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

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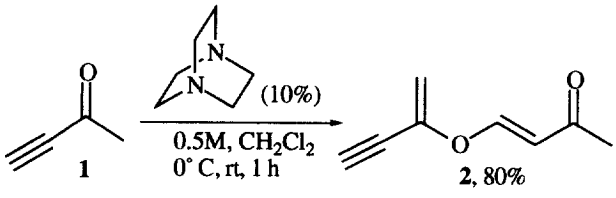
Abstract: 3-Butyn-2-one condenses with itself in the presence of 0.1 molar equiv of Dabco providing 80% yield of *E*-3-(1-buten-3-yn-2-oxy)-buten-2-one. Substitution at the acetylene terminus prevents the condensation. However, such ketones can be condensed with terminal acetylenic ketones to provide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

key words: divinyl ether, α-acetylenic ketones, trialkylamine, condensation, Dabco.

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-diketones[4] 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-butyn-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 ^{1}H 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 CH_2Cl_2 (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 ^{1}H NMR spectrum of this product revealed the presence of a lone acetylenic proton, two types of olefinic protons, and a methyl group. The ^{13}C 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).



(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

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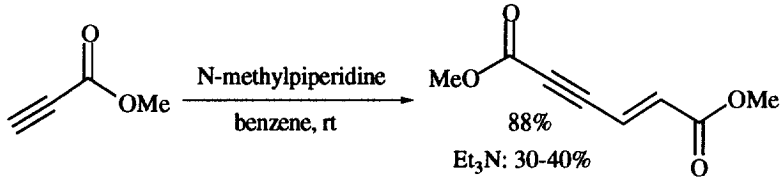
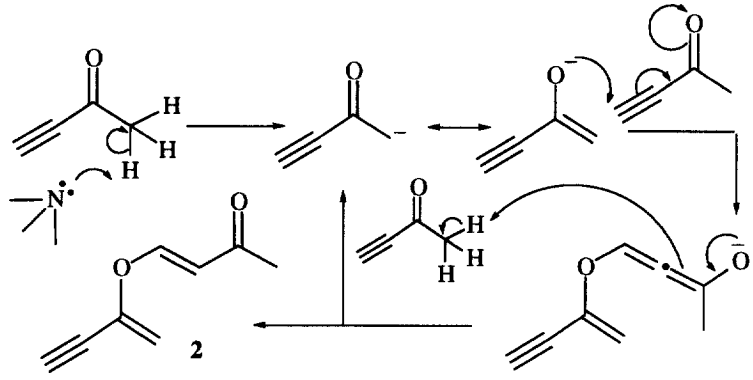
been reported thus far. A reaction of the perchlorate or fluoborate salts of triethylamine with α-acetylenic ketones and esters resulting in the Michael addition of the amines has been reported before.[9] Dialkyl and primary amines are also known to add to these substrates in a 1,4-manner.[10] Wenkert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



(2)

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, ^{13}C, and ^{17}O NMR spectral properties of divinyl ethers.[11,13,14]

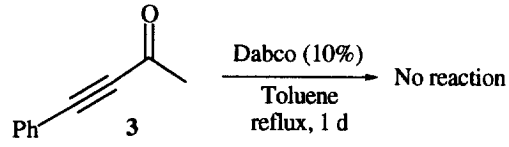
We believe that the mechanism for the catalytic cycle is as shown in scheme 1. The base promotes the formation of the enolate , followed by a Michael addition of the oxygen nucleophile to the acetylene terminus of a second ketone molecule. The vinylogous oxygen nucleophile wins over the ambidient carbon 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

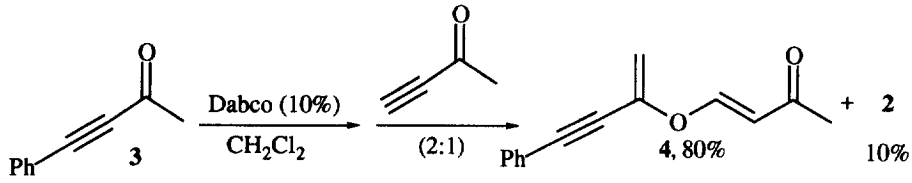
The amount of catalyst required to accomplish this transformation was determined by conducting this reaction with different ratios of Dabco to **1**, and 0.1 molar equiv was determined as the optimum. We tested the efficiency of several other di- and trialkylamines, such as diisopropylamine, triethylamine, 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-butyn-2-one (**3**) did not undergo condensation even in refluxing toluene for 24 h (eq 3).



