Direct Conversion of Aromatic Ketones to Arenecarboxylic Esters via Carbon–Carbon Bond-Cleavage Reactions

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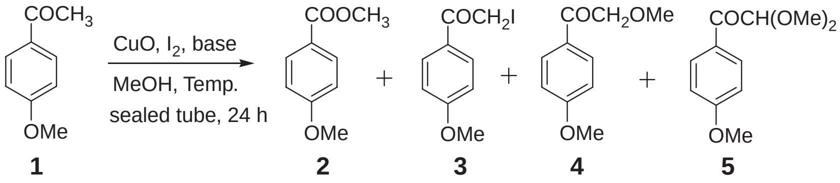
Aromatic methyl ketones, β-keto esters, and trifluoromethyl-1,3-diketones can be directly converted to arenecarboxylic esters via carbon–carbon bond cleavage of pyridinium iodide intermediates in the presence of copper(II) oxide, iodine, pyridine, and potassium carbonate in alcoholic media. The advantages of the present method in terms of good yields, mild reaction conditions, and inexpensive reagents should make this protocol a valuable alternative to the existing methods.

One of the most important tasks in organic chemistry is to perform functional group inter-conversions. During various stages in organic synthesis and natural products synthesis, it is often required to introduce a carboxylic ester group into molecules, which is usually achieved by oxidation of alcohols and aldehydes.[1] Molecular iodine, as one of the most simple, least expensive, and least toxic oxidants has been widely used to achieve the direct oxidation of alcohols or aldehydes to carboxylic esters.[2–4] Generally, the introduction of an acetyl group onto an aromatic ring is much easier than introduction of a hydroxy or aldehyde group, so the development of an efficient method for the direct synthesis of carboxylic esters from carbonyl compounds is significant. To date, few examples have been reported for performing this conversion. The Baeyer–Villiger reaction[5] is the oxidative cleavage of a carbon–carbon bond adjacent to a carbonyl group, which is the classic method for the transformation of carbonyl compounds to the corresponding carboxylic esters in the presence of peracids, hydrogen peroxides, or other peroxy compounds. However, this oxidation reaction often provides a pair of isomers. Nikishin and co-workers[6] reported an electrocatalytic method for transformation of methyl ketones into methyl esters. Zhang and Vozzolo[7] found that (dimethoxymethyl)dimethylamine (DMF•DMA) could promote a carbon–carbon bond-cleavage reaction of aryl alkyl ketones to arenecarboxylic esters in refluxing methanol. However, the substrates were limited to electron-deficient ketones. In addition, the use of strong oxidant such as KOCl (activated aromatic ketones give lower yield of the products due to ring chlorination) can also perform this conversion.[8] Recently, we have found that α-iodination of aromatic ketones can be efficiently accomplished by using a copper(II) oxide/iodine reagent combination in alcoholic media.[9] Herein, we report an efficient method for the direct conversion of aromatic ketones to their corresponding carboxylic ethyl esters, which involves carbon–carbon bond-cleavage reactions.

Results and Discussion

Initially, we expected to obtain intermediate **5** in one pot from *p*-methoxyacetophenone (**1**) in the presence of copper(II) oxide (2 equivalents), iodine (2 equivalents), and appropriate base (2 equivalents) in methanol (Scheme 1). The results are summarized in Table 1. Heating the reaction mixture at 100 °C in a sealed tube for 24 h without any other base, α-iodoketone **3** was obtained in 90% isolated yield together with the solvolytic product **4** in 8% yield (Entry 1). When triethylamine was used as base, no reaction occurred (Entry 2). The desired product **5** was only obtained in 6% yield and the conversion was about 40% when using potassium carbonate as base (Entry 3). It was interesting to find that the unexpected product methyl 4-methoxybenzoate (**2**) was obtained in 40% yield when the base was changed to pyridine. As the temperature decreased from 100 to 80 °C, the yield of ester **2** was slightly lower (Entries 4 and 5).

As early as the 1940s, King and Pearson reported that reaction of aryl methyl ketones with iodine and pyridine produced pyridinium iodide, which could be hydrolyzed to the corresponding carboxylic acid by aqueous alkali.[10] On the base of



Scheme 1.

