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α-Addition of activated methylenes to alkynoates. A straightforward synthesis of multifunctional compounds

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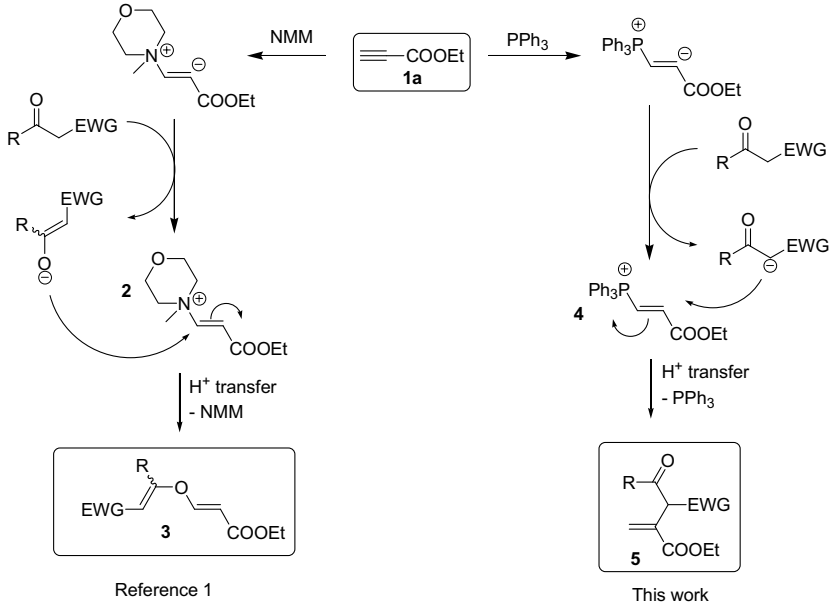
Abstract—The present work describes a simple one pot access to α-(*gem*-difunctional) acrylic esters and to polysubstituted dihydrothiophenes exploiting the addition of activated methylenes to alkynoates rerouted by triphenyl phosphine.

The Michael addition of stabilized enolates with alkynoates constitutes a fundamental synthetic reaction, which normally yields *C*-conjugate Michael adducts. This classical reactivity can be circumvented by the addition of catalytic amount of *N*-methylmorpholine (NMM) or DABCO, which have been recently described to induce the formation of unusual *O*-conjugate Michael adducts **3** through the reactivity of ammonium intermediate **2** (Scheme 1).[1] On another hand, addition of nucleophiles at the α-position of these Michael acceptors are also possible through the catalysis of phosphines. This has been described using nitrogen-based nucleophiles providing a useful synthetic route to dehydroamino acids.[2] According to the described mechanism, the first step of the process



Scheme 1. Possible mechanisms of the reaction of stabilized enolates to ethylpropiolate **1a** catalyzed by amines and phosphines.

Keywords: 1,3-Dicarbonyl compounds; Electrophilic alkyne; Nucleophilic α-addition; Acrylic esters; Dihydrothiophene.
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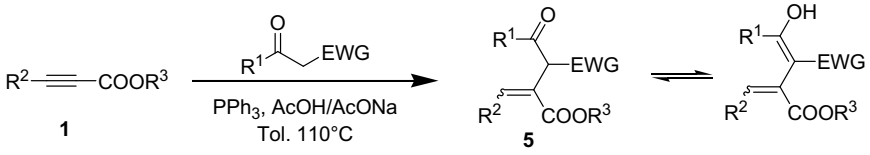
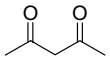
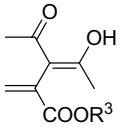
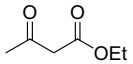
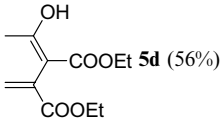
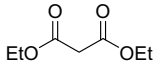
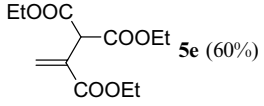
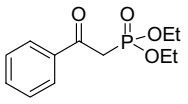
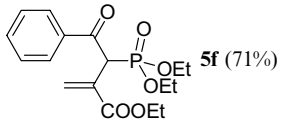
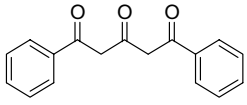
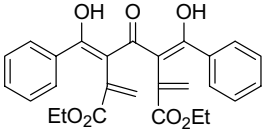
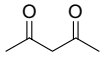
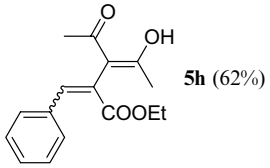
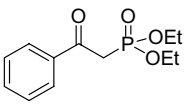
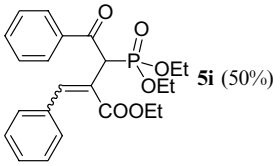
involves a Michael addition of the phosphine to the alkynoate generating an active phosphonium intermediate (**4**, Scheme 1), which undergoes nucleophilic α-addition of the nitrogen nucleophile followed by a H^+-transfer and elimination of the phosphine generating the product.