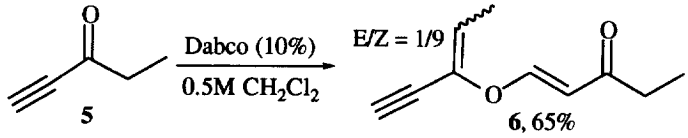
(3)

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.



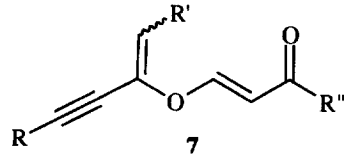
(4)

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 (^{1}H NMR) of the alkene of the enyne is 1/9.



(5)

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-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, 4-substituted-3-butyn-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-butyn-2-one (**3**) (1.44 g, 10 mmol) in 15 mL of CH_2Cl_2 and the reaction was stirred for 15 min. 3-Butyn-2-one (**1**) (0.34 g, 5 mmol) dissolved in 5 mL of CH_2Cl_2 was then

added, dropwise, at 0 °C. The reaction mixtue 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 (C≡C), 1691 (C=O). ^1H NMR (300 MHz) δ ($CDCl_3$) (ppm): 2.21 (s, 3H, -COC**H**$_3$), 5.07 (d, J = 2.1 Hz, 1H, =C**H**), 5.15 (d, J = 2.1 Hz, 1H, =C**H**), 5.91 (d, J = 12.3 Hz, 1H, CH_3COCH=), 7.34 (m, 3H, Ph), 7.48 (m, 2H, Ph), 7.89 (d, J = 12.3 Hz, 1H, CH_3COCH=C**H**); ^{13}C NMR δ ($CDCl_3$) (ppm): 28.23 (**C**H_3), 80.93 (C-**C**≡C), 93.43 (C≡**C**-Ph), 104.61 (H_2C=C), 111.46 (H_2C=**C**), 121.01(Ph), 128.59(Ph), 129.63(Ph), 131.83 (Ph), 141.32 (=CHCO), 156.87 (-O-CH), 197.07 (CO). Ms: EI: m/z: 211 (M-H^+), 127 (100%) (Ph-C≡C-C=CH_2)$^+$. CI: m/z: 213 (M+H)$^+$ (100%).

Further elution with EtOAc/hexanes (7:93) provided 0.068 g (0.5 mmol, 10%) of **2**. IR: ν: cm^{-1}: 2110 (C≡C), 1691 (C=O). ^1H NMR (300 MHz) δ ($CDCl_3$) (ppm): 2.22 (s, 3H, -COC**H**$_3$), 3.29 (s, 1H, **H**C≡C), 5.09 (d, J = 2.2 Hz, 1H, =C**H**), 5.17 (d, J = 2.2 Hz, 1H, =C**H**), 5.89 (d, J = 12.4 Hz, 1H, CH_3COCH=), 7.78 (d, J = 12.4 Hz, 1H, CH_3COCH=C**H**); ^{13}C NMR δ ($CDCl_3$) (ppm): 28.26 (**C**H_3), 75.49 (**C**≡CH), 81.83 (C≡C-H), 105.91 (H_2C=C), 111.65 (H_2C=**C**), 140.32 (=CHCO), 156.45 (-O-CH), 197.03 (CO). Ms: EI: m/z: 136 (M$^+$), 121 (M-CH_3^+), 43 (100%) (CH_3CO)$^+$. CI: m/z: 137 (M+H)$^+$ (100%).

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