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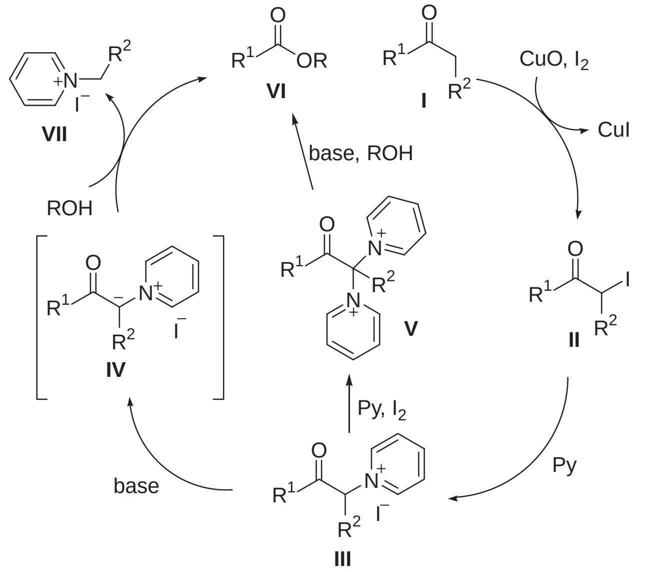
Table 1. Effect of the Base on the Yield of Ester **2**[a)]

Entry	Base[b)]	Temp	Conv.	Yield/%[d)]			
		/°C[c)]	/%	**2**	**3**	**4**	**5**
1	none	100	100	—[e)]	90	8	—
2	NEt_3	100	—	—	—	—	—
3	K_2CO_3	100	40	—	20	10	6
4	Py	100	95	40[f)]	—	—	—
5	Py	80	90	38[f)]	—	—	—

a) Reaction conditions: 2 mmol of *p*-methoxyacetophenone, CuO (4 mmol), I_2 (4 mmol), 24 h, in sealed tube for all cases. b) NEt_3 (8 mmol), K_2CO_3 (4 mmol), Py (8 mmol). c) Oil bath temperature. d) Isolated yield. e) Products were not observed. f) Pyridinium iodide was the major product.

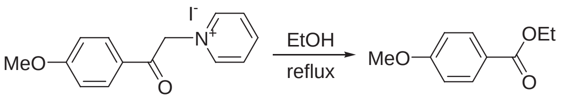


Scheme 2. Proposed reaction mechanism.

related literature,[11] our proposed pathway for this reaction is shown in Scheme 2. Initially, α-iodo ketone **II**, obtained in situ by iodination of ketone **I** in the presence of copper(II) oxide,[9b] reacts with pyridine to yield pyridinium iodide **III**.[12] Intermediate **III** deprotonates under mild basic conditions to give **IV**, which then reacts with the nucleophilic alcohol to deliver the carboxylic ester **VI** and pyridinium salt **VII** through a carbon–carbon bond-cleavage reaction. It should be noted that the possible intermediate **V**, obtained from **III** in the presence of excess iodine and pyridine, can also be transformed into carboxylic ester **VI**.

In order to further confirm the reaction mechanism, we synthesized 1-(4-methoxyphenacyl)pyridinium iodide (**6**) according to a reported method[13] and investigated the effect of base on the yield of ethyl 4-methoxybenzoate (**7**) in refluxing ethanol. As shown in Table 2, heating the ethanol solution of **6** without any base at reflux for 24 h, no expected product was detected by thin-layer chromatography (TLC) analysis (Entry 1). It was found that pyridine did not promote this conversion (Entry 2). Gladly, carboxylic ester **7** was obtained in near-quantitative yield (99%) using potassium carbonate as base because potassium carbonate or high temperature could effectively accelerate the carbon–carbon bond-cleavage reaction of pyridinium iodide (Entry 3).[14] We also found that the transformation of compound **6** to **7** could be achieved in moderate yield even using the weak base copper(II) oxide (Entry 4). It is concluded that copper(II) oxide can promote not only α-iodination of ketones in the first step but also to a certain extent cleavage of pyridinium iodide to give target product ester. To ensure the complete cleavage reaction of pyridinium iodide, it is necessary to add potassium carbonate to the solution in the second step.

