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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.

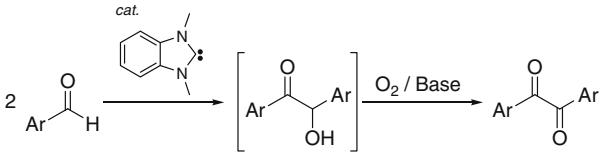
1. Introduction

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 oxidative 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 Miyashita[12] 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

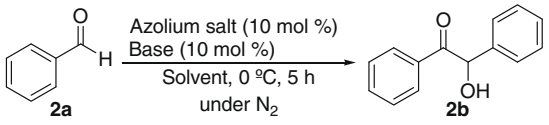
We carried out our research in a stepwise manner by first attempting the catalytic transformation of aldehyde to benzoin by using the azolium salt that was recently synthesized by our group (Table 1). Benzaldehyde (**2a**) was allowed to react in the presence of 10 mol % of benzimdazolium salt **1** and DBU in DMF at 0 °C under N_2 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 N_2 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 Cs_2CO_3 led to **2b** in satisfactory yield (Run 11), however, the other bases such as ^{t}BuOK, ^{n}BuLi, and Et_3N 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).

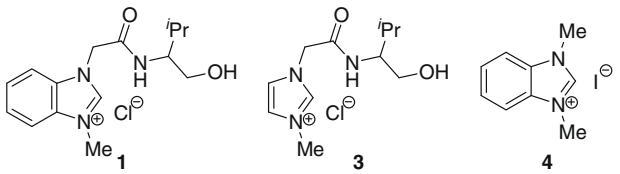
Substituted benzaldehydes were successfully converted into the corresponding benzoins in good to excellent yields (Runs 2–5). 2-Naphthaldehyde (**9a**) was dimerized by a procedure similar to that used for **2a** (Run 6). The present catalytic system was also used in the reaction of heteroaromatic aldehydes. Thus, 2-thiophenecarboxaldehyde (**10a**) and 2-furaldehyde (**11a**) were converted into the corresponding α-hydroxylketones, **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 1
Benzoin condensation of **2a** to **2b** under selected reaction conditions[a]

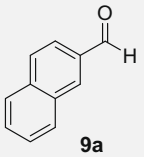
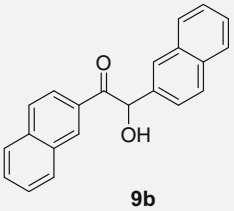
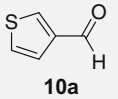
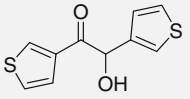
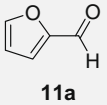
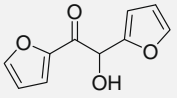
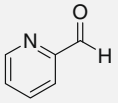
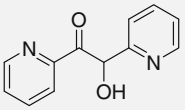
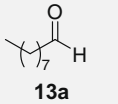
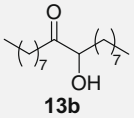


Run	Azolium salt	Base	Solvent	Yield[b] (%)
1	**1**	DBU	DMF	91
2	**3**	DBU	DMF	Trace
3	**4**	DBU	DMF	94
4[c]	**1**	DBU	DMF	7
5	**1**	DBU	DMA	92
6	**1**	DBU	CH_2Cl_2	25
7	**1**	DBU	CH_3OH	17
8	**1**	DBU	CH_3CN	57
9	**1**	K_2CO_3	DMF	69
10	**1**	Na_2CO_3	DMF	66
11	**1**	Cs_2CO_3	DMF	79
12	**1**	^{t}BuOK	DMF	50
13	**1**	^{n}BuLi	DMF	23
14	**1**	Et_3N	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 N_2 atmosphere.
[b] Isolated yield based on **2a** used.
[c] Reaction was run under air atmosphere.

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

Run	Substrate	Product	Yield[b] (%)
1	X = H **2a**	**2b**	91
2	X = *p*-Cl **5a**	**5b**	81
3	X = *m*-Cl **6a**	**6b**	87
4	X = *p*-Br **7a**	**7b**	78
5	X = *p*-Me **8a**	**8b**	92
6	 **9a**	 **9b**	83
7	 **10a**	 **10b**	85
8	 **11a**	 **11b**	94
9	 **12a**	 **12b**	43[c] (67)[d]
10	 **13a**	 **13b**	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 N_2 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 ^{1}H NMR using an internal standard method.