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Relation	

NHC-catalyzed cleavage of vicinal diketones and triketones followed by insertion of enones and ynones

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and Hiroshi Fukuoka

Abstract

Thiazolium carbene-catalyzed reactions of 1,2-diketones and 1,2,3-triketones with enones and ynones have been investigated. The diketones gave α,β-double acylation products via unique Breslow intermediates isolable as acid salts, whereas the triketones formed stable adducts with the NHC instead of the coupling products.

Introduction

N-Heterocyclic carbenes (NHCs) have been indispensable catalysts for organic synthesis, particularly for umpolung of various functional groups [1-9]. In the Stetter reaction, NHCs convert aldehydes to nucleophilic species, which react with activated alkenes to yield hydroacylation products [10-14]. When the carbonyl compounds **I** other than aldehyde behave similarly, functionalized 1,4-diketones **IV** would be produced (Scheme 1). Previously, we reported that benzils **I** (G = C(O)R^1) reacted with enones **III** in the presence of thiazolium carbene catalysts to give double acylation products **IV** in good yields [15]. If enones can be replaced by ynones **III** in the reaction with benzils, alkenes **IV** having three acyl moieties would be formed directly. Related products were recently obtained by the dimsyl

anion-promoted double acylation of enones with benzils, followed by dehydrogenation of the resulting alkanes in one pot [16]. Moreover, if the reaction of cyclic 1,2-diketone **I** (G = C(O)R^1) with activated alkenes may take place similarly, this reaction could be utilized as a ring-enlargement procedure to afford cyclic 1,4-diketones **IV**.

With respect to the active species in the Stetter reaction, aminoenols **II** (G = H, Breslow intermediates) had been postulated as true nucleophiles for a long time and those generated from imidazolinium NHC were recently isolated in pure form [17,18]. In the reaction of benzils with thiazolium NHC, aminoenol esters **II** (G = C(O)R^1) could be formed similarly,
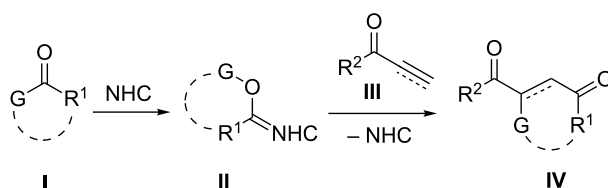
Scheme 1: Reaction process.

but this active species were found to exist as isolable acid salts unexpectedly. Moreover, the reactivity of 1,2,3-triketones was also investigated in comparison with that of 1,2-diketones. We would like to report herein these results.

Results and Discussion

The reaction of benzil (**1a**) with various ynones **2** was carried out by use of thiazolium salt **3** under similar conditions to that with enones (Table 1) [15]. In the reaction of **1a** with 1-phenyl-prop-2-yn-1-one (**2a**), tribenzoylethylene (**4aa**) was formed in

64% yield (Table 1, entry 1). Fortunately possible propargylic alcohols by cross-benzoin reaction were not detected [19]. The other products of **4** were obtained as inseparable mixtures of *E*- and *Z*-isomer, except for **4ae** and **4ar**, but their stereochemistry could not be determined by NMR. Only the major isomer of **4ai** crystallized from the mixture and thus *Z*-stereochemistry of the two aroyl groups (ClC$_6$H$_4$CO and PhCO) was confirmed by X-ray analysis (Figure 1) [20]. Electron-donating substituents of ynones **2** gave slightly better yields than electron-withdrawing ones. The yields and isomer ratios were also affected by the po-

