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Letter

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Practical Approach for Preparation of Unsymmetric Benzils from β-Ketoaldehydes

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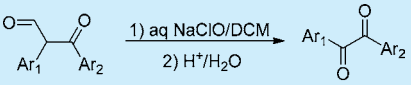
Supporting Information

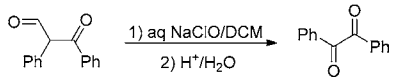
ABSTRACT: An efficient and practical method for the synthesis of unsymmetric benzils from readily available β-ketoaldehydes has been developed. Various unsymmetric 1,2-diaryldiketones bearing functional groups have been obtained in good to excellent yields under mild reaction conditions. A plausible mechanism was proposed, and α,α-dichloroketone was considered as the key intermediate. The generation of α,α-dichloroketones from β-ketoaldehydes may undergo the following steps: (1) oxidation by sodium hypochlorite, (2) decarboxylation, and (3) chlorination by Cl_2 generated from sodium hypochlorite.



Benzil derivatives have attracted a great deal of attention due to their rich applications across many fields of science.[1] Their wide applications have motivated efforts toward the synthesis of these compounds. Traditionally, benzils are prepared via benzoin condensation followed by oxidation of the obtained α-hydroxycarbonyls.[2] Although this method showed high efficiency, it was also limited to the preparation of symmetric benzils. The synthesis of unsymmetrically substituted benzils was proven to be more difficult to achieve due to lack of regiochemical control in the cross-benzoin reaction of two different aldehydes. Therefore, efficient synthesis of unsymmetric benzils has recently drawn significant attention. Over the past decade, several synthetic strategies for the preparation of unsymmetric benzils have been reported including the oxidation of alkynes, alkenes,[3] or α-methylene ketones,[4] decarboxylation of 1,3-diketones,[5] and some others.[1b,g,6] Herein, we reported a new practical synthetic route for the preparation of unsymmetric benzils from β-ketoaldehydes which can be obtained conveniently from Lewis acid catalyzed Meinwald rearrangement[7] of chalcone epoxides, and this method has been demonstrated to be of excellent substrate scope.

It was found that the oxidation of 3-oxo-2,3-diphenylpropionaldehyde with aqueous sodium hypochlorite in dichloromethane followed by hydrolysis with acid gave a product 1,2-diphenylethane-1,2-dione (benzil). To explore the reaction carefully and optimize the oxidation reaction conditions, we examined solvent, temperature, amount of the oxidant, as well as reaction time (Table 1). Most of the attempts afforded good results. When 5−6 equiv of sodium hypochlorite was employed, the yield improved to 84% (Table 1, entries 2 and 3). Solvent has no obvious impact on the reaction except for 1,4-dioxane (Table 1, entry 7). Higher temperatures accelerated the reaction to some extent (Table 1, entry 9). Thus, the optimum oxidation conditions were established as using 5 equiv of aqueous NaClO as the oxidant as well as the source of the chlorine and carrying out the reaction in DCM at room temperature.

Table 1. Optimization of the Reaction Conditions[a]



entry	x equiv NaClO	solvent[b]	temp[b] (°C)	time[b] (h)	yield[c] (%)
1	4	DCM	rt	4	80
2	5	DCM	rt	4	84
3	6	DCM	rt	4	84
4	10	DCM	rt	2.5	84
5	5	CH_3CN	rt	4	84
6	5	THF	rt	4	81
7	5	1,4-dioxane	rt	4	72
8[d]	5	DCM	rt	4	84
9	5	DCM	40	3.5	84
10	5	DCM	0	6	84

[a]Reaction conditions: β-ketoaldehyde (1 mmol), solvent (5 mL), x equiv of 5.2% (w/v) NaClO solution was added dropwise; the reaction mixture was stirred at room temperature until TLC indicated completion. After extraction and concentration in vacuo, the crude intermediate was obtained, then it was dissolved in 5 mL of 30% AcOH solution, and the reaction mixture was stirred at 60 °C, monitored by TLC. [b]The reaction in the presence of aqueous NaClO. [c]Isolated yield. [d]Tetrabutylammonium bromide (10 mol %) was added.

