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One-Pot Metal-Free Syntheses of Acetophenones from Styrenes through Aerobic Photo-oxidation and Deiodination with Iodine

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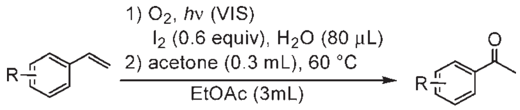
ABSTRACT



A one-pot synthetic protocol of acetophenones from styrenes with molecular oxygen, visible light, and molecular iodine is reported. This procedure involves aerobic photo-oxidation and deiodination in one pot and provides the first report of metal-free direct syntheses of acetophenones from styrenes.

Aerobic oxidation has attracted a great deal of attention in organic synthesis, since molecular oxygen is photosynthesized by plants and is a larger atom-efficient oxidant than other oxidants such as toxic heavy metals or complex organic reagents. Furthermore, molecular oxygen theoretically produces only water as the end product after oxidation.[1] The Wacker oxidation process is one of the most important reactions in industrial chemistry, where ethylene is oxidized to acetaldehyde with a catalytic amount of $PdCl_2$ and $CuCl_2$ under an oxygen atmosphere.[2] In addition, Wacker oxidation is a valuable protocol for the synthesis of acetophenones, which is an important intermediate for pharmaceuticals, perfumes, and other chemical products, from styrenes. Acetophenones are classically synthesized by Friedel–Crafts acylation with a stoichiometric amount of a Lewis acid. Thus, various Wacker type reactions for the synthesis of acetophenones from styrenes have been developed. These include (1) using solvents such as ethylene carbonate,[3] supercritical carbon dioxide (sc. CO_2),[4] polyethylene glycol (PEG),[5] ionic liquid,[6] and perfluorinated solvent;[7] (2) using a phase-transfer catalyst;[8] (3) employing other reoxidants such as nitrous oxide,[9] H_2O_2,[4,6] and *tert*-butylhydroperoxide (TBHP);[7,10] and (4) using reaction vessels such as a polydimethylsiloxane (PDMS) thimble.[11] In addition, Co,[12] Rh,[13] and Mn[14] catalysts have also been used for the oxidation of styrenes to acetophenones instead

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(1) Bäckvall, J.-E., Ed. *Modern Oxidation Methods*; Wiley-VHC: Weinheim, Germany, 2004.

(2) (a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem., Int. Ed.* **1962**, *1*, 80–88. (b) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176–182.

(3) Wang, J. L.; He, L. N.; Miao, C. X.; Li, Y. N. *Green Chem.* **2009**, *11*, 1317–1320.

(4) Wang, X.; Venkataramanan, N. S.; Kawanami, H.; Ikushima, Y. *Green Chem.* **2007**, *9*, 1352–1355.

(5) Wang, J. Q.; Cai, F.; Wang, E.; He, L. N. *Green Chem.* **2007**, *9*, 882–887.

(6) Namboodiri, V. V.; Varma, R. S.; Shale-Demessie, E.; Pillai, U. R. *Green Chem.* **2002**, *4*, 170–173.

(7) Betzemeier, B.; Lhermitte, F.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6667–6670.

(8) Ito, H.; Kusukawa, T.; Fujita, M. *Chem. Lett.* **2000**, 598–599.

(9) Ettedgui, J.; Neumann, R. *J. Am. Chem. Soc.* **2009**, *131*, 4–5.

(10) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796–2797.

(11) Miller, A. L. II; Bowden, N. B. *J. Org. Chem.* **2009**, *74*, 4834–4839.

(12) (a) Sugamoto, K.; Matsushita, Y.; Matsui, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3989–3998. (b) Matsunaga, Y.; Matsui, T.; Sugamoto, K. *Chem. Lett.* **1992**, 1381–1384.

(13) McMillan, J. W.; Fischer, H. E.; Schwartz, J. *J. Am. Chem. Soc.* **1991**, *113*, 4014–4016.

(14) Okamoto, T.; Sasaki, Y.; Sasaki, K.; Oka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4449–4450.

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of Pd. However, to the best of our knowledge, no one-pot and metal-free methods for the direct synthesis of acetophenones from styrenes have been reported so far.

