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N-Heterocyclic Carbene-Catalyzed Reaction of Alkynyl Aldehydes with 1,3-Keto Esters or 1,3-Diketones

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Abstract: The N-heterocyclic carbene-catalyzed reaction of alkynyl aldehydes with 1,3-keto esters or 1,3-diketones has been studied. This protocol offers an entirely new, mild and atom-economical access to highly functionalized 3,4-dihydropyranones.

Keywords: aldehydes; dihydropyranones; N-heterocyclic carbenes; organocatalysis; umpolung

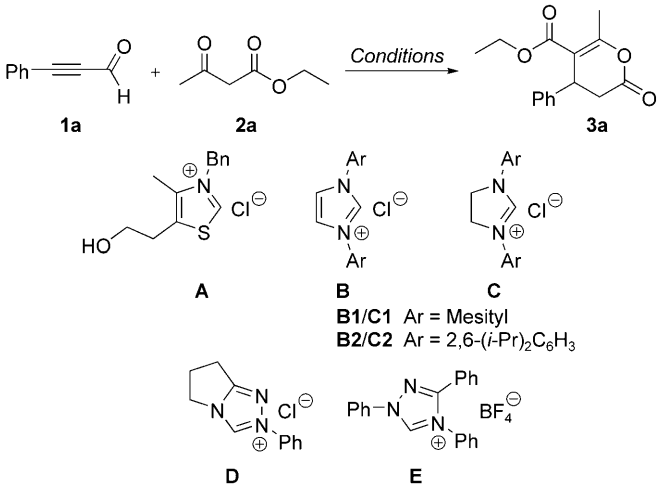
N-Heterocyclic carbene (NHC)-catalyzed umpolung reactions have attracted considerable attention due to their wide applications in organic synthesis.[1] The Breslow intermediates[2] generated from aldehydes *in situ* can react with a variety of electrophiles, such as aldehydes,[3] ketones,[4] imines,[5] diazenes,[6] activated and even unactivated C=C double bonds.[7] Among the numerous aldehydes, much attention has been paid to α,β-unsaturated aldehydes especially the α,β-unsaturated enals over the past few years. However, there were extremely few reports on the reaction involving α,β-unsaturated ynals, namely alkynyl aldehydes,[8] which also possess a rich reactivity pattern.[9] Recently, Zeitler has achieved for the first time an NHC-catalyzed redox esterification of alkynyl aldehydes. It was proposed that, similar to cinnamaldehyde and its derivatives, protonation of the Breslow intermediates generated from alkynyl aldehydes would also give activated carboxylates, which subsequently regenerate the NHC catalyst upon acylation of oxygen nucleophiles.[8a]

Making C–C bonds is a fundamental method in synthetic organic chemistry that is often used to construct complicated molecules. The development of efficient methods for C–C bond formation prompted us to investigate the NHC-catalyzed reaction of alkynyl aldehydes with carbon nucleophiles.

Our explorations commenced with the reaction of 3-phenylpropiolaldehyde with ethyl 3-oxobutanoate in the presence of carbene precursors **A**–**E** (Table 1). The thiazolium salt **A** proved unsuitable for this reaction (entry 1), making the reaction system very complicated. To our delight, with imidazolium salt **B1** (IMes·HCl) and *t*-BuOK in THF, 3,4-dihydropyranone[10] **3a** was isolated in 65% yield (entry 2), and its structure was confirmed by spectroscopic and X-ray analysis (Figure 1).[11] A similar result was obtained in the case of NHC precursor **B2** (entry 3). In comparison, imidazolinium salts **C1** and **C2** as well as triazolium salts **D** and **E** are less active for this reaction (entries 4–7). Further investigation on catalyst loading, base and solvent (entries 8–15) revealed the optimal reaction conditions: 10 mol% of **B1** and 10 mol% of *t*-BuOK in THF at ambient temperature for 2 h (entry 8).