With the optimum conditions in hand, the substrate scope was then examined. As shown in Table 2, benzil derivatives were obtained in good to excellent yields for most substrates. There was no significant difference in reactivities between 3-oxo-2,3-diphenylpropanal (Table 2, entry 1) and its derivatives containing electron-donating groups (Table 2, entries 2−5 and 12−14) or electron-withdrawing/donating groups (Table 2, entries 6−11 and 15). In addition, the reaction was not sensitive to steric hindrance. For the substrates where methyl

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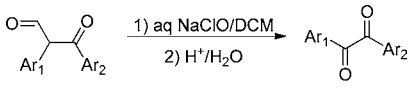
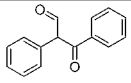
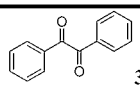
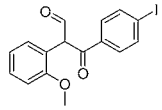
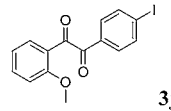
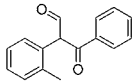
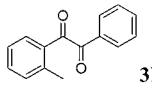
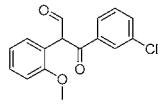
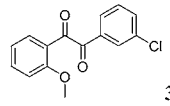
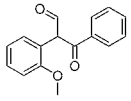
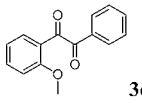
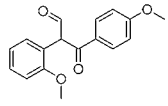
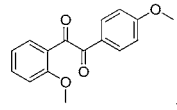
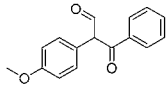
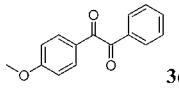
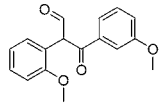
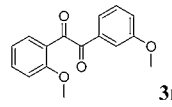
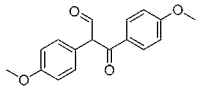
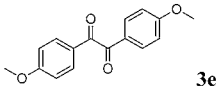
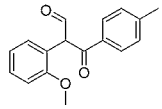
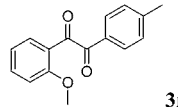
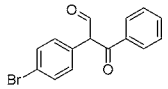
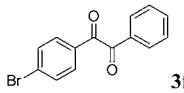
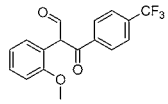
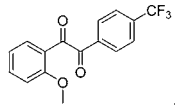
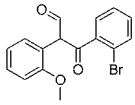
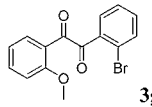
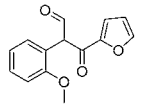
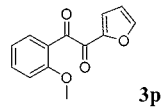
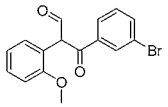
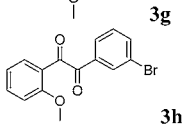
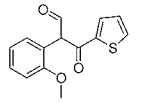
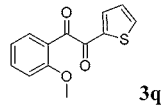
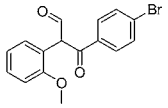
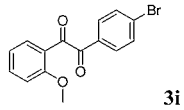
Table 2. Conversion of β-Ketoaldehydes to 1,2-Dicarbonyl Compounds[a]



