18b**) of 1,2-diphenylethanone (**18a**) was easily converted into the solvolytic product 2-methoxy-1,2-diphenylethanone (**18c**) (Table 2, entry 18). It was a pity to find that when cyclohexanone was used as the substrate, the dimethyl ketal 2-iodo-1,1-dimethoxycyclohexane was the major product.[4a,11a,21]

A possible reaction mechanism is shown in Scheme 2. Copper(II) oxide plays multiple roles in this reaction. First, it acts as the oxidizing agent or catalyst to convert molecular iodine into the reacting iodonium ion (I^+) species, analogous to the function of other copper salts reported by Dalla Cort.[4b] In addition, copper(II) oxide could act as a weak base to neutralize hydrogen iodide, and reoxidize iodide ion (I^-) into molecular iodine (I_2), which forms together with insoluble copper(I) oxide and water.



Scheme 2 A possible reaction mechanism

Support for this mechanism may be provided by the following experiments and phenomena: (a) That treatment of **1a** with iodine in refluxing methanol without copper(II) oxide did not afford the corresponding iodo ketone dem-

$$RCOCH_3 + 1/2\ CuO + 3/4\ I_2 \longrightarrow RCOCH_2I + 1/2\ CuI + 1/2\ H_2O$$

Equation 1

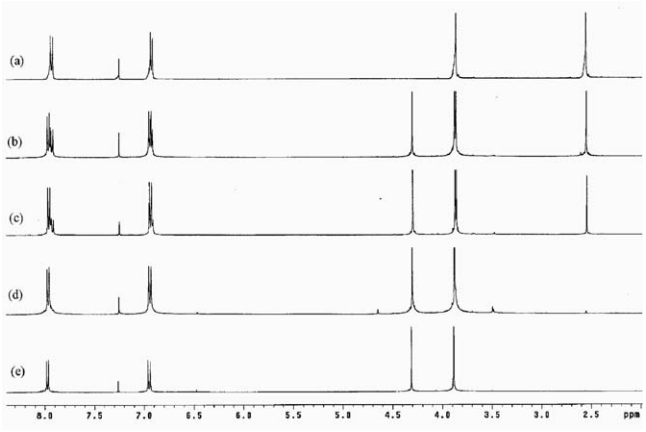


Figure 1 ^{1}H NMR spectroscopic monitoring (400 MHz, $CDCl_3$, 298 K) of the reaction of **1a** with iodine in the presence of copper(II) oxide. *Reagents and conditions*: (a) **1a**, $CDCl_3$; in all following cases: **1a** (1 equiv), CuO (1 equiv), $CDCl_3$, and (b) I_2 (0.40 equiv), 59%; (c) I_2 (0.60 equiv), 79%; (d) I_2 (0.75 equiv), 95%; (e) I_2 (0.80 equiv), >99%.

onstrates the catalytic role of copper(II) oxide. (b) The formation of insoluble copper(I) oxide was observed. (c) To further confirm the reoxidation of iodide ion to molecular iodine, we investigated the effect of the molar ratio of iodine/substrate (**1a**) on the yield. In theory, if iodide ion is reoxidized to molecular iodine, the reaction would be completed when the amount of iodine equals 0.75 equivalents of substrate (Equation 1). The yield was evaluated by ^{1}H NMR spectroscopy of the reaction mixture after 16 hours. It was found that when the amount of iodine was less than 0.75 equivalents, reactant was left behind (Figure 1, runs b and c). Product **1b** was obtained in 95% yield when the amount of iodine equaled 0.75 molar equivalent of substrate (Figure 1, run d). When the amount of iodine was continuously increased to 0.80 equivalents, **1b** was obtained in near-quantitative yield (>99%) (Figure 1, run e). This implies that iodide ion was reoxidized to iodine during the reaction process, as otherwise the amount of iodine would not be less than 1.00 molar equivalent of substrate.