After the optimal conditions had been established, the generality of the reaction was explored (Table 2). It was demonstrated that the reaction is able to accommodate a variety of substituted alkynyl aldehydes. The electronic nature of the substituents on the aromatic ring of the aldehydes has limited influence on the reaction (entries 1–7). Moreover, the reaction proceeded smoothly in the case of 3-cyclohexenylpropiolaldehyde, an aliphatic-substituted alkynyl aldehyde, which also indicated that the existence of a conjugated double bond has no effect on the reaction (entry 8). The reaction works equally well for other 1,3-keto esters like methyl 3-oxobutanoate and ethyl 3-oxopentanoate (entries 9 and 10). As for 1,3-diketones, the corresponding 3,4-dihydropyranones **3k** and **3l** were obtained in good yields (entries 11 and 12). The structure of **3l** was determined by NOE experiments (see Supporting Information). It is worth noting that the reaction of the unsymmetrical 1,3-diketone 1-phenylbutane-1,3-dione was highly selective,

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Solvent	Base	Yield[b] [%]
1	**A** (20)	THF	*t*-BuOK	–
2	**B1** (20)	THF	*t*-BuOK	65
3	**B2** (20)	THF	*t*-BuOK	63
4	**C1** (20)	THF	*t*-BuOK	45
5	**C2** (20)	THF	*t*-BuOK	48
6	**D** (20)	THF	*t*-BuOK	14
7	**E** (20)	THF	*t*-BuOK	15
8	**B1 (10)**	**THF**	***t*-BuOK**	**72**
9	**B1** (5)	THF	*t*-BuOK	38
10	**B1** (15)	THF	*t*-BuOK	69
11	**B1** (10)	THF	NaH	57
12	**B1** (10)	THF	DBU	32
13	**B1** (10)	THF	Et_3N	42
14	**B1** (10)	Toluene	*t*-BuOK	31
15	**B1** (10)	Dioxane	*t*-BuOK	57

[a] Performed on a 0.5 mmol scale at 0.25 M with 1 equiv. of 3-phenylpropiolaldehyde, 1.2 equiv. of ethyl 3-oxobutanoate, the indicated amounts of catalyst, and equal amounts (to catalyst) of base at room temperature for 2 h.

[b] Isolated yield after chromatography.

giving the corresponding 3,4-dihydropyranone **3l** as the only product (Figure 2).

Lupton and co-workers have recently reported a conjugate addition reaction involving enolate anions and α,β-unsaturated acyl azoliums.[10d] Inspired by this, we postulated that the above reaction may proceed along the following lines. As might be expected, the NHC reacted with the alkynyl aldehyde to furnish the Breslow intermediate **I**. The subsequent protonation of **II** with the more acidic (compared with alcohol) H-donor, 1,3-keto ester or 1,3-diketone, afforded the enolate anion **III** and activated carboxylate **IV**, which subsequently underwent conjugate addition, *H*-migration and acylation to deliver the product 3,4-dihydropyranone **3** and regenerated the NHC (Scheme 1).

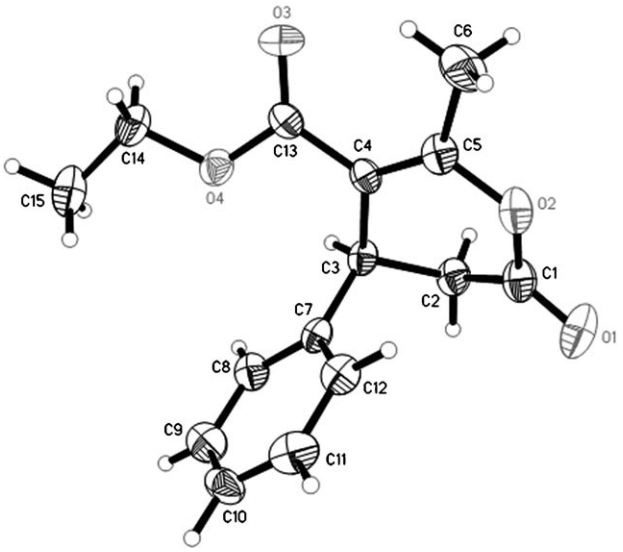
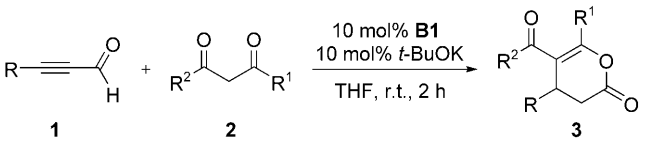


Figure 1. Single crystal X-ray structure of **3a**.