Recently, we have developed various aerobic photo-oxidations under an oxygen atmosphere and visible light (VIS) irradiation.[15] In addition, we reported the aerobic photo-oxidative synthesis of phenacyl halides from styrenes in the presence of halogen sources.[15c,i] These methods are of relevance from a viewpoint of green chemistry due to the use of visible light from a general-purpose fluorescent lamp, molecular oxygen being a terminal oxidant and inexpensive, easily handled halogen sources such as molecular iodine or 48% aq. HBr, and environmentally low impact solvent use. Phenacyl halides are made known as a versatile intermediate in organic synthesis and can be used in various reactions. Representative of such reactions, dehalogenations of phenacyl halides to acetophenone using thiols,[16] indium metal,[17] bis(triphenylstannyl)-selenide,[18] PI_3 or P_2I_4,[19] catalytic telluride reagent/reductant,[20] hydroiodic acid,[21] or iodide ion/Brønsted or Lewis acids[22] have been reported. In 2003, Horiuchi et al.[23] reported that α-iodoketones were converted to α-hydroxyketones with UV irradiation under an air atmosphere and found that α-iodoketones are deiodinated to ketones under photoirradiation. These results prompted us to study the direct transformation of styrenes to acetophenones through one-pot aerobic photo-oxidation/deiodination. Our concept involves (1) aerobic photo-oxidation of styrenes to phenacyl iodides and (2) exchange of solvent and deiodination of phenacyl iodides to acetophenones. These sequences can provide one-pot and metal-free Wacker type oxidation of styrenes to acetophenones. In the course of our effort, we found the facile deiodination of phenacyl iodides with only a catalytic amount of molecular iodine in a small portion of acetone. Herein, we report the one-pot metal-free synthesis of acetophenones from styrenes using molecular iodine (Scheme 1).

Scheme 1. Metal-Free Syntheses of Acetophenones from Styrenes

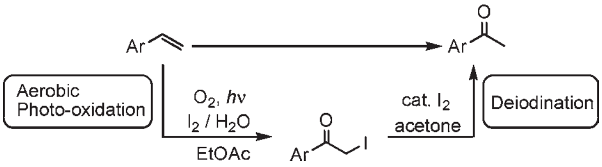
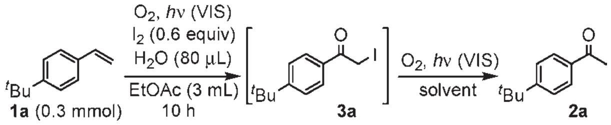


Table 1. Study of Reaction Conditions for Aerobic Photo-oxidation[a]



entry	solvent (mL)	time (h)	**3a** (%)[b]	**2a** (%)[b]
1	EtOAc (5)	10	71	2
2	MeCN (5)	10	73	3
3	MeOH (5)	10	68	1
4	^{i}PrOH (5)	10	63	3
5	THF (5)	10	73	2
6	hexane(5)	10	62	3
7	benzene(5)	10	72	3
8	$CHCl_3$ (5)	10	71	1
9	H_2O (5)	10	76	1
10	acetone (5)	10	trace	82
11[c]	acetone (5)	10	trace	76
12[d]	acetone (5)	10	trace	74
13[e]	acetone (5)	10	trace	85
14[e]	acetone (0.3)	3	trace	81

[a] A solution of 4-*tert*-butylstyrene (**1a**; 0.3 mmol), iodine (0.6 equiv), and H_2O (80 μL) in EtOAc (3 mL) under an O_2 atmosphere was stirred and irradiated externally with four 22 W fluorescent lamps. After 10 h, the reaction mixture was concentrated *in vacuo* and solvent was added and stirred for the indicated time. [b] ^{1}H NMR yields. [c] The reaction was carried out under a N_2 atmosphere in the deiodination step. [d] The reaction was carried out in the dark in the deiodination step. [e] The reaction was carried out under air and negative irradiation in the deiodination step.

Table 1 shows the results involving optimization of reaction conditions for aerobic photo-oxidation/deiodination of 4-*tert*-butylstyrene (**1a**) as a test substrate. The reaction conditions were examined with 4-*tert*-butylstyrene (**1a**) in the presence of iodine under an oxygen atmosphere (O_2 balloon) and VIS irradiation,[15] followed by concentration of the reaction mixture and addition of solvent. Among the various solvents examined, only acetone was effective as a solvent for deiodination (entries 1–10), and the corresponding acetophenone (**2a**) was obtained in good yield (entry 10). Furthermore, we found

