Synthetic Methods

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Acetylide Ion (C_2^{2-}) as a Synthon To Link Electrophiles and Nucleophiles: A Simple Method for Enaminone Synthesis**

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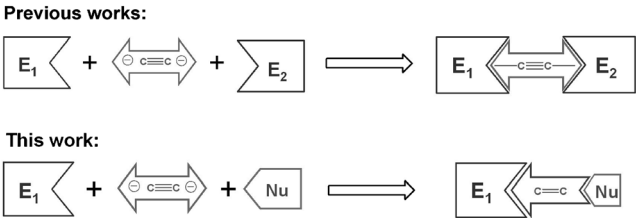
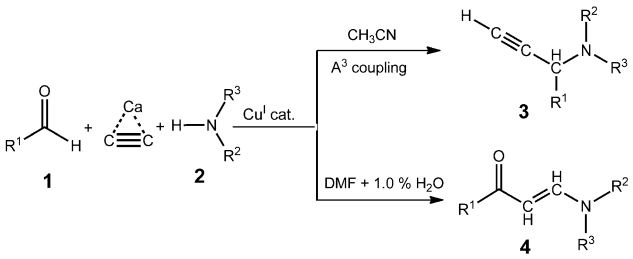
Although the dumbbell structure of the acetylide ion, C_2^{2-}, has been known for many years,[1] the direct use of metal acetylides ($M^I_2C_2$ or $M^{II}C_2$) in organic synthesis is quite rare, mainly because of the low solubility of metal acetylides in common organic solvents.[2–4] Given the demand for the alkyne functionality and its nucleophilic properties, the acetylide ion could play an important role in modern organic synthesis.[5] It was reported previously that the acetylide dianion can act as a mild nucleophile to link two identical electrophiles, such as aryl halides (Sonogashira coupling)[2] or two carbon dioxide molecules,[6] or an aldehyde with an amine (Scheme 1).[4] Conditions have also been developed for acetylides to bridge two different electrophiles to form asymmetrical internal alkynes.[4] Herein, we report that the acetylide ion (C_2^{2-}) can link an electrophile (aldehyde) with a nucleophile (amine) in one catalytic cycle (Scheme 1). This remarkable finding constitutes a simple and efficient method for the synthesis of enaminones from readily accessible small molecules.



Scheme 1. Versatile acetylide synthon for organic synthesis.

Enaminones show versatile reactivity as both electrophiles and nucleophiles and have long been used as important synthetic intermediates for a wide variety of heterocycles contained in natural products and pharmaceutical compounds.[7,8] Although a number of methods have been developed for the preparation of enaminones,[9] all are based on specific multifunctional starting materials, such as 1,3-dicarbonyl compounds,[10] enolates,[11] heterocycles,[9f,12] propargyl alcohols,[13] or ketones.[14] Thus, the development of new methods for enaminone synthesis from simple molecules is highly desired.[15] We previously developed a novel catalytic system[4] for the production of propargylamines from calcium carbide by aldehyde–alkyne–amine (AAA, A^3)[16] and alkyne–dihalomethane–amine (AHA)[17] three-component coupling reactions. In these reactions, it is believed that the nucleophilic acetylide attacks an iminium intermediate to form propargylamines.[16] Interestingly, the presence of enaminones in the reaction mixture was observed under certain conditions (Scheme 2). This observation triggered our interest on two counts: we could develop a novel, valuable method for enaminone synthesis and find out how an acetylide links an electrophile and a nucleophile in one pot.

In a reaction mixture containing an aldehyde, an amine, acetylide, and a copper(I) catalyst, different potential reactions could occur to afford different products, such as an amide, an imine, a propargylamine, or a propargyl alcohol.[17,18] Thus, tuning of the reaction conditions is crucial for enaminone production. An initial test was conducted in *N,N*-dimethylformamide (DMF; AR grade, 0.02 vol % water) with the catalyst CuI (5 mol %), benzaldehyde, calcium carbide, and diisopropylamine at 85 °C for 48 h. The reaction gave exclusively the enaminone, 3-(diisopropylamino)-1-phenylprop-2-en-1-one (**4a**), in 60 % yield with incomplete conversion of the aldehyde. Interestingly, when the solvent was changed to acetonitrile (AR grade), the reaction produced only the propargylamine, *N,N*-diisopropyl-1-phenylprop-2-yn-1-amine (**3a**), in 55 % yield. The reaction in dimethyl sulfoxide also afforded the enaminone, whereas the propargylamine was formed in THF and toluene (see Table 1 in the Supporting Information). It was found that the synthesis of the enaminone could be sped up by adding water (1 vol %) to the DMF solvent. Under these conditions, the enaminone was formed in 83 % yield in 16 h (see Table 1 in the Supporting Information). None of the desired product was observed when anhydrous DMF was used. Further screening



Scheme 2. Different pathways for the three-component coupling of an aldehyde, calcium carbide, and an amine.

