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Reactivity of a propiolate dimer with nucleophiles and an efficient synthesis of dimethyl α-aminoadipate

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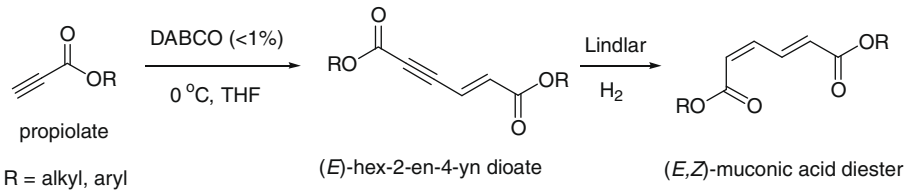
ABSTRACT

An enyne dimer (**1**) of methyl propiolate was reacted with amines to form dimethyl (*E,E*)-2-amino-2,4-hexadiene dioates with remarkable chemospecificity, regiospecificity, and stereospecificity. This enyne was also reduced by Ph_3P stereospecifically to form dimethyl (*E,E*)-muconic ester. Hydrogenation of the conjugated amino-diene led to an efficient production of dimethyl α-aminoadipate. A lactam of dimethyl α-aminoadipate was obtained in high yield by simply varying the hydrogenation conditions.

Propiolates are very useful functional precursors in organic synthesis.[1–10] For example, the nucleophilic addition of alkyl propiolates to aldehydes can generate γ-hydroxy-α,β-acetylenic esters of broad synthetic applications.[1] Propiolates can also undergo many other reactions such as Diels–Alder reaction,[2] additional cycloadditons,[3] the Baylis–Hillman-type reaction,[4] ene reaction,[5] ring annulation,[6] coupling with alkyl halides,[7] hydrosilylation,[8] reaction with ketene silyl acetals,[9a] and conjugate addition.[9b] Dimerization of propiolates in the presence of bases can produce hex-2-en-4-yne dioates. For example, Ramachandran found that a catalytic amount of DABCO (<1%) catalyzed this dimerization at 0 °C in minutes in 99% yield (Scheme 1).[11] In the presence of Lindlar's catalyst, the (*E*)-hex-2-en-4-yne dioates were hydrogenated to (*E,Z*)-muconic acid diesters for natural product synthesis.

In our laboratory, we are interested in studying the reactivity of methyl propiolate and its derivatives.[1h,i] The DABCO-catalyzed efficient synthesis of (*E*)-hex-2-en-4-yne dioates from propiolates prompted us to explore the synthetic application of these compounds.[12] Herein, our work on the reactions of a propiolate dimer with amine and phosphine nucleophiles and an efficient synthesis of dimethyl α-aminoadipate is reported.

Dimethyl (*E*)-hex-2-en-4-yne dioate (**1**) was obtained by treatment of methyl propiolate with DABCO (1%) in THF at 0 °C in almost quantitative yield.[11] When **1** was reacted with 1 equiv of dibenzylamine in CH_2Cl_2 at room temperature for 16 h, compound **2** was obtained in 99% yield (Scheme 2).[13] This nucleophilic addition proceeded with remarkable chemospecificity, regiospecificity, and stereospecificity. That is, the reaction occurred on the alkyne unit rather than the alkene unit; at position 2 rather than 3; and



Scheme 1. Catalytic dimerization of propiolates.

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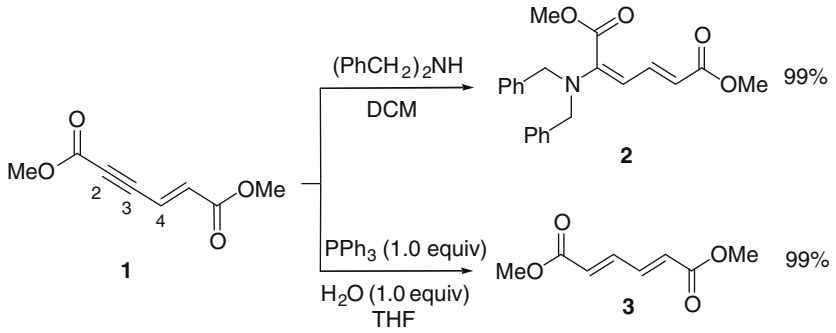
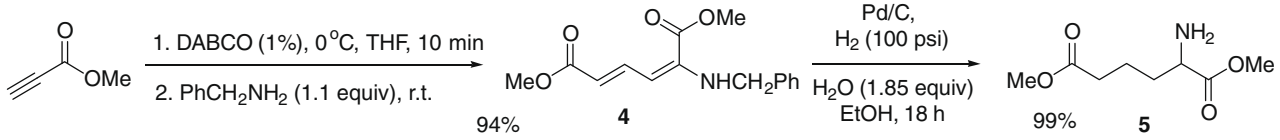


