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Metal-Free Photoinduced Transformation of Aryl Halides and Diketones into Aryl Ketones

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Abstract: The acylation of aryl halides to prepare aryl ketones without metal catalyst represents an important yet challenging topic towards more sustainable ketone synthesis. Herein, we describe a simple and efficient metal-free protocol for the acylation of aryl halides with diketone under the irradiation of light utilizing *N*-methylpiperidine base in an air atmosphere. This reaction can tolerate a wide range of functional groups and the corresponding ketones can be obtained in modest to good yields.

Introduction

Photo-induced organic reactions have opened a new era for the preparation of diverse important organic molecules in novel and meaningful ways.¹ Via light as the energy input, photoreactions can be carried out without catalysts.² More significantly, photoreactions could realize transformations challenging to achieve by traditional methodologies,³ thus complementing conventional reactions, especially the metal-catalyzed ones.

The reaction of aryl halides with carbonyl derivatives through a mediator represents one of the most useful and traditional reactions to prepare aryl ketones (Eq. 1).⁴⁻⁵ Among these, the most common reactions are via the preparation of organometallic species such as the Grignard reagent, which subsequently reacts with acyl derivatives (Scheme 1a).⁴ Such standard approaches require stoichiometric metals (and generate stoichiometric metal wastes), and are less sustainable. As an important alternative to the conventional use of stoichiometric organometallic reagents, MacMillan reported in 2015 the formation of aryl ketones by utilizing a photoredox system, through a nickel-catalyzed decarboxylative coupling of α -oxo acids with aryl halide via a radical intermediate (Scheme 1b).⁵

To the best of our knowledge, however, the metal-free coupling of aryl halide with carbonyl derivatives has yet to be developed. Recently, we have uncovered a series of metal-free light-enabled chemical transformations that traditionally require transition-metal catalysts or organometallic reagents.^{2b-2d,3a,3c,6} We thus considered the possibility of directly coupling aryl halides with carbonyl compounds to obtain aryl ketones facilitated by light under metal-free conditions (Scheme 1c). Our hypothesis consists of two steps. First, under light irradiation with the assistance of a base, aryl radical will be generated from

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aryl halide (Scheme 1d). Subsequently, the aryl radical intermediate can add to the carbonyl group to form aryl ketone after the elimination of the leaving group.

However, it is challenging for the addition of a radical intermediate to carbonyl group due to the formation of a thermodynamically unfavorable alkoxy radical intermediate,⁷ which would preferentially undergo C-C β -scission to form a more stable radical.⁸ In addition, the hydrogen abstraction from the solvent or other organic substrates by alkoxyl and aryl radical intermediates are potential side reactions considering the high reactivity of oxygen radical and aryl radical (Scheme 1c).^{7a,9} To overcome these challenges, a good leaving group is beneficial, which will accelerate the desired reaction and compete with other side reactions. Furthermore, the use of a reducing base such as amine can promote the formation of aryl radical through a single electron transfer process.¹⁰



a) Well-studied process to convert	aryl halides into aryl ketones ⁴
Metal: Mg, Cu	
Ar-X Zn, Pd, etc. Ar-M-X	or (RCO) ₂ O etc.

(b) Coupling of aryl halides with carbonyl radical intermediate from decarboxylation process (MacMillan's group)⁵







Scheme 1. Reactions of aryl halide with carbonyl derivatives.

Results and Discussion

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To begin the study, the reaction of 4-iodoanisole (1a) and diacetyl (2a) was chosen as a model reaction (Table 1). To our delight, under photo-irradiation (254 nm, 2.5 W*20) for 25 h in acetonitrile with triethylamine as base, the desired product was obtained in 17% yield (Table 1, entry 1). To minimize the side reactions of hydrogen abstraction by alkoxyl and aryl radical intermediates, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was used as the solvent. Gladly, the yield could be increased to 33% (Table 1, entry 2). Replacing triethylamine with Nmethylpiperidine (MP) is beneficial and the yield could be improved to 70% (Table 1, entry 3). Attempts to improve the yield by using other solvents such as carbon disulfide or dimethylsulfoxide were not successful (Table 1, entries 4 and 5). Various amounts of HFIP or diacetyl as well as the use of argon atmosphere were evaluated (Table 1, entries 6-12) and excellent NMR yield (95%, isolated yield 81%) could be achieved when 0.12 mL of diacetyl and 0.3 mL of HFIP were used (Table 1, entry 12).11

