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Facile synthesis of phenacyl iodides from styrenes under visible light irradiation with fluorescent lamps

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Abstract—Phenacyl iodides were easily synthesized from styrenes with iodine under irradiation of visible light from a fluorescent lamp.

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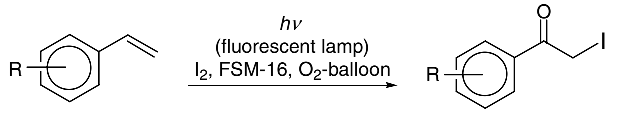
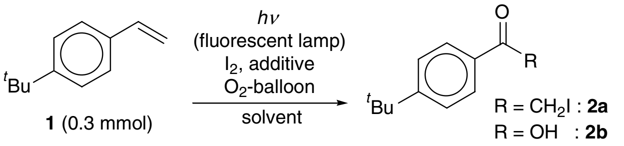
α-Halo ketones are important intermediates for many chemical products, and have attracted a great deal of interest.[1] Among them, phenacyl bromides and chlorides are commercially available and are the most widely-used α-halo ketones, while phenacyl iodides have been scarcely used due to their instability, and the few synthetic methods available are tedious and use complex and environmentally high-impact reagents. Thus far, the methods can be classified into two categories by the starting material, namely, styrene derivatives[2] or acetophenone derivatives.[3] Among them, styrene derivatives are, in general, less expensive than acetophenone derivatives, and are more suitable for large-scale synthesis. With this background in mind, we have engaged in the development of environmentally benign reactions under photo-irradiation, and already found that styrenes afforded benzoic acids, which were oxidatively cleaved at the double bond in the presence of a catalytic amount of iodine and FSM-16, a mesoporous silica, under irradiation of UV.[4] In the course of our further study of these reaction conditions, we also found the formation of a small amount of phenacyl iodides in



Scheme 1.

Table 1. Study of reaction conditions of synthesis of 4-*tert*-butylphenacyliodide under irradiation of visible light



Entry	I_2 (equiv)	Additive (mg)	Solvent	Time (h)	Yield[a] (%)	
					2a	**2b**
1	0.3	—	EtOAc	10	30	15
2	0.3	—	EtOAc	48	0	46
3	0.5	—	EtOAc	10	43	Trace
4	1.0	—	EtOAc	10	50	0
5	1.0	FSM-16 (100)	MeCN	10	22	0
6	1.0	FSM-16 (100)	Acetone	10	Trace	0
7	1.0	FSM-16 (100)	$^iPr_2O$	10	43	0
8	1.0	FSM-16 (100)	Hexane	10	17	0
9	1.0	FSM-16 (100)	EtOAc	10	64	0
10	0.5	FSM-16 (100)	EtOAc	10	54	Trace
11	1.0	FSM-16 (200)	EtOAc	10	74	0
12	1.0	FSM-16 (200)	EtOAc	10	Trace	0[b]
13	1.0	FSM-16 (200)	EtOAc	10	0	0[c]
14	—	FSM-16 (200)	EtOAc	10	0	0
15	1.0	FSM-16 (200)	EtOAc	24	65	Trace
16	1.0	FSM-16 (300)	EtOAc	10	71	0
17	1.0	MCM-41 (200)	EtOAc	10	67	0
18	1.0	H-Y (200)	EtOAc	10	45	0
19	1.0	Na-Y (200)	EtOAc	10	30	0
20	1.0	H-ZSM-5 (200)	EtOAc	10	56	0
21	1.0	SiO_2 (200)	EtOAc	10	53	0

[a] All yields are for pure, isolated products.
[b] The reaction was carried out in the dark.
[c] The reaction was carried out under Ar atmosphere.

Keywords: Iodine; Phenacyl iodides; Styrenes; Visible light.

