



Facile route to benzils from aldehydes via NHC-catalyzed benzoin condensation under metal-free conditions

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ABSTRACT

A simple and efficient one-pot procedure for the synthesis of α -diketones from aldehydes via benzoin condensation under the influence of a catalytic amount of azolium salt combined with DBU has been developed. Thus, aldehyde was allowed to react with the azolium salt/DBU catalytic system at room temperature, and then the reaction mixture was heated to 70 °C under air atmosphere to afford the corresponding 1,2-diketone in good yield. This would be an efficient alternative method of synthesizing α -diketones from aldehydes under metal-free conditions.

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1. Introduction

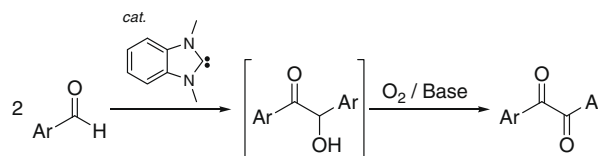
Development of a convenient and efficient synthetic route to α -diketones is desired, since α -diketones are versatile building blocks for the synthesis of biologically active and photoresponsive compounds.¹ Oxidation of 1,2-diols and/or α -hydroxyketones appears to be the most straightforward method of synthesizing 1,2-diones.² Oxidation of alkynes to the corresponding α -diketones is a promising method for preparing unsymmetrical 1,2-diones.³ Several other methods, including the oxidation of alkenes or methylene ketones and non-oxidative methods, have also been reported.⁴

In the past decade, there has been a dramatic increase in the use of N-heterocyclic carbenes (NHCs) in synthetic organic chemistry. NHCs are versatile ligands that can be used in homogenous transition metal catalysis.⁵ Furthermore, considerable attention has been paid to the use of NHCs as organocatalysts.⁶ NHCs derived from triazolium or thiazolium salts have been identified as efficient catalysis for benzoin condensation reaction,⁷ and asymmetric benzoin condensation has been successfully carried out using chiral triazolium salts.⁸ However, there is limited information on the benzoin condensation of aldehydes catalyzed by the combination of an imidazolium or benzimidazolium compound and a base.⁹

Previously, we synthesized a new class of azolium compounds known as NHC proligands. Thus, asymmetric Pd-catalyzed oxida-

tive Heck-type reaction of acyclic alkenes with arylboronic acids under molecular oxygen atmosphere has been successfully carried out.¹⁰ In addition, reversal of enantioselectivity has been achieved in the Cu-catalyzed conjugate addition of dialkylzinc to cyclic enones in the presence of an azolium compound.¹¹ During the course of these studies, our interests turn to the use of the azolium compounds as organocatalysts.

Now, we found that the azolium salts (NHC precursors) efficiently catalyze the benzoin condensation of aldehydes in the presence of a base such as DBU. We also found that the oxidation of benzoin to benzil under air atmosphere is promoted by a catalytic amount of DBU. Thus, we developed a one-pot procedure for the synthesis of benzils from aldehydes by using a combination of an azolium salt and a base as the catalytic system (Scheme 1). A similar synthetic route to benzils from aldehydes via benzoin condensation has been independently reported by Miyashita¹² and Jing.¹³ However, their method requires the use of a stoichiometric amount of Bi_2O_3 or FeCl_3 as the oxidant. In contrast, our strategy



Scheme 1. Route to benzil from aldehyde through benzoin condensation under metal-free conditions.

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is the first example of the one-pot synthesis of benzils from aldehydes under metal-free conditions.