Table 1. Optimization of reaction conditions[a]

solvent, hv 30 °C, air, 25 h 1a (0.1 mmol) 2a

			•
Entry	2a /mL	Others	Yield/%
1	0.2	CH ₃ CN(0.3 mL), NEt ₃ (1 equiv)	17
2	0.2	HFIP (0.3 mL), NEt ₃ (1 equiv)	33
3	0.2	HFIP (0.3 mL), MP (1 equiv)	70
4	0.2	CS ₂ (0.3 mL), MP (1 equiv)	trace
5	0.2	DMSO (0.3 mL), MP (1 equiv)	trace
6	0.2	HFIP (0.35 mL), MP (1 equiv)	62
7	0.2	HFIP (0.25 mL), MP (1 equiv)	67
8	0.15	HFIP (0.3 mL), MP (1 equiv)	60
9	0.1	HFIP (0.3 mL), MP (1 equiv)	76
10 ^[b]	0.1	HFIP (0.3 mL), MP (1 equiv)	73
11	0.08	HFIP (0.3 mL), MP (1 equiv)	63
12	0.12	HFIP (0.3 mL), MP (1 equiv)	95(81)

Abbreviations: HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol; MP, Nmethylpiperidine. [a] All the reactions were conducted with 1a (0.1 mmol), 2a, solvent, amine (0.1 mmol) at 30 °C under air in a quartz tube irradiated by light (254 nm) for 25 h unless otherwise specified. ¹HNMR analysis with Yields were determined by 1,3,5trimethylbenzene as internal standard. The yield in parentheses represented isolated one after purified by TLC. [b] The reaction was carried out in argon.

With the optimized conditions established, the scope of this reaction was subsequently explored (Scheme 2). Various substituted aryl iodides including 3-methoxy (3b), 3-methyl-4methoxy (3c), -OBn (3d), -OEt (3e), -NHAc (3f, 3g, 3h), -NHBoc (3i, 3j, 3k), methyl (3l, 3m) and di-methyl (3n, 3o) substituted, as well as non-substituted (3p) could give the

desired products in good to excellent yields by using this protocol, although some of the substrates required longer reaction time (3c, 3e, 3g, 3h, 3m). In addition, fluoride (3q) and 4-OCF₂H (3r) substituents could be tolerated as well, giving 36% and 41% yields, respectively. More significantly, some products obtained by this method are difficult to prepare by traditional means. For example, while ketone 30 is difficult to synthesize by the widely used Friedel-Crafts reaction with acetyl chloride and o-xylene, it could be readily accessible by this protocol.

Not only the diacetyl can serve as the ketone donor, other diketones can also participate in this reaction. For example, when 3,4-hexanedione was employed, the acylation of aryl iodide proceeded smoothly to give ketone 3s in 39% yield. When 2,3-pentanedione was used instead, products 3b and 3s could be obtained in moderate yields with nearly 1:1 ratio (Scheme 2).



^[a]All reactions were conducted with 1 (0.1 mmol), diacetyl (2a, 0.12 mL), HFIP (0.3 mL), N-methylpiperidine (0.1 mmol) at 30 °C under air in a quartz tube irradiated by UV light (254 nm) for 25 h unless otherwise specified. Yields were determined after purified by TLC. ^[b]40 h. ^[c]36 h. ^[d]3,4-hexanedione (2b, 0.10 mL, 0.82 mmol) was used. [e]2,3-pentanedione (2c, 0.10 mL, 0.96 mol) was used.