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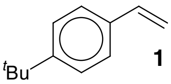
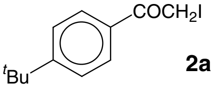
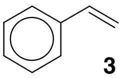
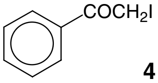
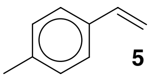
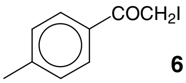
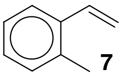
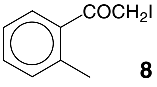
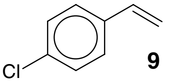
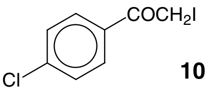
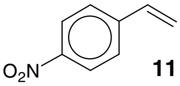
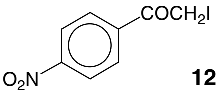
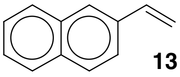
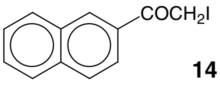
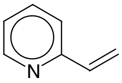
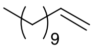
some cases. This is the driving force of our further study on this reaction, and we have successfully found that phenacyl iodides were selectively obtained under suppression of the formation of benzoic acids under irradiation of VIS from a general-purpose fluorescent lamp. In this Letter, we report our detailed study of the generality of synthesis of phenacyl iodides from styrenes under irradiation of visible light (Scheme 1).

Table 1 shows the results of our study of reaction conditions conducted with 4-*tert*-butylstyrene (**1**) as a test substrate under external irradiation by a general-purpose fluorescent lamp in the presence of iodine in an oxygen atmosphere.[5] In general, the yield of 4-*tert*-butylphenacyliodide (**2a**) decreased, and the yield of 4-*tert*-butylbenzoic acid (**2b**) increased when the reaction was conducted for a longer reaction time in the presence of a small amount of iodine (entries 1–4). We were surprised to find that the addition of FSM-16[6] and MCM-41,[7] mesoporous silicas,[8] increased the yield of **2a** (entries 9–11, 16 and 17). Other additives, H-Y,[9] Na-Y[9] and H-ZSM-5,[9] which are typical zeolites, and silica gel[10] were not effective (entries 18–21). Among the solvents examined, ethyl acetate was found to most efficiently afford **2a** (entries 5–9). That no oxidation proceeded or hardly proceeded without either irradiation by a fluorescent lamp or the addition of iodine shows the necessity of both for this reaction (entries 12 and 14). Furthermore, from the fact that **2a** was not obtained when conducting the reaction under the flow of argon, we can assume that the actual oxidant in this reaction is molecular oxygen (entry 13).

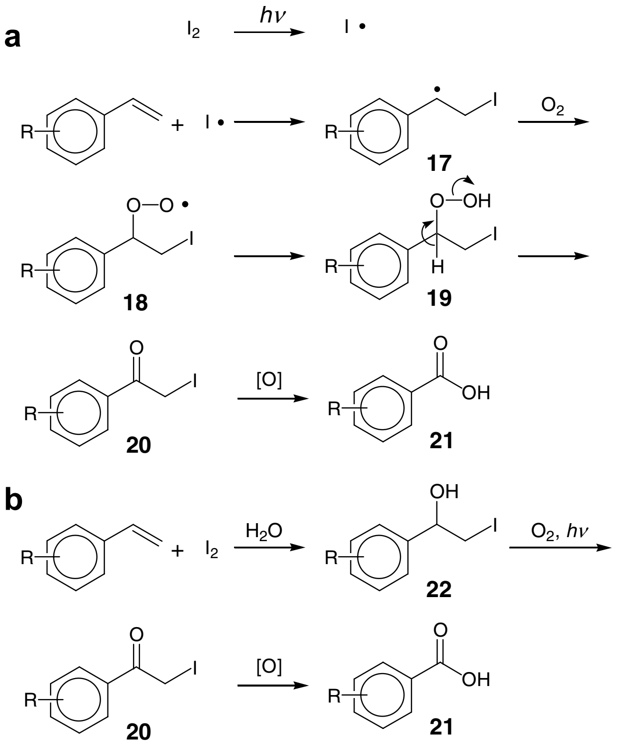
Table 2. Synthesis of phenacyl iodides from styrenes under irradiation of visible light

$$\text{substrate} \xrightarrow[\text{EtOAc, 10 h}]{h\nu\,\text{(fluorescent lamp), O}_2\text{-balloon}\quad \text{I}_2\,\text{(1.0 equiv.), FSM-16 (200 mg)}} \text{product}$$

Entry	Substrate	Product	Yield[a] (%)
1	 **1**	 **2a**	74
2	 **3**	 **4**	73
3	 **5**	 **6**	68
4	 **7**	 **8**	38[b]
5	 **9**	 **10**	72
6	 **11**	 **12**	77
7	 **13**	 **14**	46
8	 **15**	—	0
9	 **16**	—	0

[a] All yields are for pure, isolated products.

[b] 2-Iodo-1-(2-methylphenyl)ethanol (19%) was also obtained.



Scheme 2. Plausible paths for oxidation of styrenes to phenacyl iodide.

