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N-Heterocyclic carbene-catalyzed double acylation of enones with benzils†

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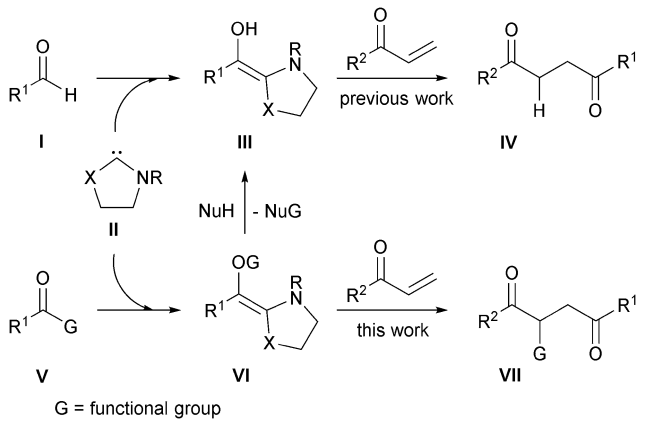
Thiazolium carbene-catalyzed reaction of aromatic 1,2-diketones with enones in aprotic solvents gave double acylation products in good yields, whereas hydroacylation products formed by Stetter reaction were not detected at all. These results suggested the generation of aroyloxyenamine species from the 1,2-diketones instead of hydroxyenamines (Breslow intermediates).

N-Heterocyclic carbenes (NHCs) have attracted much attention as organocatalysts in organic synthesis, because they can convert various electrophilic functional groups into nucleophilic ones *via* Breslow[1] and deoxy-Breslow intermediates.[2] For example, the Stetter reaction has been most frequently used in many transformations as a method for Michael addition of acyl anions.[3] However, this reaction is applicable to aldehydes only, not to ketones and esters in general. From a mechanistic point of view, when aldehydes **I** are substituted by other carbonyl compounds **V**, functional enamines **VI** would be generated by the reaction with NHC **II**, instead of Breslow intermediates **III** (Scheme 1). If the new species **VI** are sufficiently nucleophilic, acyl and functional group G could be delivered to the β- and α-position of α,β-unsaturated carbonyl compounds, respectively. This process would be expected to extend the scope of Stetter reaction.

On the other hand, few examples of generation of Breslow intermediate **III** from the carbonyl compounds **V** other than aldehydes **I** have been reported. Scheidt *et al.* employed acylsilanes[4] and α-keto carboxylates[5] in the Stetter reaction to avoid self-condensation or benzoin products, giving rise to the hydroacylation products **IV** in high yields through the elimination of alkoxysilanes or CO_2. Recently, Massi *et al.* demonstrated that aliphatic 1,2-diketones could be used as aldehyde equivalents, wherein one acyl moiety was eliminated by alcoholic solvents.[6] As a result, even though the functional enamines **VI** could be generated from **V**, they afforded the same products **IV** as those derived from the corresponding aldehydes **I**.



Scheme 1 Extension of Stetter reaction.

To develop the new double acylation reaction, we investigated the reaction of benzils **V** (G = ArCO) with enones. 1,2-Diketones have been used as acceptors of the umpolung species formed by an NHC.[7] Moreover, it has been reported that aromatic 1,2-diketones did not afford any Stetter-type products, because 1,4-thiazin-3-ones, 1 : 1 adducts of thiazolium carbenes and the diketones, were formed exclusively.[8,9] On the other hand, cyanide ion-catalyzed umpolung of benzils has been achieved in the cross-benzoin condensation,[10] which suggests the possibility of retaining the two benzoyl groups in the final products. Fortunately, we found that the reaction gave double acylation products **VII** in good yields for the first time.