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showed that the reaction proceeded well when the quantity of the water additive was in the range of 0.5–1.5 vol% (Figure 1a). When the water content in DMF was increased above 3 vol%, the yield of enaminone dropped dramatically to less than 50%. Kinetic studies showed that a small amount of water not only increased the yield of the enaminone, but could also shorten the reaction time from 48 to 16 h (Figure 1b). The reaction could only be catalyzed by Cu^I catalysts. Among the Cu^I salts tested, CuI demonstrated the highest

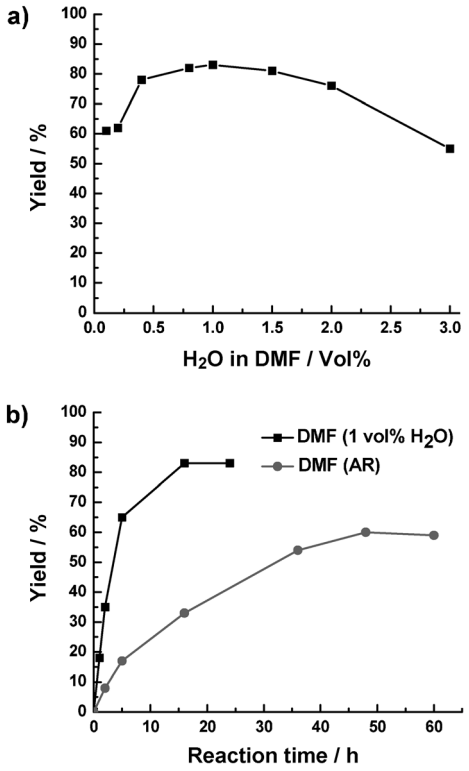
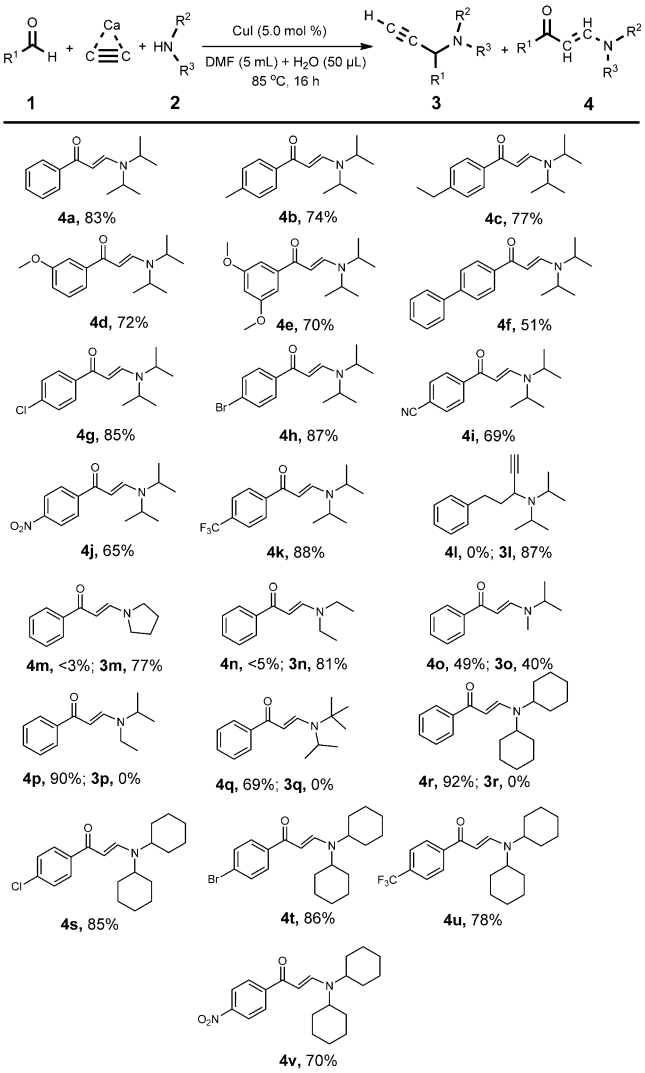


Figure 1. a) Effect of the water content of the solvent DMF on the yield of the enaminone. b) Kinetic study of the three-component coupling reaction to form an enaminone. Reaction conditions: benzaldehyde (1.0 mmol), calcium carbide (1.2 mmol), diisopropylamine (1.5 mmol), CuI (0.05 mmol, 5.0 mol%), DMF (5.0 mL), 85 °C. Yields given are for the isolated product; AR = analytical reagent.

activity (see Table 1 in the Supporting Information). A longer reaction time was required to obtain the maximum yield when the catalyst loading was lowered to 2 mol%. An increase in the catalyst loading to 10 mol% did not improve the yield (see Table 1, entries 17 and 18 in the Supporting Information). It was also revealed that reaction temperatures lower or higher than 85 °C resulted in lower yields of the desired product (see Table 1, entries 19 and 20 in the Supporting Information).

