

1,4-Diazabicyclo[2.2.2]octane-Catalyzed Self- and Cross-Condensation of α -Acetylenic Ketones

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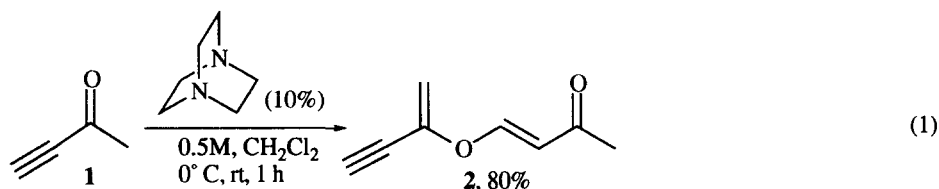
Abstract: 3-Butyn-2-one condenses with itself in the presence of 0.1 molar equiv of Dabco providing 80% yield of *E*-3-(1-buten-3-yn-2-oxy)-buten-2-one. Substitution at the acetylene terminus prevents the condensation. However, such ketones can be condensed with terminal acetylenic ketones to provide the cross-coupled products in high yields.

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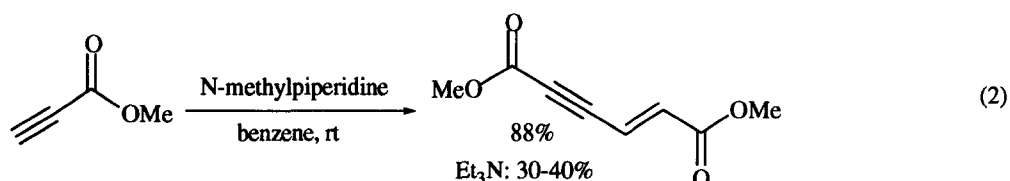
Ordinary ketones do not readily undergo Morita-Baylis-Hillman reaction.¹ However, activated ketones, such as perfluoro-ketones,² α -keto esters,³ and non-enolizable 1,2-diketones⁴ have yielded to this reaction. We anticipated that α -acetylenic ketones might also belong to this class of ketones.⁵ While carrying out such a reaction, we encountered a fascinating condensation of α -acetylenic ketones in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco) to form divinyl ethers.⁶ Herein we report a systematic study of this novel reaction.

When we mixed 3-buten-2-one (**1**) and ethyl acrylate, neat, in the presence of 0.1 equiv of Dabco, an exothermic reaction ensued and the TLC revealed the complete consumption of the ketone. The usual workup provided a product, which upon analysis by ¹H NMR spectroscopy disclosed the absence of the ester moiety! Probably due to the exothermicity of the reaction, we obtained only a poor yield of this product. We repeated the reaction by mixing **1** in CH₂Cl₂ (0.5 M) with 0.1 equiv of Dabco (without the addition of ethyl acrylate). A reaction occurred, complete within 1 h, and the removal of Dabco using column chromatography provided 80% yield of a product. The mass spectral data suggested the dimerization of **1**. The ¹H NMR spectrum of this product revealed the presence of a lone acetylenic proton, two types of olefinic protons, and a methyl group. The ¹³C NMR spectrum disclosed only one carbonyl group and the IR spectrum indicated the presence of a ketone, but no hydroxyl group. On the basis of the spectral data we have obtained *E*-3-(1-buten-3-yn-2-oxy)-buten-2-one (**2**) (eq 1).



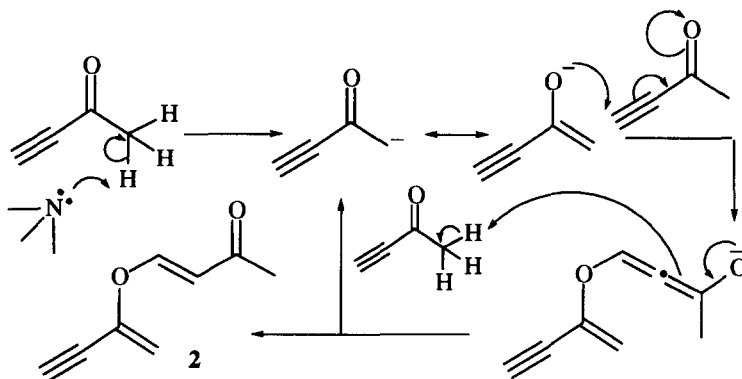
Although C-C bond forming condensation of propargylic esters in the presence of an amine (eq 2) is known for four decades,^{7,8} to the best of our knowledge, the self-condensation of acetylenic ketones has not

been reported thus far. A reaction of the perchlorate or fluoborate salts of triethylamine with α -acetylenic ketones and esters resulting in the Michael addition of the amines has been reported before.⁹ Dialkyl and primary amines are also known to add to these substrates in a 1,4-manner.¹⁰ Wenkert and co-workers have reported a failed attempt to dimerize α -acetylenic ketones in the presence of trialkylamines.⁸