Initially, benzil (**1a**) was treated with one equivalent of phenyl vinyl ketone (**2a**) under various conditions (Table 1). In the presence of the thiazolium salt **A** (20 mol%), DIPEA as base and DMF as solvent gave better yield of the double acylation product **3aa** than the Et_3N–DCE system (entries 1 and 2). Mild heating of the reaction increased the yield from 53% to 94% (entry 3). Of the NHC salts tested, thiazolium salts **B** and **C** gave **3aa** in 77% and 73% yields, respectively, along with trace amounts of hydroacylation product **4**

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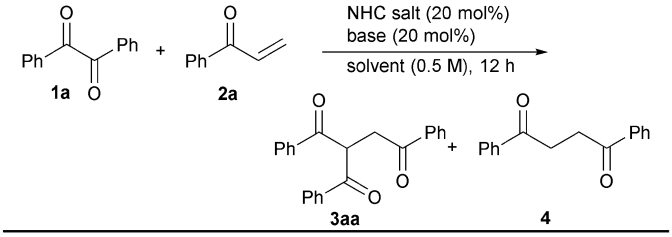
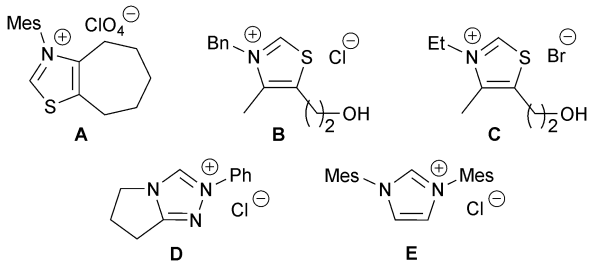
Table 1 Optimization of the reaction conditions



Entry	NHC salt	Base	Solvent	Temp. (°C)	Yield[a] (%) 3aa	4
1	**A**	Et_3N	DCE	rt	17	0
2	**A**	DIPEA	DMF	rt	53	0
3	**A**	DIPEA	DMF	50	94	0
4	**A**	DIPEA	EtOH	50	56	11
5	**B**	DIPEA	DMF	50	77	Trace
6	**B**	DIPEA	EtOH	50	60	9
7	**C**	DIPEA	DMF	50	73	Trace
8	**D**	DIPEA	DMF	50	9	0
9	**E**	DIPEA	DMF	50	0	0

[a] NMR yield.

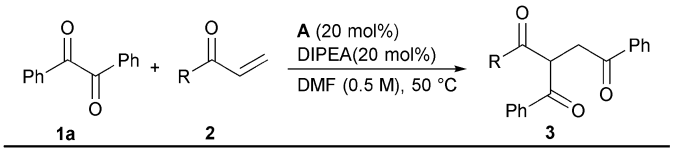


(entries 5 and 7). The triazolium and imidazolium salts **D** and **E** gave little or no expected product (entries 8 and 9). Formation of the by-product **4** with **B** and **C** might be caused by the OH group attached to the thiazolium skeleton. In fact, when the reactions with **A** and **B** were carried out in EtOH solvent, **4** was formed in 11% and 9% yields, respectively, though as a minor product (entries 4 and 6). No reaction took place, of course, in the absence of NHC salts.

The reaction of benzil (**1a**) with various aryl vinyl ketones **2** was carried out under the optimal conditions (Table 2). Substrates **2** having both electron donating and withdrawing substituents on the *p*-position of the phenyl ring gave products **3** in high yields (entries 4, 6, and 8), except for *p*-cyanopheny enone **2i** (entry 9). On the contrary, the substituents on the *o*-position afforded **3** in decreased yields, probably due to steric hindrance as well as the reaction with mesityl vinyl ketone (**2e**) (entries 2, 5, and 7).[11] A similar difference between 1- and 2-naphthyl substrates **2j** and **2k** was observed (entries 10 and 11). Moreover, the present reaction could be applicable to the heteroaromatic and aliphatic substrates **2l**, **2m** and **2n** (entries 12–14).

