



WILEY-VCH

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

Visible-Light-Promoted Synthesis of 1,4-Dicarbonyl Compounds via Conjugate Addition of Aroyl Chlorides

Chao-Ming Wang,[†] Dan Song,[†] Peng-Ju Xia, Jing Wang, Hao-Yue Xiang,^{*} Hua Yang^{*}

Abstract: A facile visible-light photocatalytic conjugate addition to prepare 1,4-dicarbonyl compounds has been developed by employing readily available aroyl chlorides as aryl radical sources. This operationally simple method shows broad scope with regard to both aroyl chlorides and Michael acceptor. As a result, a variety of 1,4-diketones were efficiently synthesized in moderate to good yields.

1,4-Dicarbonyl compounds are intriguing motifs and versatile precursors in numerous heterocyclic compounds and bioactive natural compounds.^[1] Undoubtedly, they have gained considerable attention in respect to their synthetic pathways.^[2] Of all the reported methods, conjugate addition of acyl radicals to α , β -unsaturated carbonyl compounds is considered as the most straightforward and efficient synthetic route.^[3] Traditional approaches to generate acyl radical mostly rely on harsh reaction conditions - UV irradiation or high temperature with relatively low yield.^[4] In this context, generation of acyl radical under mild conditions would be highly desirable to overcome the hurdle of this attractive methodology.

Over the past years, photoredox catalysis has emerged as a promising route to construct complex scaffolds that are otherwise difficult to be prepared by traditional methods.^[5] To date, a number of radicals have been effectively generated via visible-light photoredox catalysis to participate in a wide range of chemical transformations, giving birth to effective solutions for the synthesis of challenging and complex compounds.^[6] Recently, much attention has been directed to the conjugate addition of acyl radical to olefins. In 2015, Fu group reported a photoredox-catalyzed decarboxylative coupling, in which a-oxocarboxylic acids were employed to generate acyl radicals.^[7] Ye and co-workers used carboxylic anhydrides as the source of acyl radical to prepare 1,4-dicarbonyl compounds.^[8] In 2017, Gryko and co-workers reported the application of 2-S-pyridyl thioesters as acyl radical sources by using vitamin B12 derivative as photocatalyst.^[9] More recently, Wang described the generation of acyl radicals through C_{sp}^2 -H activation of aldehydes with quinuclidine as co-catalyst.^[10] Noticeably, though encouraging advance has been achieved in this field, current methodologies frequently suffer from the availability of substrate - requiring multistep synthesis for their preparation or costly large-scale preparation. This dilemma for acyl source would surely restrict broad application of this straightforward pathway. As we know,

 [a] Dr. C.-M. Wang, D. Song, Dr. P.-J. Xia, Dr. J. Wang, Dr. X.-Y. Xiang Prof. Y. Yang
 College of Chemistry and Chemical Engineering

Central South University

Changsha 410083, P. R. China

e-mail: hyangchem@csu.edu.cn; xianghaoyue@csu.edu.cn

[b] [†]C. Wang and D. Song contributed equally.

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

aroyl chlorides are inexpensive, abundant and important intermediates for the assembly of complex molecules.^[11] However, only rare examples have been reported using aroyl chlorides as aryl radical source in the preparation of 1,4-dicarbonyl compounds. In 2010, Wan group reported a Michael-addition-type reaction between aroyl chlorides and chalcones in the presence of samarium powder.^[12] We were curious about the performance of aroyl chloride as radical source in the synthesis of 1,4-dicarbonyl compounds. More importantly, the substrate gap in the conjugate addition of acyl radical and α , β -unsaturated carbonyl substrates needs to be filled in (Scheme 1). Herein, we describe an efficient and practical method to construct 1,4-dicarbonyl compounds from commercially available aroyl chlorides with broad functional group tolerance.



Scheme 1. Different strategies to hydroacylations of electron-deficient alkenes.