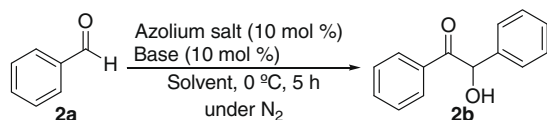
2. Benzoin condensation

We carried out our research in a stepwise manner by first attempting the catalytic transformation of aldehyde to benzoin by using the azolium salt that was recently synthesized by our group (Table 1). Benzaldehyde (**2a**) was allowed to react in the presence of 10 mol % of benzimidazolium salt **1** and DBU in DMF at 0 °C under N₂ atmosphere to afford benzoin (**2b**) in 91% yield (Run 1).¹⁴ In this reaction a small amount (<5%) of benzil (**2c**) was formed. The formation of **2c** will be discussed later. Replacement of **1** with imidazolium compound **3** as the catalyst resulted in a low yield of **2b** (Run 2). This was probably due to the formation of an adduct by the reaction of **2a** with the NHC derived from **3**. A similar observation (adduct formation) has been reported by Aggarwal et al.¹⁵ The benzoin condensation of **2a** was favored when 1,3-dimethylbenzimidazolium iodide **4**, that is, commercially available was used in combination with DBU (Run 3). The present reaction proceeded only under N₂ atmosphere, and almost no reaction occurred when **2a** was treated with the **1**/DBU catalytic system under air atmosphere (Run 4). Among the solvents used in this study, the use of aprotic polar solvents such as DMF and DMA led to **2b** in good yield, respectively (Runs 1 and 5–8). Treatment of **2a** under the influence of **1** and a carbonate base such as Cs₂CO₃ led to **2b** in satisfactory yield (Run 11), however, the other bases such as ^tBuOK, ⁿBuLi, and Et₃N resulted in low conversion of **2a** to **2b** (Runs 12–14).

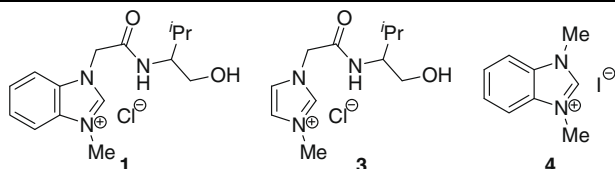
On the basis of these results, we investigated the benzoin condensation of various aldehydes (Table 2).

Substituted benzaldehydes were successfully converted into the corresponding benzoin in good to excellent yields (Runs 2–5). 2-

Table 1
Benzoin condensation of **2a** to **2b** under selected reaction conditions^a



Run	Azolium salt	Base	Solvent	Yield ^b (%)
1	1	DBU	DMF	91
2	3	DBU	DMF	Trace
3	4	DBU	DMF	94
4 ^c	1	DBU	DMF	7
5	1	DBU	DMA	92
6	1	DBU	CH ₂ Cl ₂	25
7	1	DBU	CH ₃ OH	17
8	1	DBU	CH ₃ CN	57
9	1	K ₂ CO ₃	DMF	69
10	1	Na ₂ CO ₃	DMF	66
11	1	Cs ₂ CO ₃	DMF	79
12	1	^t BuOK	DMF	50
13	1	ⁿ BuLi	DMF	23
14	1	Et ₃ N	DMF	<5



^a **2a** (1 mmol) was allowed to react in the presence of azolium salt (0.1 mmol) and base (0.1 mmol) in solvent (1.1 mL) at 0 °C for 5 h under N₂ atmosphere.

^b Isolated yield based on **2a** used.

^c Reaction was run under air atmosphere.

Naphthaldehyde (**9a**) was dimerized by a procedure similar to that used for **2a** (Run 6). The present catalytic system was also used in the reaction of heteroaromatic aldehydes. Thus, 2-thiophenecarboxaldehyde (**10a**) and 2-furaldehyde (**11a**) were converted into the corresponding α -hydroxyketones, **10b** and **11b**, in 85% and 94% yields, respectively (Runs 7 and 8).

2-Pyridinecarboxaldehyde (**12a**) underwent dimerization, but after isolation of the product by column chromatography, a considerable amount of α -pyridil (**12c**) (38%) was obtained along with the desired product α -pyridoin (**12b**) (43%) (Run 9). It is reported that **12b** is easily oxidized to **12c** in methanol at room temperature under air atmosphere.¹⁶ Therefore, there was a possibility of **12b** being converted to **12c** during the isolation procedure in our experiment. In fact, the NMR spectrum of the crude product (before isolation by column chromatography) revealed that the amount of **12c** formed was almost negligible. By using the internal standard method, the yield of **12b** after the dimerization reaction was found to be 67% (Run 9).