Our procedure appears to be the most simple for the synthesis of divinyl ethers. Earlier, these have been synthesized via the *trans*-esterification of ethyl vinyl ether with allyl alcohols in the presence of mercuric acetate for 7 d, followed by isomerization with potassium *tert*-butoxide in dimethyl sulfoxide for another 7 d.¹¹ Jeger and co-workers obtained divinyl ethers as one of the products in the photochemical excitation of methanoepoxyenones.¹² Taskinen has studied the thermodynamics, ¹³C, and ¹⁷O NMR spectral properties of divinyl ethers.^{11,13,14}

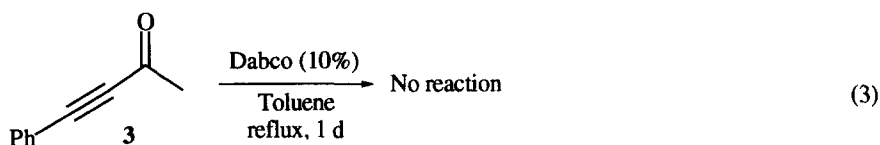
We believe that the mechanism for the catalytic cycle is as shown in scheme 1. The base promotes the formation of the enolate, followed by a Michael addition of the oxygen nucleophile to the acetylene terminus of a second ketone molecule. The vinylogous oxygen nucleophile wins over the ambident carbon nucleophile. The reaction sequence is completed by the abstraction of a proton from a third molecule of ketone, regenerating the nucleophile to continue the cycle.



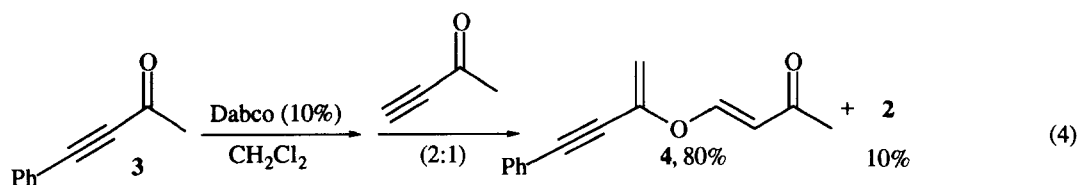
Scheme 1. Proposed mechanism for Dabco-catalyzed self-condensation of acetylenic ketones

The amount of catalyst required to accomplish this transformation was determined by conducting this reaction with different ratios of Dabco to 1, and 0.1 molar equiv was determined as the optimum. We tested the efficiency of several other di- and trialkylamines, such as diisopropylamine, triethylamine, pyridine, and DBU. Diisopropylamine added in a Michael manner to the acetylenic ketone providing *E*-4-diisopropylamino-3-buten-2-one. Triethylamine is effective in initiating the condensation reaction providing the product in 60% yield. Pyridine and, surprisingly, DBU were ineffective in achieving the condensation. We obtained complex mixtures of products with these two amines.

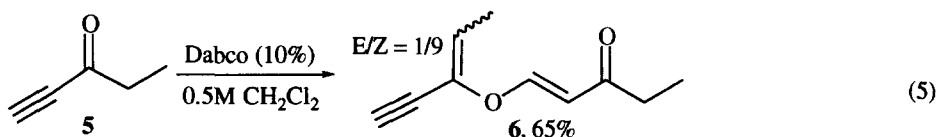
The reaction did not proceed when the acetylene terminus of **1** is substituted with a phenyl group. Thus, 4-phenyl-3-butyne-2-one (**3**) did not undergo condensation even in refluxing toluene for 24 h (eq 3).



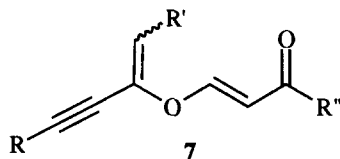
However, we achieved the condensation of **3** with the parent acetylenic ketone under controlled conditions. When one equiv each of **1** and **3** were mixed in the presence of 0.1 equiv of Dabco, we obtained 65% of the cross-condensed product **4** along with 28% of the self-condensed product **2**. Utilization of 2 equiv of **3** improved the yield of **4** to 80% along with 10% of **2** (eq 4). These were separated by column chromatography.



We then extended this reaction to 1-pentyn-3-one. The reaction proceeded readily to provide 65% of *E*-1-(3-penten-1-yn-3-oxy)-penten-3-one (**6**) (eq 5). The *E/Z* ratio (¹H NMR) of the alkene of the enyne is 1/9.