We initially began our studies by choosing benzoyl chloride (1a) and 2-cyclohexen-1-one (2a) as a model reaction under photochemical conditions to synthesize 1,4dicarbonyl product 3a (Table 1). Upon using DIPEA as a reductant, the desired product was unobtainable while the title reaction was catalyzed by 1 mol% fac-lr(ppy)₃ and irradiated by 9 W white LEDs in CH₃CN (Table 1, entry 1). Pleasingly, the desired product 3a was obtained in 51% vield with Hantzsch ester (HEH) as the reductant (entry 2). Next, among a series of common photosensitizers, fac- $Ir(ppy)_3$ was found to be the most effective catalyst (Table 1, entries 3-7).^[13] Furthermore, effects of solvent were also investigated and the yield of 3a was consistently reduced in DMF, CH₂Cl₂, toluene, THF, acetone and MeOH (Table 1, entries 8-13). To furhter improve the yield, a series of bases were tested to consume HCI produced in the process of reaction (Table 1, entries 14-18). Satisfyingly, the yield for 3a was improved to 87% upon using NaHCO₃ as the base. Switching white LEDs to blue LEDs (460 nm) resulted in a slight improvement in the yield (Table 1, entry 19). Control experiments indicated that visible light and photocatalyst were essential to this reaction (Table 1, entries 20 and 21). Ultimately, the optimal conditions were finalized as: 1 (2.0 equiv.) and 2 (1.0 equiv.) in the presence of fac-Ir(ppy)₃ (1 mol%), HEH (2.0 equiv.) and NaHCO3 (2.0 equiv.) in CH₃CN (0.2 M) under Ar irradiated by 9 W blue LEDs.

10.1002/asia.201701738

WILEY-VCH



	photocatalyst				Yield ^[b]
entry	(1 mol%)	solvent	reductant	base	(%)
1	<i>fac</i> -Ir(ppy)₃	CH₃CN	DIPEA	_	NR
2	<i>fac-</i> Ir(ppy)₃	CH₃CN	HEH	—	51
3	Ru(bpy)3(PF6)2	CH₃CN	HEH	—	43
4	Ir(ppy) ₂ (dtbbpy)PF ₆	CH₃CN	HEH	—	49
5	Eosin Y	CH₃CN	HEH	—	36
6	Rhodamin B	CH₃CN	HEH	—	35
7	Rose Bengal	CH₃CN	HEH	—	25
8	<i>fac-</i> Ir(ppy)₃	DMF	HEH	—	trace
9	<i>fac-</i> Ir(ppy)₃	CH_2CI_2	HEH	—	43
10	<i>fac-</i> Ir(ppy)₃	Toluene	HEH	—	36
11	<i>fac-</i> lr(ppy)₃	THF	HEH	—	39
12	<i>fac-</i> lr(ppy)₃	Acetone	HEH	—	44
13	<i>fac-</i> lr(ppy)₃	MeOH	HEH	—	NR
14	<i>fac-</i> lr(ppy)₃	CH₃CN	HEH	NaHCO ₃	87
15	<i>fac-</i> lr(ppy)₃	CH₃CN	HEH	Na ₂ CO ₃	52
16	<i>fac-</i> lr(ppy)₃	CH₃CN	HEH	K ₂ CO ₃	41
17	<i>fac-</i> lr(ppy)₃	CH₃CN	HEH	DIPEA	60
18	<i>fac-</i> lr(ppy)₃	CH₃CN	HEH	Et₃N	72
19°	<i>fac-</i> Ir(ppy)₃	CH₃CN	HEH	NaHCO ₃	89
20 ^d	fac-Ir(ppy)₃	CH₃CN	HEH	NaHCO ₃	NR
21°	—	CH₃CN	HEH	NaHCO ₃	NR

^[a]Unless otherwise noted, all reactions were performed on **1a** (0.4 mmol, 2.0 equiv.), **2a** (0.2 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (0.002 mmol, 1 mol %), reductant (0.4 mmol, 2.0 equiv.), base (0.4 mmol, 2.0 equiv.) and CH₃CN (1.0 mL) under Ar was irradiated by 9 W white LEDs at r.t. for 24 h. ^[b]Isolated yield. ^[c]9 W Blue LEDs (460 nm) were used. ^[d]Reaction was performed in the absence of visible light.

