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Synthesis of polyfunctionalized alkenes and α,β-unsaturated γ-lactams from the reaction of alkyl propiolates and CH-acids such as diethyl acetamidomalonate and ethyl acetamidocyanoacetate in the presence of triphenylphosphine

Sakineh Asghari, Azin Salimi, Mohammad Qandalee

Chemistry Department, Mazandaran University, Babolsar, Iran

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Abstract Dialkyl 1-(*Z*)-2-(acetylamino)-2-butenedioates, 1,1-diethyl-3-alkyl (*E*)-(1-acetylamino)-2-propene-1,1,3-tricarboxylate, 5-ethyl-1-methyl (*E*)-4-(acetylamino)-4-cyano-2-pentenedioate and ethyl 1-acetyl-2-cyano-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate were obtained from the three-component reactions between alkyl propiolates and CH-acids such as diethyl acetamidomalonate and ethyl acetamidocyanoacetate in the presence of triphenylphosphine at room temperature in dry dichloromethane.

Keywords Diethyl acetamidomalonate; Ethyl acetamidocyanoacetate; Alkyl propiolates; Intramolecular *Wittig* reaction.

Introduction

The development of simple synthesis routes for widely used organic compounds from readily available starting materials is one of the major tasks in organic synthesis [1]. The successful attack by nucleophilic trivalent phosphines on a carbon atom is facilitated when it is a part of an unsaturated bond activated by electron withdrawing groups [2–10]. There have been many studies on reactions between trivalent phosphorus nucleophiles and α,β-unsaturated carbonyl compounds in the presence of a proton source, such as an alcohol or a CH-acid [2, 8, 10].

As part of our current studies on three-component condensation reactions between acetylenic esters and CH-acids in the presence of triphenylphosphine, we report now the reaction between alkyl propiolates **1** and CH-acids such as diethyl acetamidomalonate **2** and ethyl acetamidocyanoacetate **9** in the presence of triphenylphosphine.

Reaction of diethyl acetamidomalonate **2**, alkyl propiolates, and triphenylphosphine afforded dialkyl 1-(*Z*)-2-(acetylamino)-2-butenedioate **3** and 1,1-diethyl-3-alkyl (*E*)-(1-acetylamino)-2-propene-1,1,3-tricarboxylate **4** (Scheme 1).

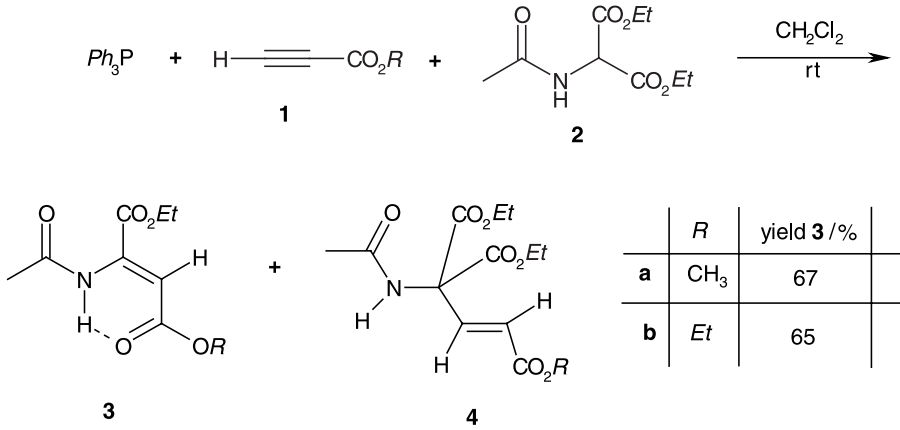
In contrast, the reaction between ethyl acetamidocyanoacetate **9** and alkyl propiolates in the presence of triphenylphosphine produced alkyl (*E*)-4-(acetyl amino)-4-cyano-2-pentenedioate **10** and ethyl 1-acetyl-2-cyano-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate **12** (Scheme 2).