Scheme 2. Reactions of enyne **1** with nucleophiles.

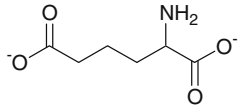


Scheme 3. Synthesis of dimethyl α-aminoadipate **5**.

giving only the (2*E*,4*E*)-stereoisomer. In C_6D_6, the ^1H NMR signals of the three vinyl protons of **2** were observed at δ 7.86 (dd, J = 14.7, 12.0 Hz, 1H, 4-H), 5.73 (d, J = 14.7 Hz, 1H, 5-H), and 5.27 (d, J = 12.0 Hz, 1H, 3-H). The large coupling constancy between 5-H and 4-H indicates a 4*E* configuration. The Noesy NMR experiment of **2** showed correlation between 3-H and those of the benzylic protons, indicating a 2*E* configuration. The regioselectivity of the amine addition is apparently controlled by the remote ester group rather than the adjacent one. This unusual regioselectivity is consistent with Houk's observation in a Diels–Alder reaction of this enyne.[12]

We also investigated the reaction of enyne **1** with Ph_3P.[14] Under nitrogen in dry THF solution, no reaction between **1** and Ph_3P was observed. However, when H_2O (1 equiv) was added, **1** was reduced stereospecifically by Ph_3P to give dimethyl (*E*,*E*)-muconic ester **3**,[15] a synthetically useful diene (Scheme 2).[12,16,17]

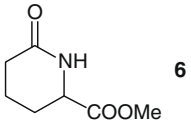
The high yield formation of **2** from **1** under the mild reaction conditions encouraged us to use this method to develop a new synthesis of dimethyl α-aminoadipate. α-Aminoadipate, a product of lysine degradation in mammals,[18] has attracted considerable research activity in neuroscience, biosynthesis, organic synthesis, and peptide chemistry.[19] For example, α-aminoadipate is probably best known as an experimental gliotoxin, which can influence various elements of glutamatergic neurotransmission.[20] α-Aminoadipate is also an essential intermediate in lysine biosynthesis in fungi[21a] and a well-known precursor in the synthesis of penicillin or cephalosporin.[21b] Its derivatives have been used as effective agents for the treatment of antileukemic, rheumatoid arthritis, psoriasis, and other autoimmune diseases.[22] Usually, α-aminoadipate was obtained from the biosynthesis and catabolism of lysine in *Penicillium chrysogenum*.[23] A number of synthetic methods for the preparation of α-aminoadipates were also reported.[24]



α-aminoadipate

We combined the catalytic dimerization of methyl propiolate and the nucleophilic addition of benzylamine into a one-pot reaction to generate the conjugated amino-diene **4** in 94% yield with the same chemospecificity, regiospecificity, and stereospecificity as the formation of **2** from the dibenzylamine addition (Scheme 3).[25a] Catalytic hydrogenation of **4** in the presence of Pd/C and H_2O gave the desired dimethyl α-aminoadipate **5** in almost quantitative yield.[25b] In this step, the hydrogenation of the diene and debenzylation occurred simultaneously. This two-pot preparation of **5** involves less number of steps than the previously reported synthesis of the racemic α-aminoadipates.[24a,b]

In the above catalytic hydrogenation of **4**, addition of H_2O was necessary. We found that in the absence of H_2O, an intramolecular cyclization of dimethyl α-aminoadipate was observed to give the lactam **6**. The addition of H_2O probably deactivated the carbon support that might be responsible for the intramolecular condensation. The formation of **6** was optimized by conducting the hydrogenation of **4** in the presence of Pd/C under 200 psi H_2 in methanol which gave the lactam **6** in 99% yield in 1 h.[26,27] This reaction provides a very convenient way to synthesize a useful lactam.