With the optimized conditions in hand, the generality of this reaction was then evaluated. To our delight, a range of electrondeficient alkenes served as suitable radical acceptors to afford the corresponding products in good to excellent yields (Scheme 2). Firstly, cyclic enones including C-4 disubstituted cyclohexenone, cyclopentenone or cycloheptenone were well tolerated to give the corresponding adducts in good yields (3b-3d). Secondly, comparable yields were also achieved for linear enones and 3e and 3f were obtained in 75% and 73% yield respectively. Finally, the employment of α,β -unsaturated aldehyde, α,β -unsaturated esters and α,β -unsaturated esters amide gave much lowered yields (3g, 3h, 3j, and 3k), except for tert-butyl ester with good yield (3i, 85% yield). Unfortunately, asubstituted α,β -unsaturated esters (2I and 2m) failed to give the desired product, which might be due to the demanding steric effect. Surprisingly, 4-phenyl-3-buten-2-one (2n) was also ineffective in the title reaction.

Next, we turned our attention to various aroyl chlorides bearing electron-withdrawing or electron-donating substituents on the aromatic moiety. Generally, moderate to high yields were obtained and the results are shown in Scheme 3. It was found that electron-donating substituent is impactful to the chemical yield of the reaction. Good yields were consistently obtained with electron-donating substituent attached (**3I** and **3r**) while the presence of electron-withdrawing group caused the decrease in yield of **3**. Meanwhile, the substituents on different positions all gave good yields. In addition, aryl halides such as bromide and chloride were well tolerated without detecting dehalogenated



3x, Ar = furan, 44%

products under photoredox conditions, enabling further transformation of these products using classic cross-coupling

For internal use, please do not delete. Submitted_Manuscript

strategies. As heteroarenes are prevalent in bioactive molecules, 2-furancarbonyl chloride was also tested in this protocol and 44% yield of **3x** was obtained. The acyl chlorides such as cinnamyl chloride or Cyclohexanecarboxylic acid chloride also was tested, however, it didn't afforded the desired product.

Having demonstrated the feasibility of this protocol to construct 1,4-dicarbonyl compounds, we decided to further investigate synthetic utility of the resulting adduct in the construction of heterocycles (Scheme 4). A highly substituted pyrrole **4a** was obtained in 92% yield through the condensation of **3e** with *p*-toluidine (Paal–Knorr synthesis) (eq. a). In addition, the synthetic operation was further optimized by developing an one-pot process for the synthesis of **4a**. A 0.5 mmol scale reaction for **2e** was conducted, in which the reaction mixture was concentrated *in vacuo* upon the completion of photocatalytic conjugate addition and the crude residue was directly used in the following Paal–Knorr synthesis without purification. Pleasantly, the desired pyrrole **4a** was obtained in 67% yield over two steps (Scheme 4, eq. b).





To gain further insight into the mechanism, some control experiments were also conducted (see supporting information for details). The results of TEMPO trapping experiments suggested the involvement of radical intermediates. As determined by Stern-Volmer fluorescence-quenching analysis, Hantzsch ester effectively quenched the photoexcited of fac-Ir(ppy)3, but aroyl chlorides did not. Additionally, none of deuterated product was observed, when D₂O was added to the reaction system. These results proved that the α -H in product **3** came from HEH.^[14] Based on the results mentioned above and previous reports,^[8, 15] a plausible mechanism of this reaction is proposed in Figure.1. Visible-light irradiation of fac-lr(ppy)₃ facilely generates photoexcited state $*Ir(ppy)_3$, which could be reduced by Hantzsch ester to Ir²⁺ species. Single electron transfer from Ir2+ species to benzoyl chloride produces radical A and thus regenerates the ground state photocatalyst. The acyl radical conjugate addition with electron-deficient olefin to forge a new C-C bond with concomitant formation of alkyl radical B, which ultimately abstracts one hydrogen atom from HEH• to form product 3.





WILEY-VCH



Figure 1. Proposed Mechanism for Constructing 1,4-Dicarbonyl Compounds.

In summary, an operationally simple and mild visible-light photoredox catalyzed conjugate addition between aroyl chloride and various Michael acceptors was developed. Using inexpensive and abundant aroyl chlorides as aryl radical source, a variety of 1,4-dicarbonyl compounds were obtained in good to excellent yields. Furthermore, the resulting 1,4-dicarbonyl compound can be readily transformed into highly substituted pyrrole, which is of wide interest in materials science and pharmaceutical industry.