Interestingly, no reaction was observed when triphenylphosphite was used instead of triphenylphosphine as a nucleophile.

Results and discussion

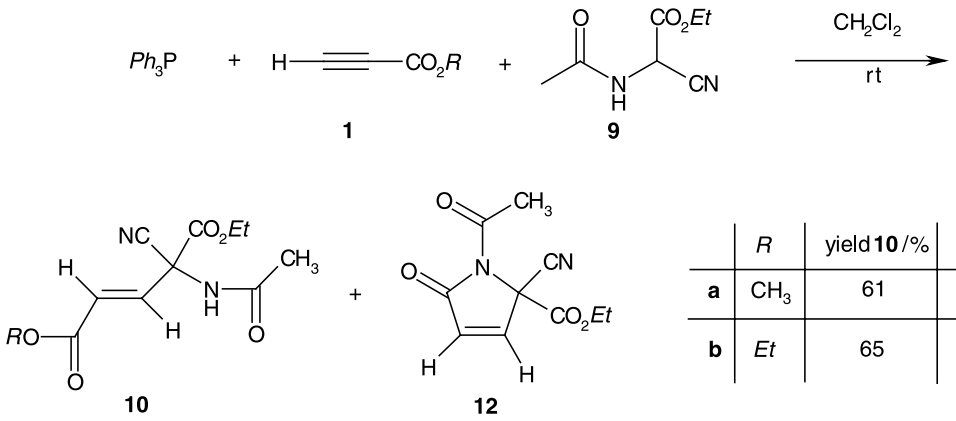
On the basis of the established chemistry of trivalent phosphorus nucleophiles [11, 12], it is reasonable to

Correspondence: Sakineh Asghari, Chemistry Department, Mazandaran University, P. O. Box 453, Babolsar, Iran. E-mail: s.asghari@umz.ac.ir



	R	yield 3 /%	yield 4 /%
a	CH_3	67	26
b	Et	65	30

Scheme 1



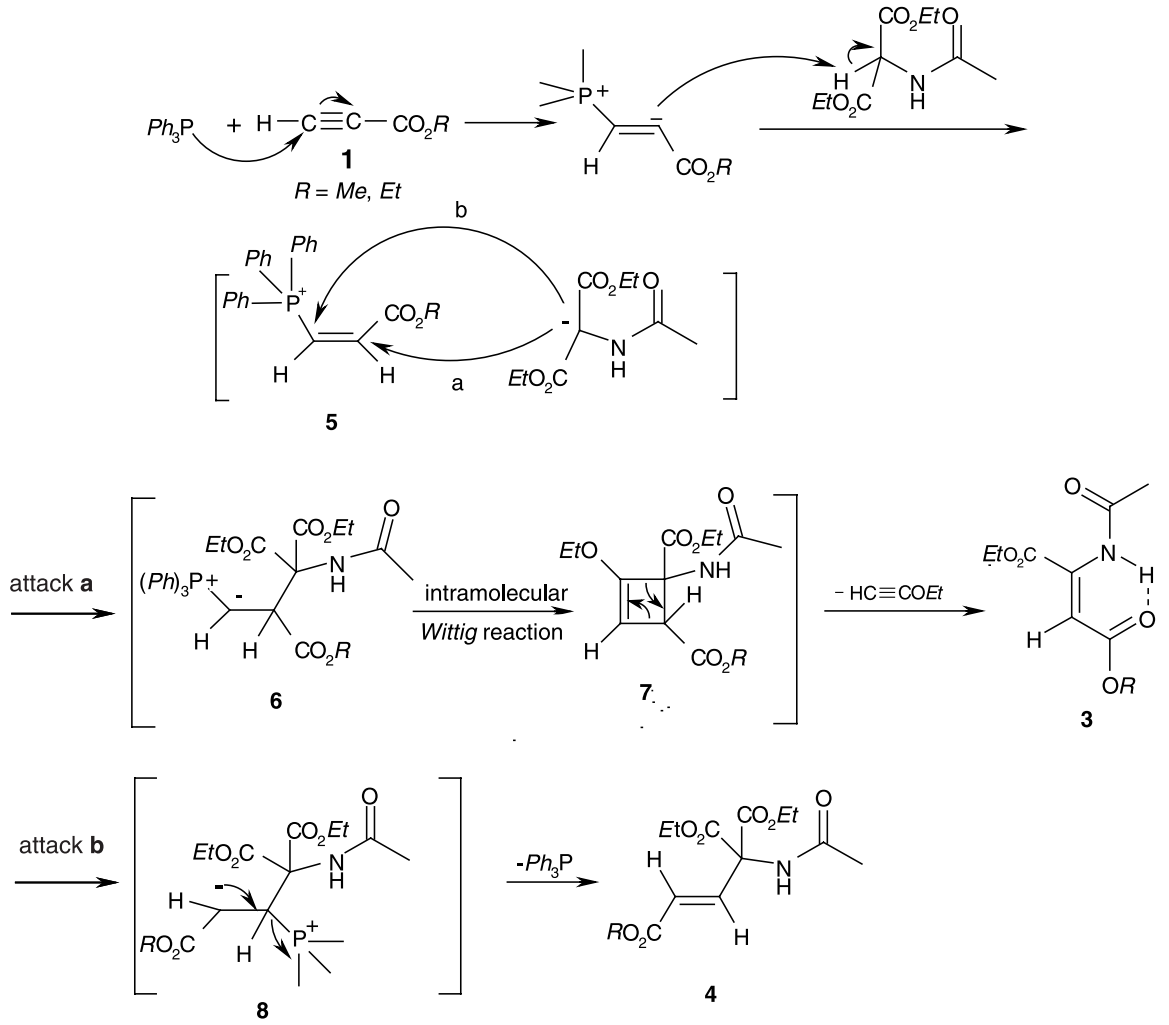
	R	yield 10 /%	yield 12 /%
a	CH_3	61	35
b	Et	65	30