Table 2. Effect of Base on the Cleavage of Carbon–Carbon Bond of Pyridinium Iodide **6** to Ethyl 4-Methoxybenzoate (**7**)[a)]

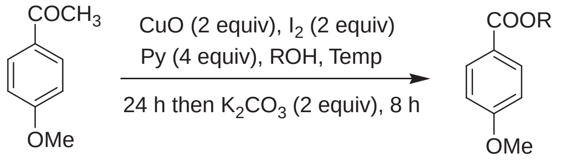


6 **7**

Entry	Base[b)]	Time/h	Yield/%[c)]
1	none	24	NR
2	Py	16	trace
3	K_2CO_3	8	99
4	CuO	8	45

a) Reaction conditions: 1 mmol of pyridinium iodide **6**, in refluxing ethanol for all cases. b) 2 mmol base was employed. c) Isolated yield.

Table 3. Conversion of Methyl Ketone **1** to Esters in Other Alcoholic Media[a)]

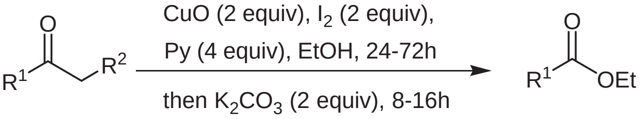


Entry	ROH	Temp/°C	Product	Yield/%[b)]
1	MeOH	65	**5**	72
2	EtOH	78	**7**	80
3	*n*-PrOH	97	**8**	51
4	*i*-PrOH	100[c)]	**9**	46
5	*n*-BuOH	100	**10**	50
6	*t*-BuOH	100[c)]	**11**	0

a) Reaction conditions: 2 mmol of *p*-methoxyacetophenone, CuO (4 mmol), I_2 (4 mmol), Py (8 mmol), ROH (20 mL) for all cases. b) Isolated yield. c) In sealed tube, oil bath temperature.

Under optimized conditions, the effect of alcoholic media on the yield of ester was investigated. The general procedure was as follows. Treatment of substrate **1** with iodine (2 equivalents), copper(II) oxide (2 equivalents), and pyridine (4 equivalents) in alcoholic media at reflux for 24 h, followed by addition of potassium carbonate (2 equivalents) for an additional 8 h of reflux provided the corresponding ester was obtained in 46–80% yield (Table 3, Entries 1–5). Heating the reaction mixture in refluxing ethanol, desired compound **7** was obtained in 80% yield. The reaction gave slightly lower yield in methanol probably due to the effect of temperature. However, in high boiling point alcoholic media, such as 1-propanol (*n*-PrOH), 2-propanol (*i*-PrOH), and 1-butanol (*n*-BuOH), the corresponding esters **8–10** were only isolated in moderate

Table 4. Conversion of Aromatic Ketones to Arenecarboxylic Esters



Entry	R^1	R^2	Time/h	Product	Yield/%[b)]
1	$4\text{-}CH_3C_6H_4$	H	24/8	**12**	74
2	$4\text{-}EtOC_6H_4$	H	24/8	**13**	75
3	$4\text{-}C_6H_5C_6H_4$	H	40/8	**14**	60
4	$4\text{-}ClC_6H_4$	H	48/8	**15**	76
5	$4\text{-}BrC_6H_4$	H	48/8	**16**	60
6	$4\text{-}NO_2C_6H_4$	H	48/10	**17**	83
7	$3,4\text{-}Cl_2C_6H_3$	H	48/10	**18**	68
8	1-Naph	H	72/12	**19**	41[c)]
9	2-Naph	H	48/12	**20**	56
10	6-Methoxy-2-naphthyl	H	24/8	**21**	75
11	2-Furyl	H	24/16	**22**	73
12	2-Thienyl	H	24/16	**23**	74
13	5-Cl-2-thienyl	H	24/8	**24**	59
14	5-Br-2-thienyl	H	24/8	**25**	62
15	3-Thienyl	H	24/16	**26**	71
16	C_6H_5	Et	24/10	**27**	30
17	$4\text{-}MeOC_6H_4$	COOEt	18/10	**7**	78
18	$3,4,5\text{-}(OMe)_3C_6H_2$	COOEt	16/6	**28**	75
19	$4\text{-}NO_2C_6H_4$	COOEt	16/6	**17**	90
20	$3\text{-}NO_2C_6H_4$	COOEt	16/6	**29**	92
21	$4\text{-}MeOC_6H_4$	$COCF_3$	24/10	**7**	82
22	6-Methoxy-2-naphthyl	$COCF_3$	24/10	**21**	85
23	$4\text{-}NO_2C_6H_4$	$COCF_3$	24/8	**17**	85
24	$PhCH_2OC_6H_4$	$COCF_3$	18/10	**30**	64