In conclusion, an efficient method for the direct synthesis of α-iodo ketones by the combination of copper(II) oxide and iodine was described. The reaction mechanism shows copper(II) oxide acting as a multifunctional reagent by random self-sorting. One part of copper(II) oxide serves as a catalyst, and another part of copper(II) oxide can serve as a base to consume the additional product hydrogen iodide in situ and to regenerate iodine. The advantages of the present method in terms of high yields, short reaction times, mild reaction conditions, neutral reaction medium, ease of manipulation, formation of cleaner products, and inexpensive reagents should make it a valuable alternative to the existing methods.

Finely powdered CuO was purchased from commercial sources (>98%). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to the internal standard of TMS. IR spectra of samples as KBr pellets were recorded on a PE-983 spectrophotometer. MS was carried out on a Finnigan Trace MS spectrometer or by the ESI method on a Quattro LCZ spectrometer (Waters-Micromass, Manchester, UK) with a nanospray inlet. Column chromatography was performed on silica gel (200–300 mesh).

Direct α-Iodination of Aromatic Ketones; General Procedure

Finely powdered CuO (0.40 g, 5.0 mmol) and I_2 (1.27 g, 5.0 mmol) were added to a well-stirred soln of the ketone (5.0 mmol) in anhyd MeOH (20 mL). The mixture was stirred for 5 min and then refluxed. After disappearance of the reactant (1–12 h, monitored by TLC), the mixture was filtered and the solvent was removed under reduced pressure. The residue was poured into 10% $Na_2S_2O_3$ soln (50 mL), the mixture was extracted with EtOAc (3 × 30 mL), and the organic layer was dried (Na_2SO_4). Removal of the solvent and purification of the residue by column chromatography or recrystallization (cyclohexane) gave the target products.

1-(4-Ethoxyphenyl)-2-iodoethanone (4b)

IR (KBr): 3298, 2980, 2935, 1657, 1600, 1422, 1259, 1177, 1097, 1035 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.2 Hz, 3 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.32 (s, 2 H, CH_2I), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.98 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.7, 14.4, 63.7, 114.3, 126.0, 131.4, 163.4, 191.6.

ESI-MS: *m*/*z* (%) = 312.7 (100) [M + Na$^+$].

1-(3-Hydroxyphenyl)-2-iodoethanone (7b)

IR (KBr): 3387, 1662, 1595, 1448, 1292, 1204 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (s, 2 H), 5.85 (s, 1 H), 7.11–7.13 (m, 1 H), 7.34–7.39 (m, 1 H), 7.52–7.56 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.8, 115.5, 121.5, 121.7, 130.1, 134.6, 156.4, 194.1.

MS (EI, 70 eV): *m*/*z* (%) = 262 (69), 127 (38), 121 (100), 107 (72).

1-Biphenyl-4-yl-2-iodoethanone (8b)[15a]

IR (KBr): 3430, 1679, 1599, 1174, 986, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.39 (s, 2 H), 7.40–7.50 (m, 3 H), 7.62–7.72 (m, 4 H), 8.07 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.7, 127.2, 127.4, 128.4, 128.9, 129.6, 132.0, 139.5, 146.4, 192.3.

MS (EI, 70 eV): *m*/*z* (%) = 322 (90), 196 (23), 181 (93), 151 (100).

1-(2-Iodo-1,1-dimethoxyethyl)-4-nitrobenzene (11c)

IR (KBr): 2941, 1530, 1350, 1281, 1111, 1064, 1045 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (s, 6 H), 3.49 (s, 2 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 8.24 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 49.8, 100.5, 123.1, 128.5, 146.2, 147.8.

MS (EI, 70 eV): *m*/*z* (%) = 306, (8) [M – OCH_3], 195 (100), 150 (74).

2-Iodo-1-(6-methoxy-2-naphthyl)ethanone (14b)

IR (KBr): 3433, 1676, 1619, 1479, 1387, 1270, 1140 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 3 H), 4.46 (s, 2 H), 7.16–7.23 (m, 2 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 8.00 (dd, *J* = 8.4, 1.6 Hz, 1 H), 8.45 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.9, 55.4, 105.7, 119.9, 125.0, 127.3, 127.6, 128.7, 130.7, 131.2, 137.5, 160.0, 192.4.