Scheme 2

assume that **3** and **4** result from the initial addition of triphenylphosphine to the alkyl propiolate. Subsequent protonation of the 1:1 adduct forms the vinylphosphonium salt **5**. Then, the positively charged ion **5** can be attacked by the negative carbon atom of the enolate anion of diethyl acetamidomalonate *via* two possible routes (Scheme 2). If the enolate anion attacks to vinylphosphonium cation *via* route **a**, the phosphorus ylide **6** will be formed. Then, it undergoes intramolecular *Wittig* reaction and gives unstable cyclobutene derivative **7**, which performs ring opening reaction and compound **3** is formed. On the other hand, addition of the enolate anion to phosphonium salt **6** (route **b**) leads to the intermediate **8**. Then, it is followed by 1,2-proton transfer and elimination of triphenylphosphine (as a catalyst) which leads to 1,1-diethyl-3-alkyl (*E*)-(1-acetylamino)-2-propene-1,1,3-tricarboxylate **4** (Scheme 3).

Reactions of another CH-acid, ethyl acetamidocyanoacetate, and alkyl propiolates in the presence of triphenylphosphine were performed similarly and two geometric isomers, (*E*)-isomer **10** and (*Z*)-isomer **11** were produced. In the resulting (*Z*)-isomer **11** the ester and the amine group are aligned so nicely, that an intramolecular amidation occurs instantaneously and α,β-unsaturated lactam **12** is produced (Scheme 4).