To showcase the scope of this transformation, we tested various aldehydes and amines. Aromatic aldehydes with electron-donating (methoxy) as well as electron-withdrawing substituents (halide, nitrile, nitro) were all good coupling partners with acetylide ion and diisopropylamine, and the corresponding enaminones were obtained in good yields (Scheme 3, products **4a–k** and **4p–v**). However, a propargylamine instead of an enaminone was obtained with an alkyl aldehyde. (Scheme 3, product **3l**). The range of possible amine substrates was investigated next. Interestingly, it was found that this reaction is very sensitive towards the bulkiness of the amine. Very bulky secondary amines, such as diisopropylamine, dicyclohexylamine, isopropylethylamine, and *tert*-



Scheme 3. Three-component reaction of calcium carbide, aldehydes, and amines to form enaminones and/or propargylamines. Yields of isolated products are reported. In all cases, the *E*/*Z* ratio was > 99:1.

butylisopropylamine, were very good substrates in this reaction and selectively produced enaminones in high yields. In contrast, with small amines, such as diethylamine, the propargylamine was produced selectively with only a very small amount of the corresponding enaminone (Scheme 3, products **3m**,**n**). In the case of moderately bulky amines, such as isopropylmethylamine, two competitive reactions occurred simultaneously, and similar amounts of the propargylamine and the enaminone were produced (Scheme 3, products **3o** and **4o**).

To overcome the limitation in the scope of the reaction with respect to the amine substrate, we successfully demonstrated substitution reactions of the synthesized enaminones with primary and secondary amines.[9a] As shown in Scheme 4,

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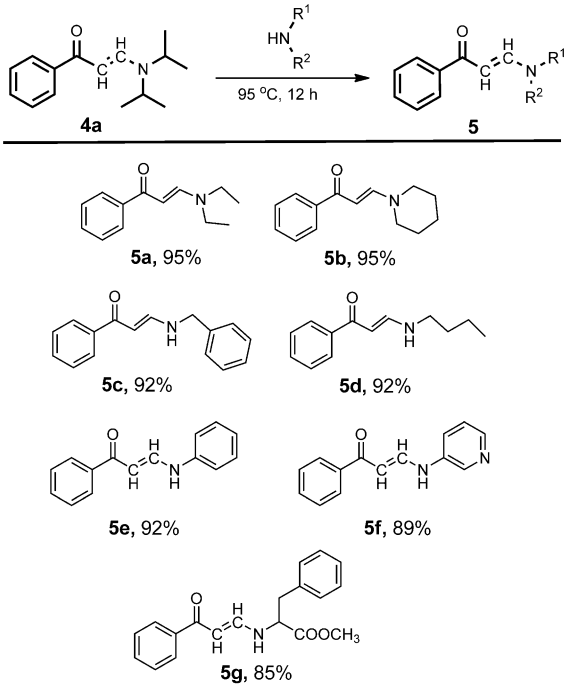
the diisopropylamine group can be replaced readily with less bulky secondary or primary amine groups in excellent yield. With this complementary amine-exchange process, a wide variety of enaminones can be synthesized directly from simple aldehydes and amines.

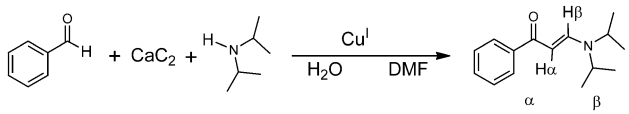
The excellent selectivity of the reaction with respect to the bulkiness of the amine indicates a kinetically controlled reaction pathway. In the case of small amines, the amine may first react with the aldehyde to form an iminium intermediate, which can react with acetylide to form the propargylamine through an A^3-coupling approach.[4] On the other hand, for bulky amines, this process is kinetically disfavored. Thus, enaminones are produced instead. A strongly binding ligand, *o*-phenanthroline, was introduced to increase the bulkiness



Scheme 4. Amine-exchange reaction. Yields of isolated products are reported.

around the copper center; however, only an amide product rather than an enaminone or propargylamine was observed. To understand how an enaminone is produced with this system, we conducted several control reactions (see Scheme S1 in the Supporting Information). There was no reaction observed between the two nucleophiles in the system, acetylide and the amine, in the absence of an aldehyde under the standard reaction conditions. However, when the amine was absent from the system, a small amount of a propargyl alcohol, the product of the reaction between acetylide and an aldehyde, was observed under the standard conditions.[19] Furthermore, when the propargyl alcohol (1-phenylprop-2-yn-1-ol) was subjected to the standard reaction conditions in the presence of diisopropylamine, a very small amount of the corresponding enaminone **4a** was detected (about 5%; see Scheme S1). It is known that a small amount of water can speed up reactions by increasing the solubility of calcium carbide.[4] However, neither the enaminone nor the propargylamine was observed when anhydrous DMF was used. Instead, the ester product of a self-redox reaction was produced. This result indicates that water may play some important role in the catalytic cycle other than to increase the solubility of calcium carbide. No reaction was observed when terminal alkynes were used instead of calcium carbide under the standard conditions.