Based on these findings,[2a,3] we envisioned that intermediate **4**, although very similar to intermediate **2**, should display complete different manifold by changing the regio- and chemo-selectivity of the addition–elimination reaction of stabilized enolates to propiolates. In this work, we explore the reactivity of carbonyl-based activated methylene toward such a reaction.

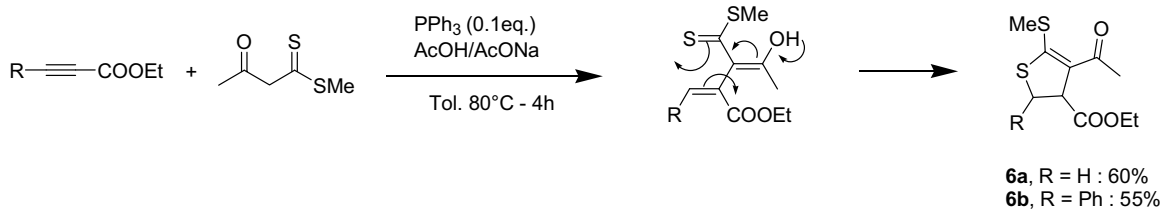
Using the system (PPh_3/AcOH/AcONa) described for nitrogen-based nucleophiles,[2] acetylacetone reacted with

Table 1. Synthesis of multifunctional acrylic esters



Entry	Alkynoate	Activated methylene	PPh_3 (equiv) time	Products[a] (yields)[b]
1	≡—COOR3 **1a**, R^3 = Et **1b**, R^3 = Bn **1c**, R^3 = *t*-Bu		(0.1 equiv) 30 min	 **5a** (88%) **5b** (85%) **5c** (83%)
2	**1a**		(0.3 equiv) 30 min	 **5d** (56%)
3	**1a**		(0.3 equiv) 30 min	 **5e** (60%)
4	**1a**		(0.1 equiv) 2 h	 **5f** (71%)
5	**1a**[c]		(0.2 equiv) 30 min	 **5g** (23%)
6	Ph—≡—COOEt **1d**		(0.2 equiv) 19 h	 **5h** (62%)
7	**1d**		(0.3 equiv) 17 h	 **5i** (50%)

[a] All compounds have been fully characterized by using ^1H, ^{13}C NMR, FT-IR, and mass spectroscopy.
[b] Isolated yield.
[c] 2 equiv of ethyl propiolate were required for this reaction.



Scheme 2. Synthesis of 4,5-dihydrothiophenes derivatives.

alkylpropiolates **1a**–**c** exclusively through α-*C*-addition generating the desired product **5a**–**c** in 83–88% yields (Table 1, entry 1). This reaction occurs for a range of enolates bearing electron withdrawing group in moderate to good yields.[4] Low yields were sometimes obtained due to a degradation of the product or starting material but no α-*O* adducts neither Michael type adducts were observed. Increasing the quantity of PPh_3 was necessary to improve the yields when malonates or β-ketoesters are used as substrates (Table 1, entries 2 and 3). The reaction proceeds with 1,3,5-trione generating double α-*C* adduct with lower yield than for simple substrates (Table 1, entry 5). Ethylphenylpropiolate **1d** participated well in this reaction, but required prolonged time of heating, to give the adducts **5h**–**i** as a mixture of *E*-*Z* isomers (Table 1, entries 6 and 7).

This procedure represents an improvement of the synthesis of functionalized acrylic esters since many steps were required using the previous preparations.[5]

We then investigated the reaction using β-oxodithiobutyricacid methylester.[6] Such compound is known to display thiol tautomeric forms,[7] which are known to be excellent nucleophiles for Michael additions. We found that, even with this substrate, PPh_3 was able to completely reroute the reaction in favor of the α-*C*-addition. Under our experimental conditions, the resulting adduct undergo cyclization generating dihydrothiophenes **6a**–**b** in reasonable yields (Scheme 2).[8] The *cis*–*trans* diastereoisomers of 3,4-dihydrothiophene **6b** were separated (*cis*/*trans* ratio: 1/4) and assigned on the basis of J_{H4-H5} values.[9]

In summary, we have shown that 1, 3-diketones, malonates, β-ketoesters, and β-ketophosphonates undergo ready α-*C*-addition to alkynoates through the catalysis of PPh_3. The functionalized acrylic esters obtained by this method are widely used as building blocks for many synthesis.