The structures of **3** and **4** were deduced from their elemental analyses, mass spectrometric data, and their ^{1}H, ^{13}C NMR, and IR spectra. The ^{1}H NMR spectrum of **3a** exhibited a triplet for methyl ($\delta =$ 1.3 ppm), a singlet for CH_3 ($\delta = 2.2$ ppm), a singlet for methoxy ($\delta = 3.8$ ppm), a quartet for OCH_2 ($\delta = 4.3$ ppm), a singlet for vinyl protons ($\delta =$ 5.5 ppm). The NH group exhibited a fairly broad peak at $\delta = 10.2$ ppm, indicating extensive intramolecular hydrogen-bond formation with the vicinal carbonyl group. The ^{13}C NMR spectrum of **3a** exhibited signals for methoxy ($\delta = 52.3$ ppm), ethoxy ($\delta = 62.8$ ppm), and olefinic carbons ($\delta = 101.2$ and



Scheme 3

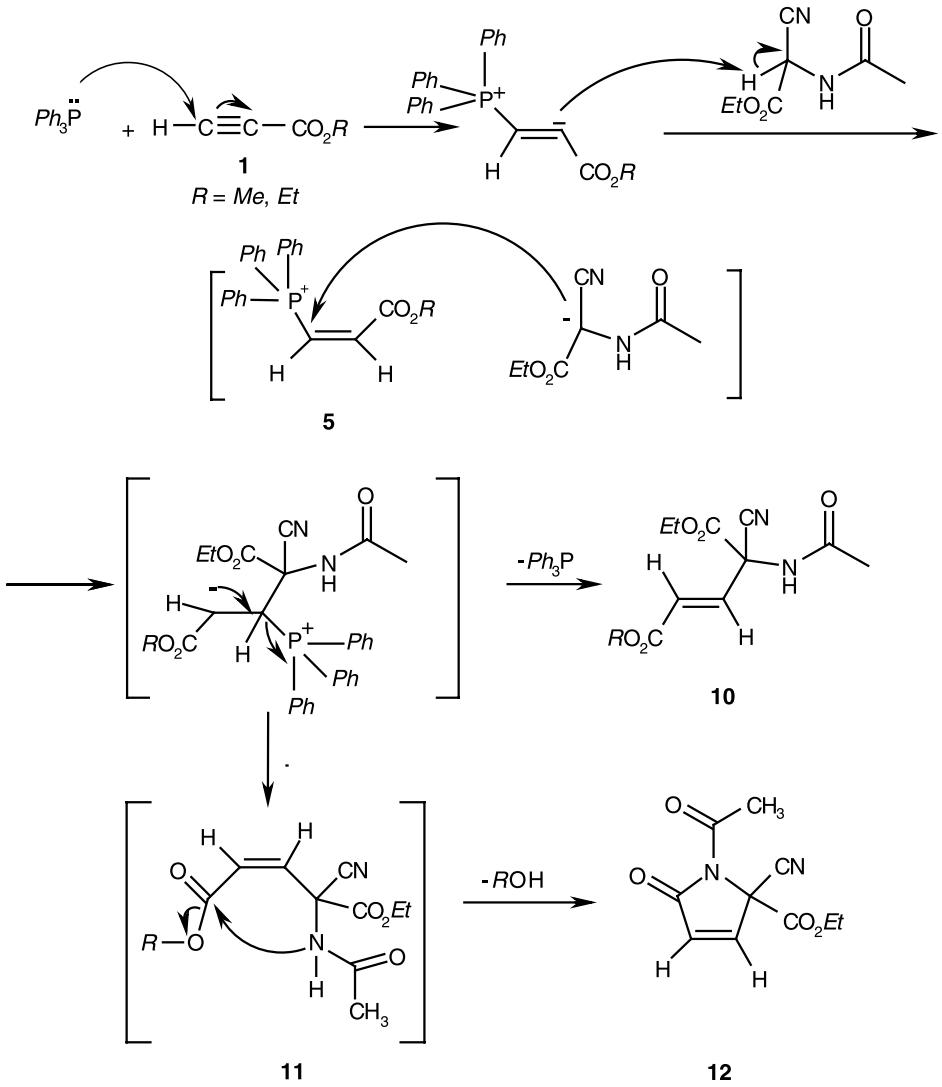
144.5 ppm) in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section. The ^{1}H and ^{13}C NMR spectra of **3b** are similar to those of **3a**, except for the signals of the ester moiety. The mass spectra of compounds **3a**, **3b** displayed molecular ion peaks at $m/z = 214$ and 229. Initial fragmentations involve loss of the side chains.