Table 2 shows the scope and limitations of this reaction using several styrene derivatives. In general, the corresponding phenacyl iodides were afforded in good yields regardless of an electron-donating group or electron-withdrawing group at the aromatic nucleus (entries 1–3, 5 and 6).[11] Since steric hindrance of the group at the aromatic nucleus slowed down the reaction rate, only 38% of **8** and 19% of 2-iodo-1-(2-methylphenyl)ethanol were afforded when using 2-methylstyrene (**7**) as the substrate. 2-Vinylnaphthalene (**13**) also reacted in a similar manner, and afforded the corresponding iodomethyl 2-naphthyl ketone (**14**) in a moderate yield (entry 7). Unfortunately, 2-vinylpyridine (**15**), which is a heterocyclic compound, gave a complex mixture and the corresponding product was not detected by NMR. On the other hand, a nonconjugated alkene, 1-dodecene (**16**), was intact under this condition (entries 8 and 9).

Scheme 2 shows two possible paths of this oxidation, which are postulated by considering the necessity of continuous irradiation and molecular oxygen in this reaction, and the result in the presence of galvinoxyl, which is a radical trap reagent.[12] Path (a) includes radical species **17**, which is thought to be generated by addition of an iodo radical, formed by irradiation of VIS from iodine. The radical species traps molecular oxygen to afford peroxy radical species **18**, which subsequently transforms to phenacyl iodide **20** via hydroperoxide **19**. We believe further oxidation to the corresponding benzoic acids **21** occurred when the reaction took longer time. The role of FSM-16 in this reaction is not yet clear; however, we think that it takes part in acceleration of both cleavage of iodine to an iodo radical and dehydration of **19** to afford **20**. On the other hand, path (b) includes the *vic*-iodohydrin intermediate **22**, which is transformed to **20** by aerobic photo-oxidation at the benzylic position.

In conclusion, this new method for the preparation of phenacyl iodides is convenient in the viewpoint of using inexpensive styrenes as the starting material and visible light irradiated from a general-purpose fluorescent lamp, and is thought to be environmentally benign, due to all the factors of the use of safe reagents, molecular oxygen as the terminal oxidant, EtOAc of environmentally low impact as solvent, and non-use of metals.

References and notes

1. For a recent review, see: Takami, K.; Usugi, S. I.; Yorimitsu, H.; Oshima, K. *Synthesis* **2005**, 824–839.
2. (a) Evans, R. D.; Schauble, J. H. *Synthesis* **1986**, 727–730; (b) Cardillo, G.; Shimizu, M. *J. Org. Chem.* **1977**, *42*, 4268–4270.
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4. Itoh, A.; Kodama, T.; Masaki, Y.; Inagaki, S. *Synlett* **2002**, 522–524.
5. *A typical procedure follows*: A solution (5 mL) of 4-*tert*-butylstyrene (0.3 mmol) and I_2 (1 equiv) in dry ethyl acetate in a Pyrex test tube under aerobic conditions was stirred and irradiated with four 22-W fluorescent lamps, which were set up at a distance of 65 mm, for 24 h. The temperature of the final stage of this reaction was about 50 °C. The reaction mixture was concentrated under reduced pressure, and the pure product was obtained by preparative TLC.
6. (a) Inagaki, S.; Koiwai, A.; Suzuki, N.; Fukushima, Y.; Kuroda, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1449–1457; (b) Inagaki, S.; Fukushima, Y.; Kuroda, K. *J. Chem. Soc., Chem. Commun.* **1993**, 680–682.
7. Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710–712.
8. IUPAC recommends classification of pores to micropore ($D < 2$ nm; D, pore diameter) and mesopore (2 nm < $D < 50$ nm), see: Everett, D. H. *Pure Appl. Chem.* **1972**, *31*, 579–638.
9. H-Y, Na-Y and H-ZSM-5 were purchased from TOSOH Co.
10. Silica gel (230-400 mesh) was purchased from Merck Co.
11. When using 4-methoxystyrene as the substrate, the product was a complex mixture, and the corresponding carboxylic acid or product of iodination at the aromatic nucleus was not detected.
12. In the presence of 0.1 equiv of galvinoxyl, 40% of 4-*tert*-butylphenacyliodide and 23% of 2-iodo-1-(4-*tert*-butylphenyl)ethanol were obtained when using 4-*tert*-butylstyrene as the substrate.