Table 2
Synthesis of α -hydroxyketones from aldehydes catalyzed by **1** combined with DBU^a

Run	Substrate	Product	Yield ^b (%)
1			91
2	X = <i>p</i> -Cl 5a	5b	81
3	X = <i>m</i> -Cl 6a	6b	87
4	X = <i>p</i> -Br 7a	7b	78
5	X = <i>p</i> -Me 8a	8b	92
6			83
7			85
8			94
9			43 ^c (67) ^d
10			79

^a Aldehyde (1 mmol) was allowed to react in the presence of **1** (0.1 mmol) and DBU (0.1 mmol) in DMF (1.1 mL) at 0 °C for 5 h under N₂ atmosphere.

^b Isolated yield based on the aldehyde used.

^c α -Pyridil (**12c**) was obtained in 38% isolated yield.

^d Yield of **12b** was determined by ¹H NMR using an internal standard method.

The dimerization of aliphatic aldehydes such as nonanal (**13a**) afforded acyloin **13b** in 79% yield (Run 10). It is known that the reaction of an aliphatic aldehyde in the presence of an imidazolium salt/DBU catalytic system would afford the aldol condensation product instead of the acyloin;¹² however, no aldol condensation product was obtained when using our catalytic system. Hence, a variety of benzoinz **2b–13b** could be synthesized by using the azolium salt **1**/DBU catalytic system under relatively mild reaction conditions.

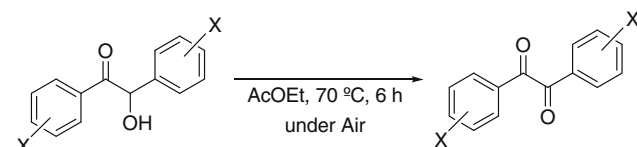
3. One-pot synthesis of benzils

Encouraged by the results obtained in the above-mentioned benzoin condensation reactions, we next attempted to develop an efficient one-pot procedure for the synthesis of benzil derivatives from benzaldehydes. As shown in Table 1 (Run 1), a small amount of benzil (**2c**) was formed in the benzoin condensation of **2a** catalyzed by the **1**/DBU system. We assumed that **2b** formed was sequentially oxidized to **2c** during the dimerization reaction. In order to obtain further information about the formation of α -diketone, we carried out an independent reaction of **2b** under selected reaction conditions (Table 3).

When **2b** was stirred in the presence of a catalytic amount of **1** and DBU in AcOEt at 70 °C under air atmosphere, **2c** was obtained in 66% yield (Run 1). On the other hand, the reaction was almost completely suppressed in the absence of DBU (Run 2). Furthermore, **2b** was oxidized by 10 mol % of DBU alone to afford **2c** in 88% yield (Run 3). However, it was difficult to oxidize **2b** under N₂ atmosphere (Run 4). These observations strongly indicated that the α -hydroxyketone formed was oxidatively dehydrogenated in the presence of molecular oxygen and DBU. The mechanism of this oxidation could be explained as follows: the carbanion formed in the reaction between **2b** and DBU was trapped by molecular oxygen to afford **2c**. Similarly, 4,4'-dichlorobenzoin (**5b**) was successfully oxidized to the corresponding α -diketone **5c** in excellent yield (Run 5). However, the aerobic oxidation of 4,4'-dimethylbenzoin (**8b**) catalyzed by DBU afforded **8c** in low yield (Run 6). This was probably due to instability of the carbanion intermediate formed from **8b**.

On the basis of these results, we established a one-pot procedure for the conversion of benzaldehyde to benzils (Scheme 2). Compound **2a** was allowed to react in the presence of **1** and DBU in DMF under N₂ atmosphere for 5 h at 0 °C, and then an additional amount of DBU in AcOEt was added. Subsequent stirring of the resulting reaction mixture at 70 °C for 6 h under open-air conditions afforded the desired **2c** in 79% yield. This is the first example