To determine the origin of the two vinyl hydrogen atoms in the enaminone, we performed experiments with deuterated substrates (Scheme 5). When deuterated water (D_2O) and/or a deuterated amine were used in the reaction, the α position of the enaminone was partially deuterated. When a deuterated aldehyde was used in the system, neither the α nor the β position of the resulting enaminone was deuterated. This result indicates that the aldehyde hydrogen atom is not incorporated in the enaminone structure. Interestingly, when all reactants (the amine, the aldehyde, water, and the solvent DMF) were replaced with deuterated reactants and the reaction was quenched with DCl, the substituent at the β position of the enaminone was still 100% hydrogen. This



				α	β
H	D	H	H	D(50%)	H
H	H	D	H	D(50%)	H
H	D	D	D	D(70%)	H
D	H	H	H	H	H
D	D	D	D	D(70%)	H

Scheme 5. A summary of experiments performed with deuterated substrates and/or solvents.

result suggests that the β hydrogen atom of the enaminone may be derived from the calcium carbide starting material.

On the basis of these observations, we suggest a plausible mechanism for enaminone formation in Scheme 6. First, copper(I) coordinates with the amine and interacts with calcium carbide. The calcium cation then activates the aldehyde and induces the nucleophilic attack of acetylide on the enolate **6** derived from the aldehyde to give a propargyl alcohol **7**.[19] In fact, a small amount of the free propargyl alcohol was observed in the reaction system in the absence of an amine. A redox isomerization process[20] of the secondary propargyl alcohol then leads to the formation of an allenyl enolate intermediate **8**. During this redox isomerization process, the amine attacks the terminal β carbon atom, and the hydride from the aldehyde is abstracted by water with the release of one molecule of H_2. This mechanism explains why the experiment with deuterated aldehyde gave an enaminone without any deuterium. In the presence of a proton source, such as water or an amine, isomerization of the structure leads to the final product, an enaminone. This proposed mechanism explains all our experimental observations. The redox isomerization of secondary propargyl alcohols has also been observed in other systems.[20] In the case of tertiary propargyl alcohols, amination of the β carbon atom is a challenge,[13] and structural isomerization mostly occurs by the Meyer–Schuster rearrangement.[21] In fact, no enaminone product was observed when the aldehyde was replaced with a ketone in our system.

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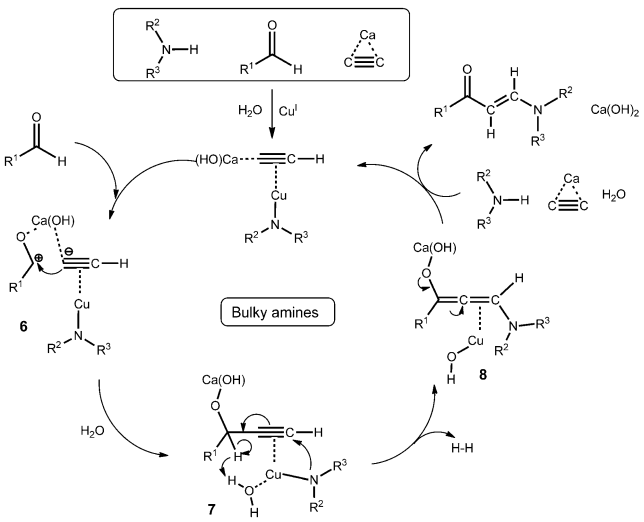

Scheme 6. Proposed catalytic cycle for enaminone production.

In conclusion, we have developed a step-economical protocol for the synthesis of enaminones through a three-component reaction of calcium carbide, an aryl aldehyde, and an amine. This very simple and cost-efficient method can be used for the synthesis of various enaminones from readily accessible small molecules. Investigation of the reaction mechanism demonstrated the versatility of the acetylide ion (C_2^{2-}), which can bridge both electrophiles and nucleophiles. The direct use of the acetylide ion (C_2^{2-}) in synthesis avoids multiple protection and deprotection steps. This great reduction in the number of synthetic steps results in more efficient and greener organic synthesis.

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