MS (EI, 70 eV): *m*/*z* (%) = 326 (100), 253 (8), 199 (15), 185 (94), 171 (67), 127 (39).

Acknowledgment

This work was supported by the Central China Normal University, the National Natural Science Foundation of China (grant nos. 20472022 and 20672042), and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (no. [2005]383). We also thank Zhejiang University for performing the structural analysis.

References

(1) Erian, A. W.; Sherif, S. M.; Gaber, H. M. *Molecules* **2003**, *8*, 793.
(2) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575.
(3) Cardillo, G.; Shimizu, M. *J. Org. Chem.* **1977**, *42*, 4268.
(4) (a) Dolenc, D. *Synth. Commun.* **2003**, *33*, 2917. (b) Cort, A. D. *J. Org. Chem.* **1991**, *56*, 6708. (c) Rubottom, G. M.; Mott, R. C. *J. Org. Chem.* **1979**, *44*, 1731.
(5) Vankar, Y. D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233.
(6) Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1731.
(7) Barluenga, J.; Marco-Arias, M.; González-Bobes, F.; Ballesteros, A.; González, J. M. *Chem. Commun.* **2004**, 2616.
(8) Barluenga, J.; Martinez-Gallo, J. M.; Najera, C.; Yus, M. *Synthesis* **1986**, 678.
(9) Higgins, S. D.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 235.
(10) Horiuchi, C. A.; Satoh, J. Y. *Synthesis* **1981**, 312.
(11) The method was limited to aliphatic ketones: (a) Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 421. (b) Horiuchi, C. A.; Kiji, S. *Chem. Lett.* **1988**, 31.
(12) (a) Pavlinac, J.; Stavber, S.; Zupan, M. *Synthesis* **2006**, 2603. (b) Pavlinac, J.; Stavber, S.; Zupan, M. *J. Org. Chem.* **2006**, *71*, 1027. (c) Jereb, M.; Stavber, S.; Zupan, M. *Synthesis* **2003**, 853. (d) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2002**, 488.
(13) Bekaert, A.; Barberan, O.; Gervais, M.; Brion, J. D. *Tetrahedron Lett.* **2000**, *41*, 2903.
(14) Whang, J. P.; Yang, S. G.; Kim, Y. H. *Chem. Commun.* **1997**, 1355.
(15) (a) Rao, M. L. N.; Jadhav, D. N. *Tetrahedron Lett.* **2006**, *47*, 6883. (b) Le Bras, G.; Provot, O.; Bekaert, A.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Synthesis* **2006**, 1537. (c) Lee, J. C.; Park, J. Y.; Yoon, S. Y.; Bae, Y. H.; Lee, S. J. *Tetrahedron Lett.* **2004**, *45*, 191. (d) Lee, J. C.; Bae, Y. H. *Synlett* **2003**, 507. (e) Lee, J. C.; Jin, Y. S. *Synth. Commun.* **1999**, *29*, 2769.
(16) Kim, K. M.; Chung, K. H.; Kim, J. N.; Ryu, E. K. *Synthesis* **1993**, 283.
(17) Fukuyama, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4363.
(18) (a) Meshram, H. M.; Reddy, P. N.; Vishnu, P.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 991. (b) Yang, D.; Yan, Y. L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429. (c) Kang, J.; Lee, J. H.; Noh, S. B.; Oh, C. S.; Kim, H. Y.; Chung, B. Y. *Synlett* **1990**, 153. (d) Curran, D. P.; Chen, M. S.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872.
(19) Yin, G. D.; Zhou, B. H.; Meng, X. G.; Wu, A. X.; Pan, Y. J. *Org. Lett.* **2006**, *8*, 2245.
(20) The possible reason is that a trace amount of H^+, which was produced by treatment of iodine with methanol, could initiate the reaction; see: (a) Cruickshank, F. R.; Benson, S. W. *J. Phys. Chem.* **1969**, *73*, 733. (b) Togo, H.; Iida, S. *Synlett* **2006**, 2159.
(21) Zacuto, M. J.; Cai, D. *Tetrahedron Lett.* **2005**, *46*, 447.