The structural assignment of **3a**, **3b** on the basis of their NMR and mass spectra were supported by their IR spectra. A strong NH absorption band at about $\bar{\nu} = 3250\,\mathrm{cm}^{-1}$ was observed.

The ^{1}H NMR spectrum of **4a** displayed a triplet for two methyl groups ($\delta = 1.04$ ppm), a singlet for methyl ($\delta = 1.86$ ppm), a singlet for methoxy ($\delta =$ 3.5 ppm), a multiplet for two ethoxy ($\delta = 3.97$–4.10 ppm), two doublet for vinyl ($\delta = 5.74$ and 7.23 ppm, $^{3}J_{\mathrm{HH}} = 15.8$ Hz), and a broad band for NH ($\delta = 7.3$ ppm) protons. Assignment of the (*E*) configuration to the carbon-carbon double bond in **4** is based on the coupling constant of vinylic protons ($^{3}J_{\mathrm{HH}} = 15.8$ Hz). The ^{13}C NMR spectrum of **4a** exhibited eleven sharp lines in agreement with the proposed structure. Partial assignment of these resonances is given in the experimental section. The mass spectra of compounds **4a**, **4b** displayed molecular ion peaks at $m/z = 301$ and 315. Initial fragmentations involve loss of the side chains.

The structures of **10** and **12** were characterized from their elemental analyses, mass spectrometric data, and their ^{1}H, ^{13}C NMR, and IR spectra of which the results are given in the experimental section.

We anticipate that the described reaction represents a simple entry into the synthesis of polyfunc-



Scheme 4

tional alkenes and α,β-unsaturated γ-lactams. The present method carries the advantage that not only the reaction is performed under neutral conditions, but also the substances can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches [1, 2, 9].

Experimental

Alkyl propiolates **1**, diethyl acetamidomalonate, and triphenylphosphine were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer; their results where in agreement with calculated values. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Chromatography columns were prepared from Aldrich silica gel 70–230 mesh.

*General procedure for the preparation of **3** and **4** (examplified by **3a** and **4a**)*

To a magnetically stirred solution of 0.43 g diethylacetamidomalonate (2 mmol) and 0.168 g methyl propiolate (2 mmol) in 10 cm^3 dry dichloromethane, a solution of 0.52 g triphenylphosphine (2 mmol) in 2 cm^3 dry dichloromethane was added dropwise at room temperature over 10 min. The reaction mixture was stirred for 2 days. The solvent was removed under reduced pressure and the residue was purified by column chromatography using *n*-hexane:ethyl acetate (50:50) as elu-

ent. The products **3a** and **4a** were isolated from the reaction mixture, respectively.

1-Ethyl 4-methyl (Z)-2-(acetylamino)-2-butendioate (**3a**, $C_9H_{13}NO_5$)
Yellow oil, yield: 26%; $R_f = 0.8$ (*n*-hexane/ethyl acetate 50/50, *v*/*v*) IR (KBr): $\bar{\nu}_{max} = 3250$ (NH), 3040 (CH), 1750, 1735, and 1680 (C=O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta =$ 1.3 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 2.2 (3H, s, CH_3), 3.8 (3H, s, OCH_3), 4.3 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 5.5 (1H, s, CH), 10.2 (1H, s, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 14.3$ (CH_3), 23.9 (CH_3), 52.3 (OCH_3), 62.8 (OCH_2), 101.2 and 144.5 (olefinic carbons), 164.2, 168.4, and 168.8 (3C=O) ppm; MS: m/z (%) = 215 (M^+, 4), 173 ($M^+ - CH_3CO + 1$, 4), 155 ($M^+ - OEt - CH_3$, 8), 58 (CH_3CONH^+, 37), 44 (CH_3COH^+, 100).