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In summary, we have studied the reactions of the methyl propiolate dimerization product **1** with the amine and phosphine nucleophiles. The reaction of **1** with dibenzylamine or benzylamine has exhibited unusual chemospecificity, regiospecificity, and stereospecificity to generate the corresponding conjugated amino-diene products. The base-catalyzed dimerization of methyl propiolate and the benzylamine addition can be conducted in one-pot to form **4** which can then be hydrogenated to give dimethyl α-aminoadpate, a molecule of significant biological interests. This is a new and efficient synthesis of an α-aminoadpate. Modification of the hydrogenation condition allows an easy preparation of lactam **6**.

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13. *Preparation and characterization of* **2**. Under nitrogen, to a stirred solution of **1** (0.1 mmol, 16.8 mg) in CH_2Cl_2 (3 mL) was added dibenzylamine (0.1 mmol, 20 mg) at rt. After 16 h, the reaction was shown to be complete by TLC. The solvent was evaporated and **2** was obtained as a colorless liquid in 99% yield after column chromatography on silica gel eluted with 25% ethyl acetate in hexanes. ^{1}H NMR (300 MHz, C_6D_6) δ 7.86 (dd, J = 14.7, 12.0 Hz, 1H), 7.12–6.98 (m, 10H), 5.73 (d, J = 14.7 Hz, 1H), 5.27 (d, J = 12.0 Hz, 1H), 3.86 (s, 4H), 3.41 (s, 3H), 3.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 165.7, 148.7, 142.0, 135.9, 128.6, 128.5, 128.3, 128.1, 127.6, 127.3, 113.5, 101.2, 53.5, 52.6, 51.0. HRMS (ESI) calcd for $C_{22}H_{23}NO_4$+H$^+$: 366.1700; found: 366.1710.
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25. (a) *Preparation and characterization of* **4**: Under nitrogen, to a stirred solution of methyl propiolate (0.2 mmol, 18 μL) in THF (2 mL) was added DABCO (1 mg) at 0 °C. After 10 min, benzylamine (0.11 mmol, 24 μL) was added and the resulting solution was stirred at rt for 16 h. After TLC showed the completion of the reaction, the solvent was evaporated and the residue was purified by column chromatography on silica gel eluted with 25% ethyl acetate in hexanes which gave **4** as a colorless liquid in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, J = 15.0, 12.0 Hz, 1H), 7.37–7.29 (m, 5H), 5.70 (d, J = 15.0 Hz, 1H), 5.53 (d, J = 12.0 Hz, 1H), 5.26 (br, 1H), 4.24 (2, 2H), 3.92 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 164.1, 142.2, 139.0, 136.8, 128.5, 127.4, 127.3, 115.9, 102.9, 52.5, 50.9, 47.4. HRMS (ESI) calcd for $C_{15}H_{17}NO_4$+H$^+$: 276.1230; found: 276.1234.(b) *Preparation and characterization of* **5**: Under nitrogen in a par reactor, a mixture of 5 wt % Pd/C (3 mg) and H_2O (3 μL, 1.85 equiv) in ethanol (3 mL) was stirred at rt for 10 min. A degassed solution of **4** (24 mg, 0.09 mmol) in ethanol (2.5 mL) was added, and the mixture was degassed by bubbling with nitrogen. Hydrogen (100 psi) was introduced and the mixture was stirred at rt for 18 h. After filtration and evaporation of ethanol, **5** was obtained as a colorless liquid in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (br, 1H), 4.19 (s, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 2.40 (t, J = 7.2 Hz, 1H), 2.15–2.08 (m, 2H), 1.91–1.80 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43, 169.82, 53.20, 52.96, 51.68, 33.01, 29.71, 20.45.
26. *Preparation of* **6**: In a par reactor, a solution of **4** (50 mg, 0.18 mmol) in methanol (3 mL) was treated with 5 wt % Pd/C (3 mg) and the mixture was degassed by bubbling with nitrogen. Hydrogen (200 psi) was introduced and the mixture was stirred at rt for 2 h. After filtration and evaporation of methanol, **6** was obtained as a colorless liquid in 99% yield.
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