a) Reaction conditions: ketone (2.5 mmol), CuO (5 mmol), I_2 (5 mmol), Py (10 mmol), K_2CO_3 (5 mmol), EtOH (15 mL), at reflux for all cases. b) Isolated yield. c) In sealed tube at 100 °C.

yields. When *t*-butyl alcohol (*t*-BuOH) was used as the nucleophilic alcohol, the expected product *tert*-butyl 4-methoxybenzoate (**11**) was not detected (Entry 6). It could be concluded that the yield of ester was influenced not only by the reaction temperature but also steric hindrance of the nucleophilic alcohol. In refluxing ethanol, the reaction gave the best result.

Next, we explored the scope of substrates and the limitation of this reaction by treating a variety of aromatic ketones with copper(II) oxide, iodine, pyridine, and potassium carbonate in refluxing ethanol. The results are summarized in Table 4. The reaction yield was insensitive to the electron density of the carbonyl group of substrates. As for compounds bearing electron-donating or electron-withdrawing groups in the phenyl rings, the corresponding ethyl esters **12–18** were obtained in good yields (60–83%) although a longer reaction time was required for the latter case (Table 4, Entries 1–7). Under refluxing ethanol, we found that substrate methyl 1-naphthyl ketone gave ethyl 1-naphthoate in only 10% yield. Even when the reaction temperature was elevated to 100 °C and the reaction time was prolonged to 72 h, ethyl 1-naphthoate (**19**) was obtained in only 41% yield probably owing to steric hindrance (Entry 8). Much to our satisfaction, methyl 2-naphthyl ketone, methyl 6-methoxy-2-naphthyl ketone, methyl furyl ketone, and methyl thienyl ketones all delivered the corresponding products **20–26** in good yields (56–75%) under the above optimized conditions (Entries 9–15). With these successful results in hand, we set out to extend the scope of substrates to non-methyl ketones. 1-Phenyl-1-butanone provided the expected ethyl benzoate (**27**) in only 30% yield along with an unidentified mixture of by-products (Entry 16). We were glad to find that β-keto esters and trifluoromethyl-1,3-diketones also gave the corresponding ethyl esters (**7**, **17**, **21**, and **28–30**) in excellent yields (Entries 17–24). It was reasoned by the possible reaction mechanism that the electron-withdrawing group of R^2 (such as –COOEt and –$COCF_3$) could promote the pyridinium iodide intermediate to deprotonate under basic conditions. However, the donor-withdrawing group of R^2 (such as an ethyl group) did not facilitate this process (see Scheme 2).

Conclusion

In conclusion, we have developed an efficient method for the direct conversion of aromatic methyl ketones, β-keto esters, and trifluoromethyl-1,3-diketones to the corresponding arenecarboxylic esters via carbon–carbon bond-cleavage reaction of pyridinium iodide intermediates. The mild reaction conditions, inexpensive reagents, and good yields are advantages of the present procedure.

Experimental

General. Finely powdered copper(II) oxide was purchased from commercial sources (>98%). Ethanol was freshly distilled from sodium metal. Melting points were determined on an XT4A Meltemp apparatus and are uncorrected. ^1H spectra were recorded on a Varian Mercury 400 spectrometer operating at 400 MHz. ^{13}C spectra were recorded on a Varian Mercury 600 spectrometer operating at 150 MHz. Chemical shifts are reported in ppm, relative to the internal standard of tetramethylsilane (TMS) or 3-(trimethylsilyl)propanesulfonate (DSS). IR spectra of samples as KBr pellets were recorded on a PE-983 spectrophotometer. MS was carried out on a Finnigan Trace MS spectrometer. Column chromatography was performed on silica gel (200–300 mesh).