Table 1: Reaction of benzil (**1a**) with ynones **2**[a].
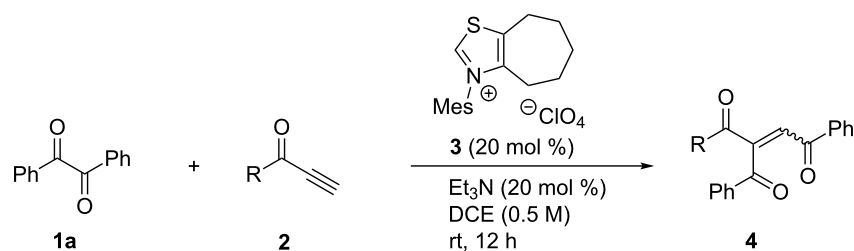
Entry	Ynone **2**	R	Product **4**	Yield (%)[b]	Isomer ratio[c]
1	**2a**	Ph	**4aa**	64	–
2	**2b**	2-MeC$_6$H$_4$	**4ab**	54	74:26
3	**2c**	3-MeC$_6$H$_4$	**4ac**	64	52:48
4	**2d**	4-MeC$_6$H$_4$	**4ad**	63	52:48
5	**2e**	2,4,6-Me$_3$C$_6$H$_2$	**4ae**	32	–[d]
6	**2f**	4-MeOC$_6$H$_4$	**4af**	63	53:47
7	**2g**	2-ClC$_6$H$_4$	**4ag**	31	80:20
8	**2h**	3-ClC$_6$H$_4$	**4ah**	49	61:39
9	**2i**	4-ClC$_6$H$_4$	**4ai**	53	60:40[e]
10	**2j**	4-BrC$_6$H$_4$	**4aj**	57	59:41
11	**2k**	4-MeO$_2$CC$_6$H$_4$	**4ak**	44	59:41
12	**2l**	4-NCC$_6$H$_4$	**4al**	20	71:29
13	**2m**	2-furyl	**4am**	41	65:35
14	**2n**	2-thienyl	**4an**	54	67:33
15	**2o**	3-thienyl	**4ao**	61	67:33
16	**2p**	1-naphthyl	**4ap**	52	69:31
17	**2q**	2-naphthyl	**4aq**	50	53:47
18	**2r**	Ph(CH$_2$)$_2$	**4ar**	13	–[d]

[a]Equimolar amounts of **2** were used. [b]Isolated yields. [c]Estimated by NMR. [d]One stereoisomer was formed. [e]*E/Z* = 40:60 determined by X-ray analysis.

sition of the substituents on the aroyl groups, i.e., *ortho*-substituents decreased the product yields and increased the isomer ratios (Table 1, entries 2–4 and 7–9). Mesityl and aliphatic ynones **2e** and **2r** gave the single isomers **4ae** and **4ar** in low yields (Table 1, entries 5 and 18).
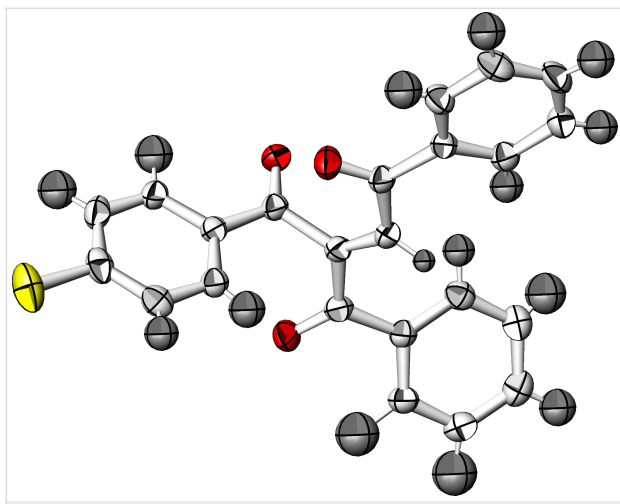

Figure 1: ORTEP drawing of *Z*-**4ai**.

Then, the substituent effect of benzils **1** was investigated (Table 2). Electron-donating groups decreased the reaction efficiency slightly. The yields were improved by catalytic amounts of MgCl$_2$ as reported previously [15], whereas the isomer ratios of **4** were nearly unchanged irrespective of the Lewis acid. When a mixture of benzils **1b** and **1c** (0.5 equiv each) was treated with **2a** (1.0 equiv) under similar conditions, the products **4ba** and **4ca** were formed in 52% and 20% yields, respectively. However, cross products having three different aroyl groups were not detected at all. Thus, the present reaction was proved to take place by an intramolecular process.