Experimental Section

To an oven-dried 15 mL Schleck flask equipped with a magnetic stir bar, aroyl chlorides (0.4 mmol, 2.0 equiv.), Michael Acceptors (0.2 mmol, 1.0 equiv.), *fac*-lr(ppy)₃ (0.002 mmol, 1 mol %), NaHCO₃ (0.4 mmol, 2.0 equiv.), HEH (0.4 mmol, 2.0 equiv.) and CH₃CN (1.0 mL) were added. The vessel was evacuated and backfilled with Ar. The tube was screwcapped and stirred at room temperature under irradiation of blue LEDs (9 W, 460 nm) for 24 h (distance app. 3 cm). After the reaction was completed (monitored by TLC analysis), the solvent was removed under reduced pressure, and then the residue was purified by flash column chromatography (PE/EA:9/1) to afford the desired product **3**.

Acknowledgements

We gratefully acknowledge the financial support from National Natural Science Foundation of China (21776318, 21676302 & 81703365), Natural Science Foundation of Hunan Province (2017JJ3401), China Postdoctoral Science Foundation (2017M610504) and Central South University.

Conflict of interest

The authors declare no conflict of interest.

Keywords: photocatalysis • conjugate addition • 1,4-dicarbonyl compounds • aroyl chloride • radical reactions

- a) F. Bellina, R. Rossi, *Tetrahedron* 2006, *62*, 7213-7256; b) Y. Enomoto, K. Shiomi, M. Hayashi, R. Masuma, T. Kawakubo, K. Tomosawa, Y. Iwai, S. Omura. *J. Antibiot.* 1996, *49*, 50–53; c) T. Kosuge, K. Tsuji, K. Hirai, K. Yamaguchi, T. Okamoto, Y. litaka, *Tetrahedron Lett.* 1981, *22*, 3417-3420.
- [2] (a) E. J. Corey, L. S. Hegedus, J. Am. Chem. Soc. 1969, 91, 4926-4928; (b) H. Stetter, M. Schreckenberg, Angew. Chem. Int. Ed. 1973,

For internal use, please do not delete. Submitted_Manuscript

10.1002/asia.201701738

WILEY-VCH

12, 81-81; (c) D. Seyferth, R. C. Hui, *J. Am. Chem. Soc.* **1985**, *107*, 4551-4553; (d) M. C. Myers, A. R. Bharadwaj, B. C. Milgram, K. A. Scheidt, *J. Am. Chem. Soc.* **2005**, *127*, 14675-14680.