3a-3q

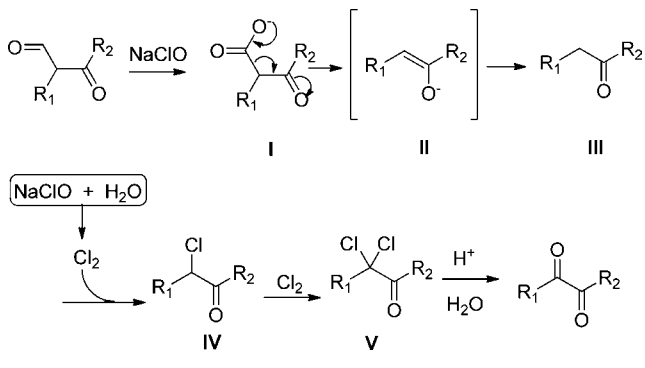
entry[a]	substrate	product	yield[b] (%)	entry[a]	substrate	product	yield[b] (%)
1		 **3a**	84	10		 **3j**	94
2		 **3b**	90	11		 **3k**	86
3		 **3c**	93	12		 **3l**	89
4		 **3d**	85	13		 **3m**	87
5		 **3e**	87	14		 **3n**	91
6		 **3f**	86	15		 **3o**	92
7		 **3g**	93	16		 **3p**	92
8		 **3h**	91	17		 **3q**	92
9		 **3i**	92				

[a]All reactions were run under the same conditions: 2 mmol β-ketoaldehyde was dissolved in 10 mLof CH_2Cl_2; 13.6 mL of 5.2% (w/v) NaClO solution was added dropwise, and the reaction mixture was stirred at room temperature. After chlorination, reaction was complete, and the crude dichloroketone was obtained by extraction and concentration. Then it was dissolved in 5 mL of 30% AcOH solution, and the reaction mixture was stirred at 60 °C, monitored by TLC. [b]Isolated yield.

and methoxy groups are substituted at the *ortho* position of the aromatic ring Ar_1, satisfactory yields of the products were successfully obtained (Table 2, entries 2, 3, and 7−17). It was noteworthy that when Ar_2 was altered with heterocyclic groups (Table 2, entries 16 and 17), the corresponding heteroaromatic products **3p** and **3q** were also obtained in excellent yields (92%).

To clarify the reaction mechanism, we attempted to trap reaction intermediates. To our delight, when 3-oxo-2,3-diphenylpropionaldehyde was treated with 5 equiv of aqueous sodium hypochlorite in DCM, 1,2-diphenylethanone (**III**, when $R_1 = R_2 =$ Ph), 2-chloro-1,2-diphenylethanone (**IV**, when $R_1 = R_2 =$ Ph), and 2,2-dichloro-1,2-diphenylethanone (**V**, when $R_1 = R_2 =$ Ph) were isolated from the reaction mixture by quenching the reaction at 0.5 h. While being treated 3-oxo-2,3-diphenylpropionaldehyde with 3 equiv of sodium hypochlorite solution in dichloromethane for 4 h, 2-chloro-1,2-diphenylethanone (**IV** when $R_1 = R_2 =$ Ph, 21%) and 2,2-dichloro-1,2-diphenylethanone (**V** when $R_1 = R_2 =$ Ph, 71%) were obtained. On the basis of the above facts, we proposed a pathway for the aqueous sodium hypochlorite mediated transformation of β-ketoaldehydes to benzils (Scheme 1). Oxidation of β-ketoaldehydes by sodium hypochlorite gave the corresponding 3-oxo-2,3-diarylpropanoic acids (**I**), and then decarboxylation of **I** provided deoxybenzoins (**III**); chlorination of **III** by chlorine, released from the decomposition of NaClO in water,

Scheme 1. Possible Reaction Pathway



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produced α,α-dichloroketones (**V**) which were hydrolyzed in the presence of acetic acid and finally afforded the desired benzils.

In conclusion, we have developed an efficient and practical method for the synthesis of unsymmetric benzils from readily available and inexpensive β-ketoaldehydes. Various unsymmetric 1,2-diaryldiketones bearing functional groups have been obtained in high to excellent yields under mild reaction conditions. Notably, the products which have halogen substituents at aromatic rings allow further functionalization via transition-metal-catalyzed cross-coupling reactions and thus the accessibility of unsymmetric diketone derivatives. Furthermore, due to easy access to a variety of β-ketoaldehyde substrates by Meinwald rearrangement of chalcone epoxides, this work provides a very convenient and straightforward protocol to construct useful unsymmetric 1,2-dicarbonyls from simple starting materials. Further studies of other related applications of this protocol are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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