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[15] (a) Kanai, N.; Nakayama, H.; Tada, N.; Itoh, A. *Org. Lett.* **2010**, *12*, 1948–1951. (b) Hirashima, S.; Nobuta, T.; Tada, N.; Miura, T.; Itoh, A. *Org. Lett.* **2010**, *12*, 3645–3647. (c) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2010**, 2335–2339. (d) Tada, N.; Ban, K.; Hirashima, S.; Miura, T.; Itoh, A. *Org. Biomol. Chem.* **2010**, *8*, 4701–4704. (e) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. *Tetrahedron Lett.* **2010**, *51*, 4576–4578. (f) Hirashima, S.; Itoh, A. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 748–756. (g) Hirashima, S.; Itoh, A. *Photochem. Photobiol. Sci.* **2007**, *6*, 521–524. (h) Hirashima, S.; Itoh, A. *Green Chem.* **2007**, *9*, 318–320. (i) Nakayama, H.; Itoh, A. *Tetrahedron Lett.* **2007**, *48*, 1131–1133. (j) Nakayama, H.; Itoh, A. *Chem. Pharm. Bull.* **2006**, *54*, 1620–1621.

[16] (a) Fuji, K.; Node, M.; Kawabata, T.; Fujimoto, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1043–1047. (b) Fuji, K.; Node, M.; Kawabata, T.; Fujimoto, M. *Chem. Lett.* **1984**, 1153–1156. (c) Seshadri, R.; Pegg, W. J.; Israel, M. *J. Org. Chem.* **1981**, *46*, 2696–2598.

[17] (a) Pauk, L.; Keum, G.; Kang, S. B.; Kim, K. S.; Kim, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4462–4463. (b) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1139–1140.

[18] Schultz, E. K. V.; Harpp, D. N. *Synthesis* **1998**, 1137–1140.

[19] Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 1431–1432.

[20] Huang, Z. Z.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 5320–5326.

[21] (a) Penso, M.; Mttadelli, S.; Albanese, D. *Synth. Commun.* **1993**, *23*, 1385–1391. (b) Mandal, A. K.; Nijasure, A. M. *Synlett* **1990**, 554.

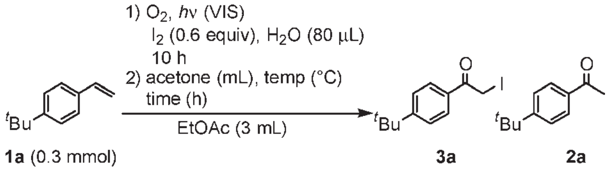
[22] (a) Ono, A.; Kamimura, J.; Suzuki, N. *Synthesis* **1987**, 406–407. (b) Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1980**, 3195–3198. (c) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, *45*, 3531–3532. (d) Townsend, J. M.; Spencer, T. A. *Tetrahedron Lett.* **1971**, 137–140.

[23] (a) Chi, W.; Takeda, A.; Hara, M.; Ji, S. J.; Horiuchi, C. A. *Tetrahedron* **2005**, *61*, 2453–2463. (b) Horiuchi, C. A.; Takeda, A.; Chi, W.; Ohwada, K.; Ji, S. J.; Takahashi, T. T. *Tetrahedron Lett.* **2003**, *44*, 9307–9311.

that both molecular oxygen and VIS irradiation were not necessary in the deiodination step (entries 11–13). As a result of detailed examinations, the optimal result was obtained when using 0.3 mL of acetone for 3 h (entry 14).

To simplify this reaction, acetone was directly added to the reaction mixture without removal of ethyl acetate *in vacuo* after aerobic photo-oxidation (Table 2). At room temperature, deiodination proceeded slowly in spite of using 1 mL of acetone; however, after the temperature was raised to 60 °C, the reaction was smoothly carried out (entries 1 and 2). As a result of detailed examinations, the optimal result was obtained by using 0.3 mL of acetone (entry 3).

Table 2. Study of Reaction Conditions for the One-Pot Synthesis of Acetophenone (**2a**) from Styrene (**1a**)[a]



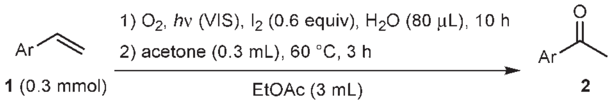
entry	acetone (mL)	temp (°C)	time (h)	**2a** (%)[b]	**3a** (%)[b]
1	1.0	r.t.	12	47	40
2	1.0	60	3	80	trace
3	0.3	60	3	83 (85)	trace

[a] A solution of 4-*tert*-butylstyrene (**1a**; 0.3 mmol), iodine (0.6 equiv), and H_2O (80 μL) in EtOAc (3 mL) under an O_2 atmosphere was stirred and irradiated externally with four 22 W fluorescent lamps. After 10 h, acetone was added to the reaction mixture and stirred for the indicated time and temperature. [b] ^{1}H NMR yields. Number in parentheses is isolated yield.