- [3] a) R. Scheffold, R. Orlinski, J. Am. Chem. Soc. 1983, 105, 7200-7202;
 b) D. L. Boger, R. J. Mathvink, J. Org. Chem. 1989, 54, 1777-1779; c) I.
 Ryu, M. Hasegawa, A. Kurihara, A. Ogawa, S. Tsunoi, N. Sonoda, Synlett 1993, 1993, 143-145; d) T. Punniyamurthy, B. Bhatia, J. Iqbal, J.
 Org. Chem. 1994, 59, 850-853; e) S. Esposti, D. Dondi, M. Fagnoni, A.
 Albini, Angew. Chem. Int. Ed. 2007, 46, 2531-2534; f) I. Ryu, A. Tani, T.
 Fukuyama, D. Ravelli, M. Fagnoni, A. Albini, Angew. Chem., Int. Ed.
 2011, 50, 1869-1872;
- [4] a) S. Bath, N. M. Laso, H. Lopez-Ruiz, B. Quiclet-Sire, S. Z. Zard, *Chem. Commun.* 2003, 2, 204-205; b) W. Liu, Y. Li, K. Liu, Z. Li, *J. Am. Chem. Soc.* 2011, 133, 10756-10759; c) L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, S. Strazzari, *Org. Lett.* 2003, 5, 1313-1316.
- [5] For review of Photoredox Catalysis: a) M. H. Shaw, J. Twilton, D. W. C. MacMillan, J. Org. Chem. 2016, 81, 6898-6926; b) X.-J. Lang, J.-C. Zhao, X.-D. Chen, Chem. Soc. Rev. 2016, 45, 3026-3038; c) D. Ravelli, S. Protti, M. Fagnoni. Chem. Rev. 2016, 116, 9850-9913; d) J. K. Matsui, S. B. Lang, D. R. Heitz, G. A. Molander. ACS Catal. 2017, 7, 2563–2575.
- [6] For selected examples, see: a) S. M. Thullen, T. Rovis, J. Am. Chem. Soc. 2017, 139, 15504–15508; b) D.-F. Chen, J. C. K. Chu, T. Rovis, J. Am. Chem. Soc. 2017, 139, 14897–14900; c) X.-H. Zhang, D. W. C. Macmillan, J. Am. Chem. Soc. 2017, 139, 11353–11356; d) H. Huang, C.-G. Yu, T.-T. Zhang, Y.-Q. Zhang, P. S. Mariano, W. Wang, J. Am. Chem. Soc. 2017, 139, 9799–9802.
- [7] G.-Z. Wang, R. Shang, W.-M. Cheng, Y. Fu, Org. Lett. 2015, 17, 4830-4833.
- [8] S.-P. Dong, G.-B. Wu, X.-Q. Yuan, C.-C. Zou, J.-X. Ye, Org. Chem. Front. 2017, 4, 2230-2234.
- [9] M. Ociepa, O. Baka, J. Narodowiec, D. Gryko, *Adv. Synth. Catal.* 2017, 359, 3560-3565.
- [10] M. D. Vu, M. Das, X.-W. Liu, Chem. Eur. J. 2017, 23, 15899-15902
- [11] a) S.-M. Xu, J.-Q. Chen, D. Liu, Y. Bao, Y.-M. Liang, P.-F. Xu, Org. Chem. Front. 2017, 4, 1331–1335; b) C.-G. Li, G.-Q. Xu, P.-F. Xu, Org. Lett. 2017, 19, 512–515; c) C.-J. Lee, C.-C. Tsai, S.-H. Hong, G.-H. Chang, M.-C. Yang, L. Möhlmann, W.-W. Lin, Angew. Chem. Int. Ed. 2015, 54, 8502-8505; d) L. Wang, X.-Y. Ren, J.-T. Yu, Y. Jiang and J. Cheng, J. Org. Chem. 2014, 79, 10599-10604.
- [12] Y.-J. Liu, Y.-Y. Li, Y. Qi, J. Wan, Synthesis 2010, 24, 4188-4192.
- [13] The reduction potential: *fac*-Ir(ppy)₃ (E $\frac{NV''''}{12}$ = -1.73 V vs. SCE), Ru(bpy)₃(PF₆)₂ (E $\frac{W'''}{12}$ = -0.81 V vs. SCE), Eosin Y (E $\frac{NV''}{12}$ = -1.06 V vs. SCE) and benzoyl chloride (E $\frac{NV''}{12}$ = -0.972 V vs. SCE).
- [14] See the ESI for more details of TEMPO trapping experiment, the Stern-Volmer experiments and the Deuteration using D₂O as additive experiment.
- [15] For the use of Hantzsch ester in photoredox-catalyzed systems: a) S. Sumino, M. Uno, T. Fukuyama, I, Ryu, M. Matsuura, A. Yamamoto, Y. Kishikawa, *J. Org. Chem.* 2017, *82*, 5469–5474; b) W.-X. Chen, Z. Liu, J.-Q. Tian, J. Li, J. Ma, X. Cheng, G.-G, Li, *J. Am. Chem. Soc.* 2016, 138, 12312–12315.

Accepted Manuscrip

For internal use, please do not delete. Submitted_Manuscript

COMMUNICATION



- mild reaction conditions
- broad functional group tolerance

A facile visible-light photocatalytic conjugate addition to prepare 1,4-dicarbonyl compounds has been developed by employing readily available aroyl chlorides as aryl radical sources. The operationally simple method shows broad scope with regard to both aroyl chlorides and Michael acceptor, in which a variety of 1,4-diketones were synthesized in moderate to good yields.

Chao-Ming Wang,[†] Dan Song,[†] Peng-Jue Xia, Jing Wang, Hao-Yue Xiang,^{*} Hua Yang^{*}

Page No. – Page No.

Visible-Light-Promoted Synthesis of 1,4-Dicarbonyl Compounds Using Aroyl Chlorides

WILEY-VCH