A reaction mechanism is proposed in Scheme 2, which is similar to that with enones [15]. The monoacylated Breslow intermediate **C** is formed by addition of thiazolium NHC **A** to benzil (**1a**), followed by migration of the benzoyl group. Then, this nucleophilic species **C** reacts with ynones **2** to generate the intermediate **D**. The second migration of the benzoyl group to the α-position of **2** and simultaneous elimination of **A** affords product **4**.
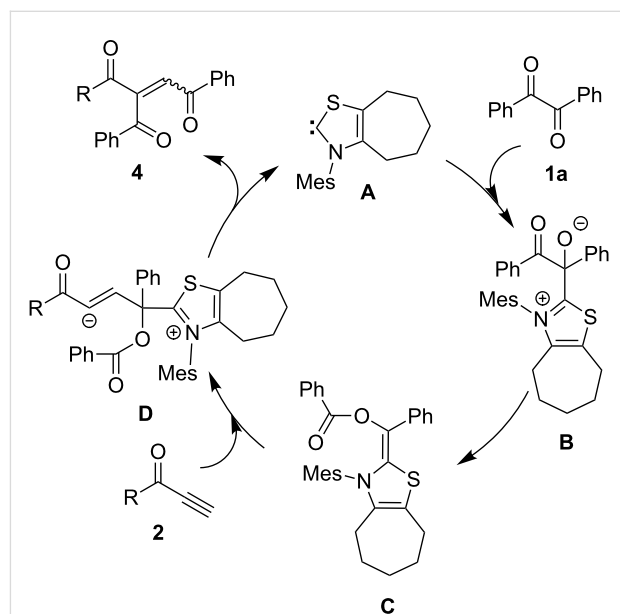
Scheme 2: Reaction mechanism.

According to the intramolecular mechanism shown in Scheme 2, the two benzoyl groups of **1a** should be delivered to the ynones **2** from the same side to yield *E*-products **4** exclusively. However, **4** were obtained as a mixture of *E*- and

Table 2: Reaction of substituted benzils **1** with ynone **2a**[a].
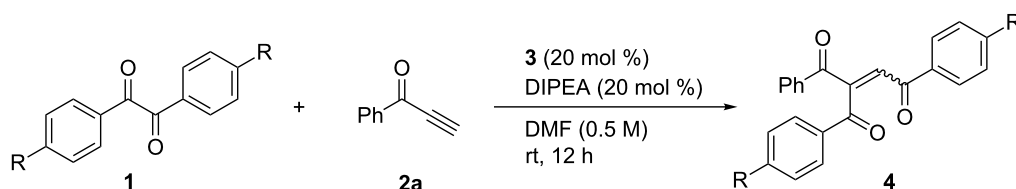
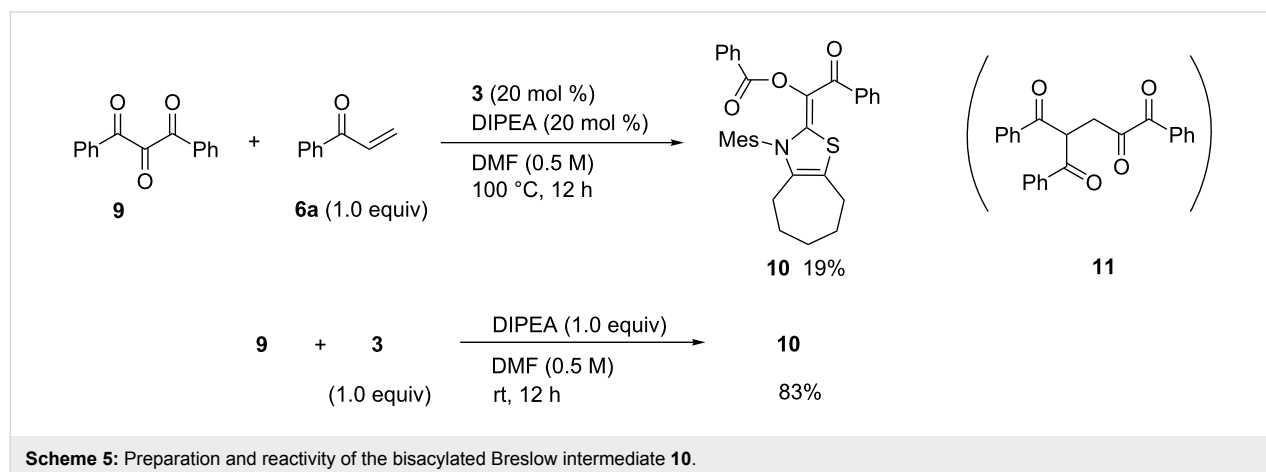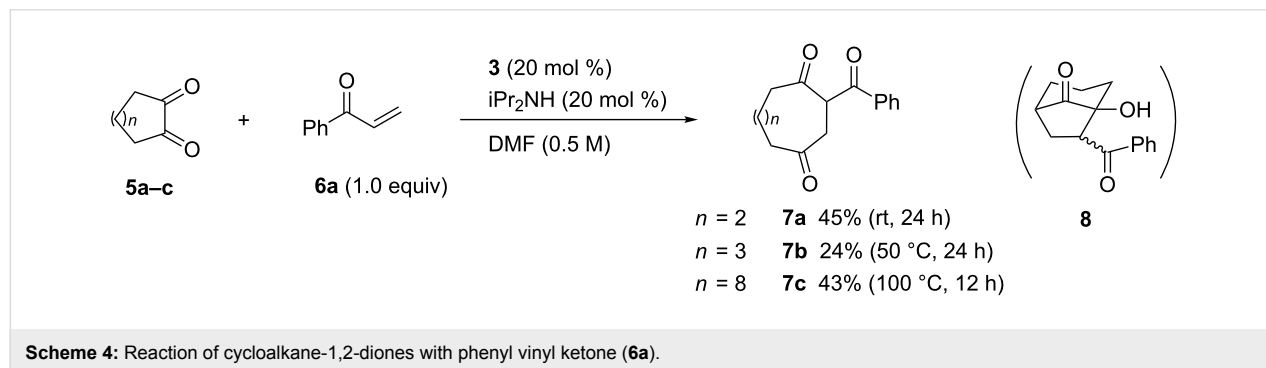| Entry	Benzil **1**	R	Product **4**	Yield (%)[b,c]	Isomer ratio
1	**1b**	Me	**4ba**	48 (76)	50:50
2	**1c**	OMe	**4ca**	16 (25)	50:50
3	**1d**	Cl	**4da**	56 (74)	53:47
4	**1e**	Br	**4ea**	42 (63)	58:42