We believe that this procedure can be used for a general synthesis of compounds with the structure **7**. The alkyl chain length (R, R', R'') in **7** should not be a limitation to this cross-condensation reaction.



In conclusion, we have found that 3-butyne-2-one condenses with itself in the presence of 0.1 molar equiv of Dabco providing 80% yield of *E*-3-(1-buten-3-yn-2-oxy)-buten-2-one. Substitution at the acetylene terminus prevents the condensation. However, 4-substituted-3-butyne-2-ones can be condensed with terminal acetylenic ketones to provide the cross-coupled products in high yields. We are examining the applications of these divinyl ethers in organic synthesis, including transition metal catalyzed carbocyclizations.

A typical experimental procedure for the preparation of **4** is as follows. Dabco (0.066 g, 0.5 mmol) was added to a stirred solution of 4-phenyl-3-butyne-2-one (**3**) (1.44 g, 10 mmol) in 15 mL of CH₂Cl₂ and the reaction was stirred for 15 min. 3-Butyn-2-one (**1**) (0.34 g, 5 mmol) dissolved in 5 mL of CH₂Cl₂ was then

added, dropwise, at 0 °C. The reaction mixture was further stirred for 1 h at rt. The solvent was removed under vacuum and the crude product mixture was purified by silica gel column chromatography. Elution with EtOAc/hexanes (2: 98) recovered 0.65 g (4.5 mmol) of **3**, followed by elution with EtOAc/hexanes (5:95) provided 0.85 g (4 mmol, 80%) of **4**.

IR: ν : cm^{-1} : 2224 ($\text{C}\equiv\text{C}$), 1691 ($\text{C}=\text{O}$). ^1H NMR (300 MHz) δ (CDCl_3) (ppm): 2.21 (s, 3H, $-\text{COCH}_3$), 5.07 (d, $J = 2.1$ Hz, 1H, $=\text{CH}$), 5.15 (d, $J = 2.1$ Hz, 1H, $=\text{CH}$), 5.91 (d, $J = 12.3$ Hz, 1H, $\text{CH}_3\text{COCH}=\text{CH}$), 7.34 (m, 3H, Ph), 7.48 (m, 2H, Ph), 7.89 (d, $J = 12.3$ Hz, 1H, $\text{CH}_3\text{COCH}=\text{CH}$); ^{13}C NMR δ (CDCl_3) (ppm): 28.23 (CH_3), 80.93 ($\text{C}-\text{C}\equiv\text{C}$), 93.43 ($\text{C}\equiv\text{C}-\text{Ph}$), 104.61 ($\text{H}_2\text{C}=\text{C}$), 111.46 ($\text{H}_2\text{C}=\text{C}$), 121.01(Ph), 128.59(Ph), 129.63(Ph), 131.83 (Ph), 141.32 ($=\text{CHCO}$), 156.87 ($-\text{O}-\text{CH}$), 197.07 (CO). Ms: EI: m/z : 211 ($\text{M}-\text{H}^+$), 127 (100%) ($\text{Ph}-\text{C}\equiv\text{C}-\text{C}=\text{CH}_2$) $^+$. CI: m/z : 213 ($\text{M}+\text{H}^+$) (100%).

Further elution with EtOAc/hexanes (7:93) provided 0.068 g (0.5 mmol, 10%) of **2**. IR: ν : cm^{-1} : 2110 ($\text{C}\equiv\text{C}$), 1691 ($\text{C}=\text{O}$). ^1H NMR (300 MHz) δ (CDCl_3) (ppm): 2.22 (s, 3H, $-\text{COCH}_3$), 3.29 (s, 1H, $\text{HC}\equiv\text{C}$), 5.09 (d, $J = 2.2$ Hz, 1H, $=\text{CH}$), 5.17 (d, $J = 2.2$ Hz, 1H, $=\text{CH}$), 5.89 (d, $J = 12.4$ Hz, 1H, $\text{CH}_3\text{COCH}=\text{CH}$), 7.78 (d, $J = 12.4$ Hz, 1H, $\text{CH}_3\text{COCH}=\text{CH}$); ^{13}C NMR δ (CDCl_3) (ppm): 28.26 (CH_3), 75.49 ($\text{C}\equiv\text{CH}$), 81.83 ($\text{C}\equiv\text{C}-\text{H}$), 105.91 ($\text{H}_2\text{C}=\text{C}$), 111.65 ($\text{H}_2\text{C}=\text{C}$), 140.32 ($=\text{CHCO}$), 156.45 ($-\text{O}-\text{CH}$), 197.03 (CO). Ms: EI: m/z : 136 (M^+), 121 ($\text{M}-\text{CH}_3^+$), 43 (100%) (CH_3CO) $^+$. CI: m/z : 137 ($\text{M}+\text{H}^+$) (100%).

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