Next we investigated the reaction of symmetrical and unsymmetrical benzil derivatives **1b–1h** with phenyl vinyl ketone (**2a**) (Table 3). Bis-*p*-tolyl and bis-*p*-anisyldiketones **1b** and **1c** gave product **3ba** and **3ca** in 48% and 16% yields, respectively, whereas 4-chloro and 4-bromo-substituted diketone **1d** and **1e** produced **3da** and **3ea** in better yields (entries 1–4). In the

Table 2 Reaction with various enones



Entry	Enone 2	R	Time (h)	Product 3	Yield[a] (%)
1	**2a**	Ph	12	**3aa**	92
2	**2b**	*o*-Tolyl	18	**3ab**	58
3	**2c**	*m*-Tolyl	12	**3ac**	80
4	**2d**	*p*-Tolyl	12	**3ad**	89
5	**2e**	Mesityl	36	**3ae**	13
6	**2f**	*p*-Anisyl	12	**3af**	75
7	**2g**	*o*-ClC_6H_4	12	**3ag**	53
8	**2h**	*p*-ClC_6H_4	12	**3ah**	87
9	**2i**	*p*-NCC_6H_4	12	**3ai**	37
10	**2j**	1-Naphthyl	12	**3aj**	67
11	**2k**	2-Naphthyl	12	**3ak**	87
12	**2l**	2-Thienyl	12	**3al**	87
13	**2m**	3-Thienyl	12	**3am**	89
14[b]	**2n**	Me	20	**3an**	68

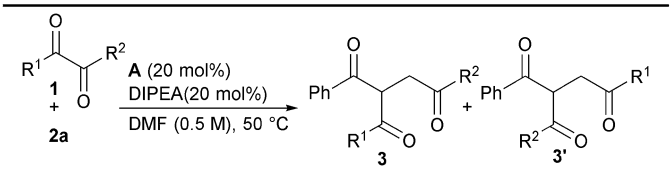
[a] Isolated yield. [b] 3 equiv. of **2n** were used.

reaction of unsymmetrical diketones **1f** and **1g**, two regioisomers **3** and **3′** were formed as inseparable mixtures, wherein relatively electron deficient aryl groups were introduced into the β-position of enone **2a**, though with low selectivities (entries 5 and 6). The reaction of 1-phenypropane-1,2-dione (**1h**) gave products **3ha** and **3an** in 42% yield with a ratio of 83/17 (entry 7).

As can be seen in Table 3, electron donating groups of the diketones decreased the product yields (entries 1, 2, and 7). Thus, we attempted their improvement by use of Lewis acid co-catalysts.[12] The yields of **3ba**, **3ca** and (**3ha** + **3an**) actually increased to 90%, 49% and 62%, respectively, with 20 mol% of $MgCl_2$. However, the effect was not always so positive for all products **3** (see ESI†).

More importantly, the reaction of unsymmetric benzils **1f–1h** gave no cross-products, for example, neither **3aa** nor **3ba** was formed in the reaction of **1f**. These results suggested that double acylation would take place intramolecularly. In order to confirm this hypothesis, the reaction of **2a** with an equimolar mixture of

Table 3 Reaction of substituted benzils



Entry	Benzil 1 R[1]		R[2]	Product 3	3′	Yield[a] (%) (3 + 3′)	Ratio (3/3′)
1	**1b**	*p*-Tolyl	*p*-Tolyl	**3ba**	—	48	—
2	**1c**	*p*-Anisyl	*p*-Anisyl	**3ca**	—	16	—
3[b]	**1d**	*p*-ClC_6H_4	*p*-ClC_6H_4	**3da**	—	70	—
4[b]	**1e**	*p*-BrC_6H_4	*p*-BrC_6H_4	**3ea**	—	73	—
5	**1f**	Ph	*p*-Tolyl	**3fa**	**3ad**	80	40/60
6	**1g**	Ph	*p*-ClC_6H_4	**3ga**	**3ah**	85	55/45
7	**1h**	Ph	Me	**3ha**	**3an**	42	83/17

[a] Total isolated yield. [b] DMF (0.25 M).