[a]Equimolar amounts of **2** were used. [b]Isolated yields. [c]Yields in parentheses were observed in the presence of MgCl$_2$ (20 mol %).

Z-isomer in the most cases. Since pure *Z*-isomer of the product **4ai** was exceptionally isolated, its isomerization was tested in order to explain the stereochemistry (Scheme 3). When the *Z*-**4ai** was dissolved in CDCl$_3$ and monitored by NMR, the ratio of *E/Z* changed slowly to 38:62 after 21 days. In contrast, the original ratio of 40:60 was quickly attained in the presence of the NHC catalyst **A**.
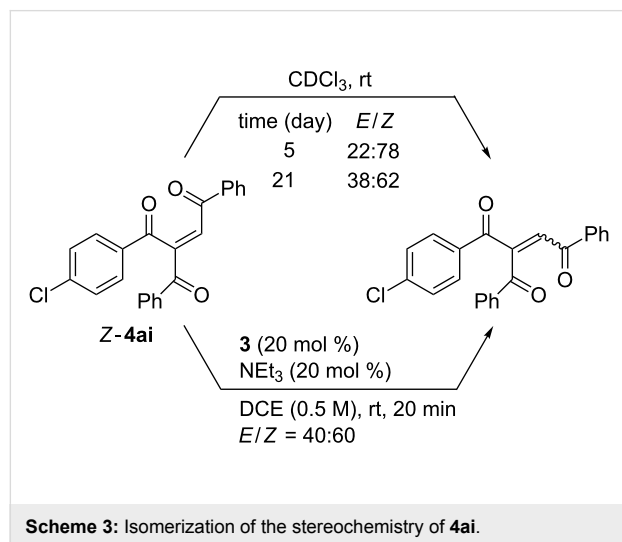
We demonstrated previously the reaction of cyclohexane-1,2-dione (**5a**) with phenyl vinyl ketone (**6a**) to afford 2-benzoylcyclooctane-1,4-dione (**7a**) in 27% yield [15]. Since this reaction would be a unique ring enlargement by two carbons, an improvement of the reaction conditions has been tested. Although the yield increased to 45% by the use of diisopropylamine instead of DIPEA, the reaction efficiency was much lower than that of benzil (**1a**) (Scheme 4). The only isolated by-product in the reaction of **5a** was bicyclo[3.2.1]octanone **8** (ca. 10%), which was formed by competitive tandem Michael–aldol reaction [21]. Cycloheptane-1,2-dione (**5b**) and cyclododecane-1,2-dione (**5c**) gave the 9- and 14-membered 1,4-diketones **7b** and **7c** at elevated temperature, respectively.

Next, we investigated the NHC-catalyzed reaction of 1,2,3-triketone **9** with enone **6a**. Since the central carbonyl group of **9** could be more electrophilic than the others at 1- and 3-positions, nucleophilic addition of NHC followed by migration of one neighboring acyl group to the central carbonyl oxygen would generate bisacylated Breslow intermediate **10** (Scheme 5). If this species behaves in a similar manner as the monoacylated intermediate **C** derived from 1,2-diketone **1**, its reaction with enone **6a** would be expected to yield tetraketone **11**. However, when triketone **9** was treated with equimolar

Scheme 3: Isomerization of the stereochemistry of **4ai**.