1-(4-Methoxyphenacyl)pyridinium Iodide (6).[13] A mixture of *p*-methoxyacetophenone **1** (7.5 g, 0.05 mol), iodine (12.7 g, 0.05 mol), and pyridine (50 mL) was heated at 100 °C for 3 h and allowed to stand overnight. The reaction mixture was filtered then thoroughly washed with 40 mL ether to remove unreacted starting substrate. The solid was washed with 50 mL of cold water to remove pyridine hydroiodide and compound **6** was obtained in 80% (14.2 g, 0.04 mol) isolated yield. mp 213–215 °C (lit.[13] 218–219 °C); ^1H NMR (400 MHz, DMSO-d_6, 20 °C): δ 8.98 (d, $J = 6.8$ Hz, 2H), 8.73 (t, $J = 7.6$ Hz, 1H), 8.27 (t, $J = 6.8$ Hz, 2H), 8.05 (d, $J = 8.8$ Hz, 2H), 7.19 (d, $J = 8.8$ Hz, 2H), 6.42 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3); ^1H NMR (400 MHz, D_2O/DSS, 20 °C): δ 8.78 (d, $J = 7.0$ Hz, 2H), 8.68 (t, $J = 7.6$ Hz, 1H), 8.17 (t, $J = 6.8$ Hz, 2H), 8.09 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 8.8$ Hz, 2H), 3.95 (s, 3H, OCH_3), the signal of CH_2 was not observed due to the fast hydrogen–deuterium exchange in neutral D_2O at room temperature; ^{13}C NMR (150 MHz, DMSO-d_6, 20 °C): 188.8, 164.2, 146.1, 130.7, 127.8, 126.2, 114.4, 66.0, 55.9 (10 resonances expected, 9 observed); IR (KBr): 1677, 1605, 1247, 1176, 1027 cm^{-1}.

Typical Procedure for the Preparation of Ester. A mixture of ketone (2.5 mmol), powdered copper(II) oxide (0.40 g, 5.0 mmol), iodine (1.27 g, 5.0 mmol), and pyridine (10 mmol) in 15 mL of anhydrous ethanol was heated at reflux for 24–72 h, then potassium carbonate (0.69 g, 5.0 mmol) was carefully added to the mixture and stirring was continued for 8–16 h. The mixture was cooled to room temperature and filtered, and the solvent was removed under reduced pressure. The residue was poured into 30 mL 5% $Na_2S_2O_3$ solution and extracted with EtOAc (3 × 30 mL), and then the organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent and purification of the residue by column chromatography over silica gel with petroleum ether as eluent to give the corresponding products.

4-(Ethoxycarbonyl)biphenyl (14):[15] Mp 47–48 °C (lit.[13] 48–49 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 8.12 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.65–7.62 (m, 2H), 7.49–7.46 (m, 2H), 7.42–7.40 (m, 1H), 4.41 (q, $J = 7.2$ Hz, 2H), 1.42 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 20 °C): 166.4, 145.4, 139.9, 129.9, 129.1, 128.8, 128.0, 127.1, 126.9, 60.8, 14.2; IR (KBr): 1710, 1606, 1277, 1115, 748 cm^{-1}. MS (EI, 70 eV): m/z (%) = 226 (89), 198 (59), 181 (98), 152 (100), 127 (8), 91 (11), 76 (29).

Ethyl 4-(Phenoxymethyl)benzoate (30): Pale white oil; ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 8.01 (d, $J = 8.8$ Hz, 2H), 7.45–7.35 (m, 5H), 6.99 (d, $J = 8.8$ Hz, 2H), 5.12 (s, 2H), 4.35 (q, $J = 7.2$ Hz, 2H), 1.38 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 20 °C): 166.3, 162.3, 136.2, 131.5, 128.6, 128.1, 127.4, 123.1, 114.3, 70.0, 60.6, 14.3; IR (KBr): 1708, 1607, 1510, 1278, 1258, 1168, 1107 cm^{-1}. MS (EI, 70 eV): m/z (%) = 256 (62), 211 (26), 91 (100).

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Supporting Information

Spectral data and ^{1}H NMR (or ^{13}C NMR) spectra of compounds **6**, **7**, **12**–**26**, and **28**–**30**. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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