Scheme 2. Scope of the metal-free acylation reaction [a]

Other less reactive aryl halides such as aryl bromides and aryl chlorides were also evaluated (Eq. 2-5). Aryl bromides can smoothly deliver the corresponding products (3a, 3p, 3t) in

AcHN

BocHN

Me

modest to good yields (Eq. 2-4). Product **3p** was obtained in 32% yield for the less activated substrate chlorobenzene (**5a**, Eq. 5).



To understand the reaction mechanism, the crude reaction mixture was analyzed by GC-MS, which showed the side product of Ar-H via hydrogen abstraction by aryl radical intermediate derived from aryl halide. This side product is especially prominent for substrates with 4-hydroxyl or 2-carboxylic group. For example, 83% of PhCO₂H was obtained for the reaction of 2-iodobenzoic acid (**1s**) with diacetyl (**2a**) under standard conditions with 2 equiv of *N*-methylpiperidine as the base (Eq. 6). Without the use of *N*-methylpiperidine, only 40% of PhCO₂H was obtained (Eq. 7). Thus, the use of amine could promote the reduction of aryl halides. Moreover, compound **7**, which was derived from the reaction of acetyl radical with diacetyl (**2a**), was observed as a byproduct in all these reactions. This observation is consistent with the mechanism described above (Scheme 1c).



Conclusion

In conclusion, we described herein a simple and efficient method to convert aryl halides into aryl ketones with the irradiation of light under metal-free conditions. Via this strategy, aryl ketones can be prepared readily from aryl halides in modest to high yields at room temperature under air, tolerating various functional groups. More significantly, this work demonstrates the successful coupling of radical intermediates with C=O double

bond in the preparation of ketones without the use of any metal. This protocol allows to be expanded to other reaction systems that involve the formation of aryl radical intermediates. Further exploration of the methodologies is on the way in our laboratory, which will be reported in due course.

Experimental Section

All commercially available compounds were used without further purification. NMR spectra were recorded on Agilent-NMR-VNMRs 400 spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced to chloroform-d (7.16 ppm) for ¹HNMR, chloroform-d (77.16 ppm) for ¹³CNMR. Thin-layer chromatography (TLC) was performed with Qing Dao TLC silica gel 60 F₂₅₄. Photoreactors with household UV lamps was from Philips Company (TUV, 2.5 W each, 47 V, T5 16 mm).

Procedure for the reaction of arylhalide1, **4** or **5** with diketone **2** in the synthesis of aryl ketone **3**: To a 10 mL quartz flask under air was added arylhalide1, **4** or **5** (0.1 mmol) and diacetyl (**2a**, 0.12 mL, 1.38 mmol) for **3a-3r**, or 3,4-hexanedione (**2b**, 0.10 mL, 0.82 mmol) for **3s**, or 2,3-pentanedione (**2c**, 0.10 mL, 0.96 mmol). Then, (CF₃)₂CHOH (HFIP, 0.3 mL, dried over 3 Å molecular sieve before using) and 1-methylpiperidine (12 μ L, 0.1 mmol) were added subsequently. The reaction mixture was irradiated in the photoreactors with household UV lamps (254 nm, 2.5 W*20) at 30 °C. After the time indicated in Scheme 2 and Eq. 2-5, the reaction mixture was concentrated and purified by TLC on silica gel with eluent (petroleum ether : EtOAc 50:1 or 3:2) to give aryl ketone **3**.

Acknowledgements

This work is supported by NSERC, FQRNT, CFI, McGill University and the Canada Research Chair. Q. Yao is grateful for NSFC (Nos 21462056, 21801261) and China Scholarship Council (CSC).

Keywords: Photosynthesis • radical reactions • cross-coupling • metal-free

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- [11] Other conditions were also examined with PhI and diacetyl as model substrates by using a standard LZC-4V photoreactor from Luzchem Company (254 nm, 2.5 W*8). Please see the Electronic Supplementary Information.

10.1002/ejoc.201801650

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