Scheme 4: Reaction of cycloalkane-1,2-diones with phenyl vinyl ketone (**6a**).

Scheme 5: Preparation and reactivity of the bisacylated Breslow intermediate **10**.

amounts of **6a** in the presence of **3** and DIPEA (20 mol %, each), the predicted intermediate **10** was obtained in 19% yield based on **9**, but any coupling products of **9** with **6a** such as **11** were not formed. The yield of **10** increased to 83% in the equimolar reaction of **9** with **3**. In addition, the product **10** was recovered unchanged after treatment with **6a** irrespective of DIPEA. The nucleophilicity of **10** may be canceled by the two benzoyl groups. The product **10** was fairly stable to air and moisture, and thus *E*-structure was confirmed by X-ray analysis as shown in Figure 2 [20].

Isolation of **10** prompted us to get the monoacylated Breslow intermediate **C** also as a stable compound. Treatment of benzil **1d** with equimolar amounts of **3** and DIPEA at room temperature, followed by non-aqueous work-up and column chromatography gave crystalline product **12** in 92% yield (Scheme 6). Although **12** did not provide single crystals suitable for X-ray analysis, its structure was determined by NMR and elemental analysis. ^{1}H NMR spectra of **12** showed eleven protons in the aromatic region, i.e., two ClC_6H_4, $Me_3C_6H_2$, and one particular proton at δ 6.68. In ^{13}C NMR spectra, one unknown signal appeared in the neighborhood of the ester carbon (δ 163.1 and 167.1). Moreover, an unusual signal appeared at δ 71.5. These data indicated definitely that the isolated product **12** was different from the expected intermediate **C**. Instead, the iminium salt **12**, that is, the $HClO_4$ salt of **C**, could account for all unusual signals. Furthermore, elemental analysis of **12** agreed very closely with its theoretical value and deviated much from that of **C**.
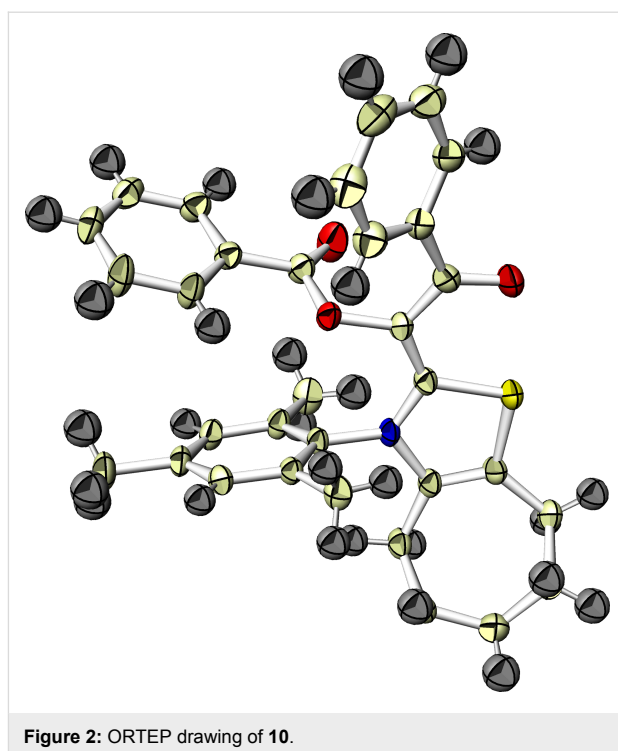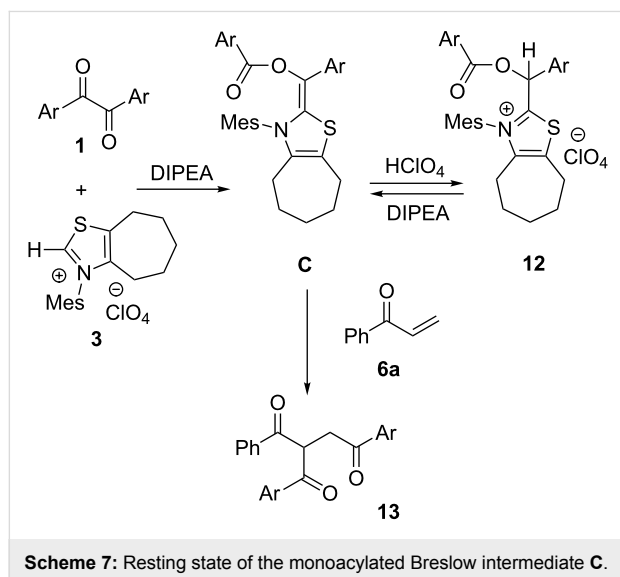

Figure 2: ORTEP drawing of **10**.