Table 2. Substrate scope.[a]



Entry	R	R^1, R^2	Product	Yield[b] [%]
1	Ph	Me, OEt	**3a**	72
2	4-MeO-C_6H_4	Me, OEt	**3b**	54
3	4-Me-C_6H_4	Me, OEt	**3c**	69
4	4-F-C_6H_4	Me, OEt	**3d**	58
5	4-Br-C_6H_4	Me, OEt	**3e**	41
6	1-naphthyl	Me, OEt	**3f**	56
7	2-thienyl	Me, OEt	**3g**	71
8	1-cyclohexenyl	Me, OEt	**3h**	75
9	Ph	Me, OMe	**3i**	74
10	Ph	Et, OEt	**3j**	70
11	Ph	Me, Me	**3k**	65
12	Ph	Me, Ph	**3l**	66

[a] Performed on a 0.5 mmol scale at 0.25 M with 1 equiv. of alkynyl aldehyde, 1.2 equiv. of 1,3-keto ester or 1,3-diketone, 10 mol% **B1**, and 10 mol% *t*-BuOK in THF at room temperature for 2 h.

[b] Isolated yield after chromatography.

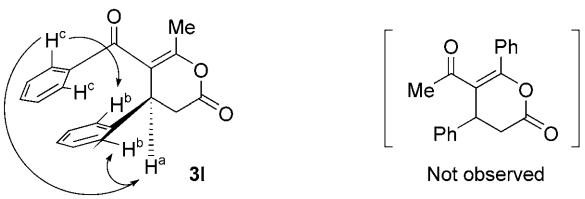
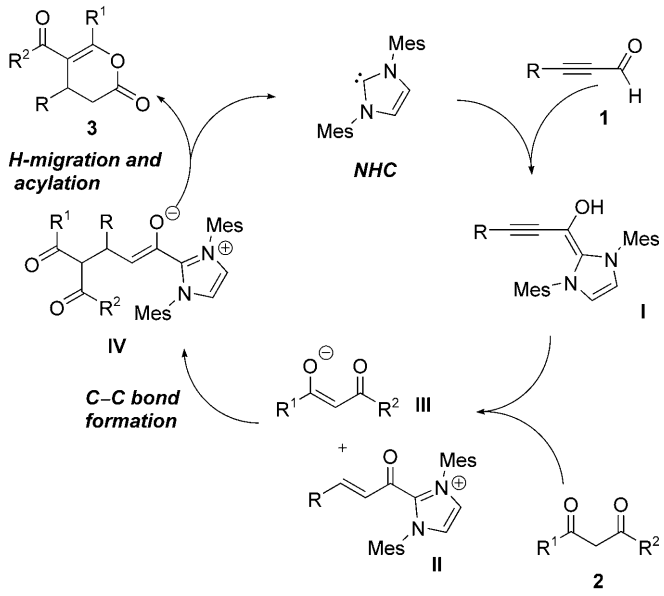


Figure 2. Proof of the structure by NOE experiments.



Scheme 1. Proposed reaction mechanism.

In conclusion, an NHC-catalyzed reaction of alkynyl aldehydes with 1,3-keto esters or 1,3-diketones was disclosed, which might become an efficient method for the direct synthesis of highly functionalized 3,4-dihydropyranones from simple substrates. The ready availability of the starting materials, atom economy of the reaction and the usefulness of the products[12] would make this strategy quite attractive. Additionally, we anticipate that the reaction presented in this paper will not only improve our understanding of the reactivity of alkynyl aldehydes and their derived Breslow intermediates, but also expand the application of NHC-catalyzed reactions. The development of an enantioselective variant of this protocol as well as exploration of the diversity of the NHC-catalyzed reaction of alkynyl aldehydes is currently underway.

Experimental Section

Typical Procedure for the NHC-Catalyzed Reaction of Alkynyl Aldehydes and 1,3-Keto Esters or 1,3-Diketones

Into an oven-dried 10-mL vial were weighed catalyst **B1** (17 mg, 0.05 mmol) and *t*-BuOK (6 mg, 0.05 mmol). THF (1 mL) was added to the mixture. The resulting mixture was stirred at room temperature under N_2 for 10 min followed by the addition of a solution of alkynyl aldehyde (0.5 mmol), 1,3-keto ester or 1,3-diketone (0.6 mmol) in THF (1 mL). The mixture was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (hexane/EtOAc, 7:1).

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[11] CCDC 767267 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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