Moreover, using β-oxodithiocarboxylates the procedure allows a one step preparation of functionalized dihydrothiophenes. This straightforward transformation should find useful applications in heterocycles chemistry.

References and notes

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3. (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935; (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167–3168.
4. A typical procedure for functionalized acrylic esters synthesis: Under argon atmosphere, a mixture of 2,4-pentanedione (1 g; 10 mmol), triphenylphosphine (262 mg; 1 mmol), and sodium acetate (410 mg; 5 mmol) in toluene (20 mL) was heated to reflux. After introduction of acetic acid (300 mg; 5 mmol) in one portion, ethyl propiolate (981 mg; 10 mmol) was added dropwise. The resulting mixture was stirred under reflux for 0.5 h, filtered, and concentrated. Purification by flash chromatography (silica gel; hexane/ethyl acetate (90/10)) gave pure product (1.74 g; 88% yield). The ^{1}H NMR spectrum allowed the identification of the desired α-*C*-addition product thanks to characteristic singlets corresponding to the olefinic signals. Spectral data for selected compounds. For **5a**: colorless oil; $R_f = 0.3$ (Hex/EtOAc = 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 16.29$ (s, OH enol), 6.59 (d, $J = 1.8$ Hz, 1H), 5.71 (d, $J = 1.8$ Hz, 1H), 4.23 (q, $J = 7.3$ Hz, 2H), 2 (s, 6H), 1.29 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75.47 Hz, $CDCl_3$): $\delta = 190.5$, 166.2, 136.6, 131.7, 110.1, 61.0, 23.3, 13.9; IR (NaCl, cm^{-1}) 1719, 1625, 1185; MS: *m*/*z* 221 $[M+23]^+$. For **5f**: yellow oil; $R_f = 0.4$ (Hex/EtOAc = 30/70); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.96$ (d, 2H), 7.51–7.40 (m, 3H), 6.51 (d, $J = 4.9$ Hz, 1H), 6.28 (d, $J = 4.9$ Hz, 1H), 5.63 (d, $J_{HCP} = 23.2$ Hz, 1H), 4.13 (m, 6H), 1.20 (m, 9H); ^{13}C NMR (75.47 Hz, $CDCl_3$): $\delta = 192.9$, 165.5 (d, $J_{CP} = 7.3$ Hz), 136, 133.3, 130.9 (d, $J_{CP} = 9.8$ Hz), 130.6 (d, $J_{CP} = 7.3$ Hz), 128.7, 128.4, 62.9 (d, $J_{CP} = 4.9$ Hz), 62.5 (d, $J_{CP} = 4.9$ Hz), 61.4, 46.8 (d, $J_{CP} = 136.7$ Hz), 16 (d, $J_{CP} = 7.3$ Hz), 15.9 (d, $J_{CP} = 7.3$ Hz), 13.8; ^{31}P NMR (161.97 Hz, $CDCl_3$): $\delta = 19.2$; IR (NaCl, cm^{-1}) 1711, 1686, 1625; MS: *m*/*z* 355 $[M+1]^+$.
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8. The 4,5-dihydrothiophenes were obtained using identical procedure as for acrylic esters synthesis. Select data for *trans*-**6b**: beige crystal; $R_f = 0.24$ (Hex/EtOAc = 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.29$ (m, 5H), 5.02 (d, $J = 3.0$ Hz, 1H), 4.32 (d, $J = 3.0$ Hz, 1H), 4.17 (m, 2H), 2.45 (s, 3H), 2.21 (s, 3H), 1.22 (m, 3H); ^{13}C NMR (75.47 Hz, $CDCl_3$): $\delta = 191.0$, 171.2, 163.1, 140.9, 128.9, 128.2, 126.4, 122.4, 62.3, 61.5, 53.9, 29.0, 17.7, 13.9; IR (NaCl, cm^{-1}) 1727, 1714, 1632, 1462, 1247; MS: *m*/*z* 323 $[M+1]^+$. For *cis*-**6b**: beige crystal; $R_f = 0.18$ (Hex/EtOAc = 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$ (m, 2H), 7.29 (m, 3H), 5.41 (d, $J = 9.8$ Hz, 1H), 4.41 (d, $J = 9.8$ Hz, 1H), 3.77–3.63 (m, 2H), 2.554 (s, 3H), 2.15 (s, 3H), 0.81 (m, 3H); ^{13}C NMR

(75.47 Hz, $CDCl_3$): δ = 190.7, 169.4, 164.4, 134.9, 128.2, 124.5, 60.6, 60.4, 55.4, 28.9, 17.7, 13.4; IR (NaCl, cm^{-1}) 1729, 1636, 1468, 1243; MS: *m/z* 345 $[M+23]^+$.

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