Table 3 presents the scope and limitation of one-pot and metal-free syntheses of acetophenones from styrenes. In general, the corresponding acetophenones were obtained in good yields regardless of an electron-donating or -withdrawing group at the aromatic ring (entries 1–3, 5–7). *o*-Methylstyrene (**1d**) and 2-vinylnaphtharene (**1h**) were converted to the corresponding acetophenones **2d** and **2h** in moderate yields since these were poor substrates for aerobic photo-oxidative syntheses of phenacyl iodides (entries 4 and 8).[15] 2-Vinylpyridine (**1i**), a heterocyclic compound, also provided the corresponding ketone **2i** in moderate yields. In this reaction, deiodination of 2-iodo-1-(2-pyridinyl)ethanone, which was synthesized separately, was slow under the typical conditions, probably due to the basic nature of pyridine. Thus, addition of trifluoroacetic acid accelerated the deiodination (entry 9).

To clarify the reaction mechanism, we studied deiodination of phenacyl iodide under several reaction conditions (Table 4). When phenacyl iodide (**3b**) was treated with acetone in ethylacetate without iodine at 60 °C for 3 h, deiodinated product **2b** was not obtained at all (entry 1); however, interestingly, deiodination proceeded smoothly in the presence of 0.2 equiv of iodine to afford the corresponding acetophenone (**2b**) in good yields (entry 2).

Table 3. Scope and Limitation[a]

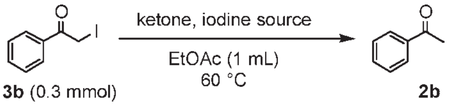


entry	Ar	product	yield (%)[b]
1	C_6H_5	**2b**	69 (85)
2	*p*-^{t}Bu-C_6H_4	**2a**	85
3	*p*-Me-C_6H_4	**2c**	86
4	*o*-Me-C_6H_4	**2d**	42
5[c]	*p*-MeO-C_6H_4	**2e**	75
6	*p*-Cl-C_6H_4	**2f**	85
7[d]	*p*-NO_2-C_6H_4	**2g**	76
8[e]	2-naphthalenyl	**2h**	60
9[c,f]	2-pyridinyl	**2i**	64

[a] A solution of substrate (0.3 mmol), iodine (0.6 equiv), and H_2O (80 μL) in EtOAc (3 mL) under an O_2 atmosphere was stirred and irradiated externally with four 22 W fluorescent lamps. After 10 h, acetone (0.3 mL) was added and stirred for 3 h at 60 °C. [b] Isolated yields. Number in parentheses is ^{1}H NMR yield. [c] The reaction was carried out with NIS (1.2 equiv) and H_2O (180 μL) in EtOAc (5 mL) for 7 h in the oxidation step. [d] The reaction was carried out for 15 h in the oxidation step. [e] The reaction was carried out for 24 h in the oxidation step. [f] Trifluoroacetic acid (1.0 equiv) was added in the deiodination step.

Use of 2-heptanone (1 equiv) as a ketone instead of acetone in the presence of iodine results in acetophenone (**2b**), 3-iodo-2-heptanone, and 1-iodo-2-heptanone in 79%, 68%, and 7% yields, respectively (entry 3). In marked contrast, deiodination was not carried out without either iodine or ketone (entries 4 and 5). These results suggest that the deiodination requires both a stoichiometric amount of ketone and a catalytic amount of iodine. HI has been known as a dehalogenative reagent for phenacyl halides,[21] so deiodination may proceed by HI generated at the aerobic photo-oxidation or deiodination step. Acetophenone (**2b**) was obtained from phenacyl iodide (**3b**) by treatment of 55% aq. HI (0.4 equiv)

Table 4. Study of Deiodination

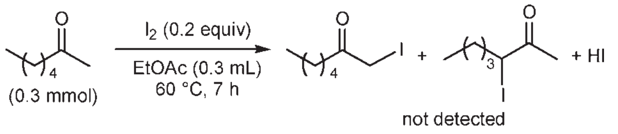


entry	ketone	additive (equiv)	time (h)	**2b** (%)[a]	**3b** (%)[a]
1	acetone (0.3 mL)	I_2 (0)	3	trace	90
2	acetone (0.3 mL)	I_2 (0.2)	3	82	3
3[b,c]	2-heptanone (1 equiv)	I_2 (0.2)	7	79	11
4[c]	2-heptanone (1 equiv)	I_2 (0)	7	0	100
5	–	I_2 (0.2)	3	trace	88
6	acetone (0.3 mL)	55% aq HI (0.4)	3	88	7
7	–	55% aq HI (0.4)	2	27	77

[a] ^{1}H NMR yields. [b] 3-Iodo-2-heptanone (68%) and 1-iodo-2-heptanone (7%) were obtained. [c] EtOAc (0.3 mL) was used.