After identification of the product **12**, we noticed that Massi and his group obtained the similar adducts during their study on the multicomponent reaction of thiazolium carbenes, benzils and water to yield 1,4-thiazin-3-ones [22]. Although the initial process producing the salt **12** was similar, the total mode of the two reactions was quite different, that is, stoichiometric vs cata-
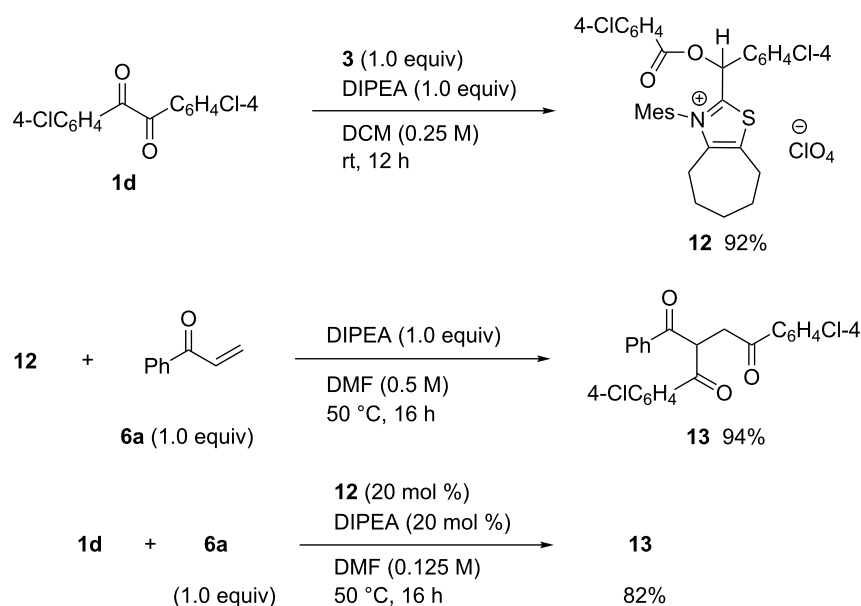
Scheme 6: Preparation of the iminium salt **12** and its reactivity.

lytic reaction with respect to the thiazolium carbenes. In the Massi reaction, monoacylated Breslow intermediate **C** was readily hydrolyzed by hydroxide, whereas Stetter reaction took place exclusively in our reaction. The difference would be caused by the reaction conditions, particularly by the solvent system.

Since the product **12** was obtained unexpectedly, its reactivity and role in the catalytic cycle were investigated. The stoichiometric reaction of **12** with phenyl vinyl ketone (**6a**) in the presence of DIPEA gave the product **13** in 94% yield, while no product was formed without the base. Moreover, the reaction of benzil **1d** with enone **6a** was catalyzed by **12** to give the product **13** in good yield, which are comparable results to the use of **3** [15]. These results suggested that compound **12** played a resting state of the monoacylated Breslow intermediate **C** as shown in Scheme 7. Accordingly, when enone **6a** was present in the mixture, facile regeneration of **C** and its reaction with **6a** took place predominantly. It seems surprising that compound **12** could be quantitatively generated from **C** and HClO₄ regardless of equimolar amounts of DIPEA, while analogous intermediates derived from imidazole NHC were protonated by the acid alone [23].

It was also found that the monoacylated Breslow intermediates changed reversibly to the resting state of acid salts.

Supporting Information

Supporting Information File 1
Experimental procedure, characterization data and copies of ¹H and ¹³C NMR spectra of the products.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-176-S1.pdf]

Scheme 7: Resting state of the monoacylated Breslow intermediate **C**.

Conclusion
We have demonstrated the thiazolium NHC-catalyzed reaction of benzils with ynones to give triacylated alkenes in fairly good yields. When this reaction was applied to aliphatic cyclic diketones with enones, two carbon ring-enlarged products were formed, though in low yields. Moreover, aromatic 1,2,3-triketones reacted with NHCs to afford bisacylated Breslow intermediates in high yield. However, their nucleophilicity was so weak that they were recovered unchanged in the reaction with enones.

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20. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1506357 (**4ai**) and CCDC 1506358 (**10**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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