Table 3
Aerobic oxidation of benzoinz to benzils^a

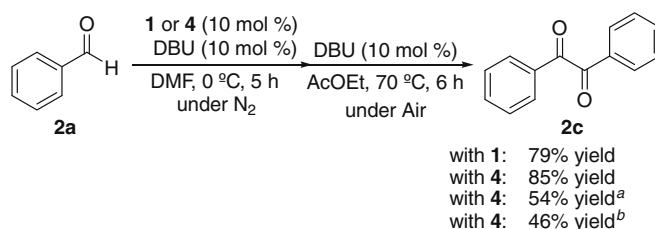


Run	Substrate	Catalyst	Conv. (%)	Product (yield/%) ^b
1	2b	1 /DBU	80	2c (66)
2	2b	1	8	Not detect
3	2b	DBU	>99	2c (88)
4 ^c	2b	DBU	8	2c (7)
5	5b	DBU	>99	5c (93)
6	8b	DBU	43	8c (31)

^a Benzoinz (1 mmol) was allowed to react in the presence of **1** (0.2 mmol) and DBU (0.2 mmol) in AcOEt (15 mL) at 70 °C for 6 h under air atmosphere.

^b Isolated yield based on the benzoinz used.

^c Reaction was run under N₂ atmosphere.



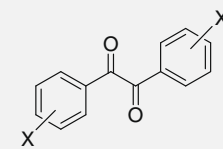
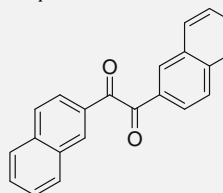
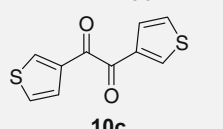
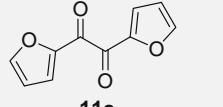
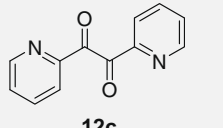
^a The reaction was run without additional DBU in second step.
^b The reaction was run without additional AcOEt in second step.

Scheme 2. One-pot synthesis of **2c** from **2a**.

of the synthesis of a 1,2-diketone from an aldehyde under metal-free conditions. The benzimidazolium salt **4** can be used as the NHC precursor in place of **1**. The reaction of **2a** in the presence of the **4**/DBU catalytic system afforded **2c** in 85% yield. The yield of **2c** was somewhat lowered in the absence of the additional AcOEt or DBU.

Finally, we carried out the one-pot synthesis of various benzil derivatives from the corresponding aldehydes by using **1** or **4** in combination with DBU (Table 4). After benzoin condensation, an

Table 4
One-pot synthesis of α -diketones from aldehydes^a

Run	Substrate	Product	Yield ^b (%)	
			With 1	With 4
				
1	2a	X = H 2c	79	85
2	5a	X = <i>p</i> -Cl 5c	72	91
3	6a	X = <i>m</i> -Cl 6c	75	78
4	7a	X = <i>p</i> -Br 7c	70	81
5	8a	X = <i>p</i> -Me 8c	51	55
6	9a		77	92
7	10a		67	88
8	11a		86	89
9 ^c	12a		70	78

^a Aldehyde (1 mmol) was allowed to react in the presence of **1** or **4** (0.1 mmol) and DBU (0.1 mmol) in DMF (1.1 mL) under N₂ atmosphere at 0 °C for 5 h. After the benzoin condensation reaction, DBU (0.1 mmol) in AcOEt (15 mL) was added, and then the reaction mixture was stirred at 70 °C for 6 h under air atmosphere.

^b Isolated yield based on the aldehyde used.

^c After benzoin condensation, MeOH (15 mL) was added, and then the reaction mixture was stirred at 25 °C for 5 h under air atmosphere.

additional amount of DBU in AcOEt was added, and the reaction mixture was stirred at 70 °C for 6 h under air atmosphere. The desired α -diketones were obtained in moderate to good yields in all cases, and the product yields were slightly improved when **4** was used as the catalyst in place of **1** (Runs 1–8). Conversion of **12a** to **12c** was achieved by treating the reaction mixture with methanol at room temperature under air after the dimerization (Run 9). However, it was difficult to obtain aliphatic 1,2-diketones from **13a**.

4. Conclusions

A one-pot synthetic method for synthesizing α -diketones from aldehydes in the presence of a benzimidazolium compound has been developed. A variety of α -diketones could be obtained by reaction of the corresponding aldehydes in the presence of a catalytic amount of **1** (or **4**) and DBU and subsequent oxidation under air atmosphere. This is a convenient method of obtaining 1,2-diketones from aldehydes via the above-mentioned dimerization-oxidation sequence under metal-free conditions.

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.103.

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