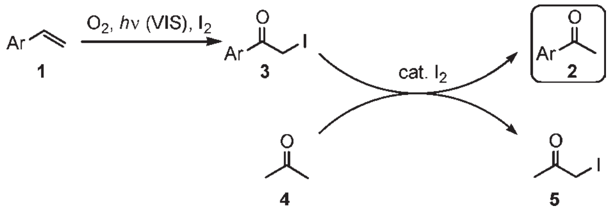
(entries 6 and 7); however, we found that deiodination proceeded minimally without acetone in our one-pot reaction (Table 1, entries 1−9), compared to the formation of **2b** in 27% yield in the presence of HI without acetone (Table 4, entry 7). Furthermore, the result that no iodinated product was obtained when 2-heptanone was treated with iodine in ethyl acetate indicates that HI was not generated in the deiodination step (Scheme 2). These results suggest that HI does not contribute to deiodination. And it was found that various acids were efficient for deiodination of phenacyl iodides.[24,25]

Scheme 2. Study of Deiodination



Scheme 3 shows the postulated reaction mechanism for these aerobic photo-oxidation/deiodination reactions, based on the results mentioned above. First, styrenes **1** are oxidized to phenacyl iodides **3** with iodine under an oxygen atmosphere and VIS irradiation, and HI, generated *in situ*, is also oxidized to iodine.[15] In the second deiodination step, iodine, which remains at the amount of at least 0.1 equiv in the oxidation step and functions as a Lewis acid,[26] activates both phenacyl iodides **3** and acetone **4** to provide the enol of acetone.[27] This enol results from nucleophilic attack on the iodine atom of phenacyl iodide activated by iodine to produce acetophenone **2**. Finally, acetone (**4**) is transformed to 2-iodoacetone (**5**).

Scheme 3. Plausible Reaction Path



In conclusion, we report a facile aerobic photo-oxidation/deiodination of styrenes to acetophenones with iodine under molecular oxygen and VIS irradiation. This novel reaction is interesting as it uses only 0.6 equiv of molecular iodine for both aerobic photo-oxidation and deiodination and provides the first report of metal-free direct syntheses of acetophenones from styrenes.

Supporting Information Available. Experimental details and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) When 4-*tert*-butylphenacyl iodide (**3a**) was treated to several acids, such as *p*-TSA·H_2O, TFA, $AlCl_3$, or BF_3·OEt_2, in 0.3 mL of acetone, 4′-*tert*-butylacetophenone (**2a**) was obtained in 80%, 38%, 72%, and 55% yields, respectively.

(25) Lee, J. C.; Bae, Y. H. *Synlett* **2003**, 507–508.

(26) Iodine has been used as a Lewis acid in organic synthesis. See: (a) Rao, M. L. N.; Jadahav, D. N. *Tetrahedron Lett.* **2006**, *47*, 6883–6886. (b) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett.* **2006**, *8*, 2491–2494. (d) Lee, B. S.; Mahajan, S.; Janda, K. D. *Synlett* **2005**, 1325–1327. (e) Phukan, P. *Tetrahedron Lett.* **2004**, *45*, 4785–4787. (f) Bhosale, R. S.; Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 7187–7188. (g) Chavan, S. P.; Kale, R. R.; Shivasankar, K.; Chandake, S. I.; Benjamin, S. B. *Synthesis* **2003**, 2695–2698. (h) Karimi, B.; Golshani, B. *Synthesis* **2002**, 784–788. (i) Yadav, J. S.; Chand, P. K.; Anjaneyulu, S. *Tetrahedron Lett.* **2002**, *43*, 3783–3784. (j) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Synlett* **2002**, 319–321. (k) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Rao, K. V. *J. Chem Soc., Perkin Trans. 1* **2002**, 1401–1404. (j) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527–7529.

(27) 4-Methoxystyrene (**1e**) and 2-vinylpyridine (**1i**) were oxidized with *N*-iodosuccinimide (NIS), but the black dark purple color of the reaction mixture indicates that iodine was generated *in situ*.