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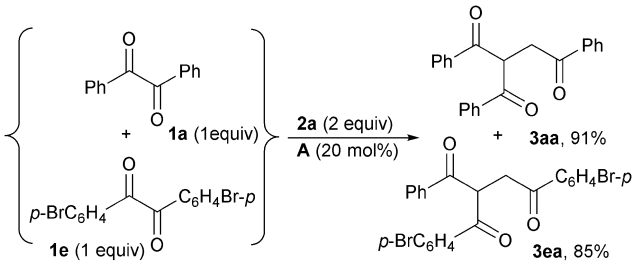


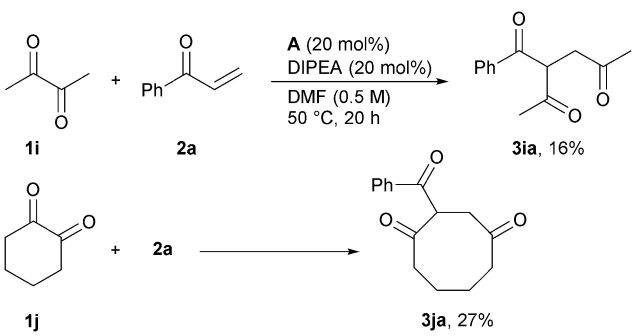
Scheme 2 Intramolecular double acylation.

symmetrical benzils **1a** and **1e** was carried out under standard conditions (Scheme 2). The two diketones reacted independently with **2a** to yield products **3aa** and **3ea** in 91% and 85% yields, respectively, whereas cross-products were not detected.

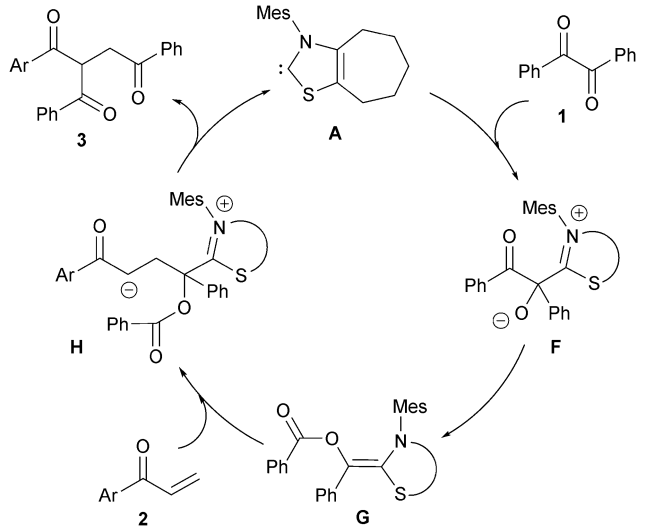
Compared to benzil derivatives, aliphatic 1,2-diketones gave the expected product in lower yields (Scheme 3). Thus, the double acylation product **3ia** was obtained in only 16% yield by the reaction of biacetyl (**1i**) with enone **2a**, but the corresponding hydroacylation product was not formed. Interestingly, the reaction of cyclohexane-1,2-dione (**1j**) gave 8-membered triketone **3ja** in 27% yield. It is noteworthy that this ring-expansion reaction showed a striking contrast to the thiazolium carbene-catalyzed ring-opening hydroacylation of chalcones with **1j** in EtOH.[6a]

A plausible mechanism of the double acylation is proposed in Scheme 4. Addition of carbene **A** to benzil (**1**), followed by migration of the benzoyl group to the alkoxide moiety, yields the acylated Breslow intermediate **G**. Michael addition of **G** to enone **2** generates zwitterion **H**. Then, intramolecular abstraction of the benzoyl group by enolate results in the formation of product **3** and regeneration of **A**. Although this mechanism is analogous to that of Stetter reaction, suppression of the benzoyl group elimination from the intermediate **F** or **G** in anhydrous aprotic solvent would lead to double acylation. The low yields with aliphatic 1,2-diketones may be caused by inefficient alkanoyl migration in **F** as well as enolization of the diketone.

In summary, we have succeeded in the extension of Stetter reaction, *i.e.*, thiazolium carbene-catalyzed reaction of benzils with enones gave double acylation products in good yields, whereas hydroacylation by classical Stetter reaction was completely excluded. These results provide new potential for NHC-catalyzed reaction, by allowing the insertion of activated carbon–carbon multiple bonds into other acyl compounds than aldehydes.



Scheme 3 Reaction of aliphatic 1,2-diketone.



Scheme 4 Proposed mechanism.

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