Diethyl (Z)-2-(acetylamino)-2-butenedioate (**3b**, $C_{10}H_{15}NO_5$)
Yellow oil, yield: 30%; $R_f = 0.8$ (*n*-hexane/ethyl acetate 50/50, *v*/*v*); IR (KBr): $\bar{\nu}_{max} = 3250$ (NH), 3040 (CH) 1745, 1730, and 1675 (C=O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.25$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 1.29 (3H, t, $^3J_{HH} =$ 7.2 Hz, CH_3), 2.1 (3H, s, CH_3), 4.17 (2H, q, $^3J_{HH} = 7.1$ Hz, OCH_2), 4.27 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 5.4 (1H, s, CH), 10.15 (1H, s, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta =$ 13.85 (CH_3), 14.1 (CH_3), 23.3 (CH_3), 60.8, and 62.2 ($2OCH_2$), 101 and 144 (olefinic carbons), 163.7, 167.93, and 167.97 (3C=O) ppm; MS: m/z(%) = 229 (M^+, 6), 215 ($M^+ - CH_3$ +1, 100), 173 ($M^+ - 2CH_2{=}CH_2$, 2), 68 ($M^+ - CO_2Et -$ *Et*–CH_3CO, 3), 44 (CH_3COH^+, 10).

1,1-Diethyl 3-methyl (E)-(1-acetylamino)-2-propene-1,1,3-tricarboxylate (**4a**, $C_{13}H_{19}NO_7$)
Yellow oil, yield: 67%; $R_f = 0.5$ (*n*-hexane/ethyl acetate 50/50, *v*/*v*); IR (KBr): $\bar{\nu}_{max} = 3268$ (NH), 3056 (CH), 1740, 1730, and 1665 (C=O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.04$ (6H, t, $^3J_{HH} = 7.1$ Hz, $2CH_3$), 1.86 (3H, s, CH_3), 3.50 (3H, s, OCH_3), 3.97–4.10 (4H, m, $2CH_2O$), 5.74 (1H, d, $^3J_{HH} = 15.8$ Hz, CH), 7.23 (1H, d, $^3J_{HH} = 15.8$ Hz, CH), 7.30 (1H, bs, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta =$ 13.61 ($2CH_3$), 22.12 (CH_3), 51.51 (OCH_3), 62.90 [$C(CO_2E)_2$], 63.03 and 66.67 ($2OCH_2$), 121.89 and 141.4 (olefinic carbons), 165.62, 165.63, 165.64, and 169.22 (4C=O) ppm; MS: m/z(%) = 301 (M^+, 74), 258 ($M^+ - CH_3CO$, 66), 228 ($M^+ - CO_2Et$, 41), 186 [$M^+ - (CO_2Et + CH_3CO)$ +1, 100], 43 (CH_3CO, 33).

Triethyl (E)-1-(acetylamino)-2-propene-1,1,3-tricarboxylate (**4b**, $C_{14}H_{21}NO_7$)
Yellow oil, yield: 65%; $R_f = 0.5$ (*n*-hexane/ethyl acetate 50/50, *v*/*v*); IR (KBr): $\bar{\nu}_{max} = 3280$ (NH), 3040 (CH), 1735, 1723, and 1670 (C=O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.95$–1.02 (9H, m, $3CH_3$), 1.84 (3H, s, CH_3), 3.83–4.06 (6H, m, $3OCH_2$), 5.71 (1H, d, $^3J_{HH} = 15.8$ Hz, CH), 7.20 (1H, d, $^3J_{HH} = 15.8$ Hz, CH), 7.26 (1H, bs, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.62$ ($2CH_3$), 13.86 (CH_3), 22.15 (CH_3), 62.80 [$C(CO_2Et)_2$], 60.48, 62.99, and 66.68 ($3OCH_2$), 122.33 and 141.09 (olefinic carbons), 165.20, 165.40, 165.66, and 169.13 (4C=O) ppm; MS: m/z(%) = 315 (M^+, 14.5), 270 ($M^+ - OEt$, 33), 242 ($M^+ - CO_2Et$, 24), 200 [$M^+ - (CH_3CO + CO_2Et)$ +1], 44 (CH_3COH^+).

*General procedure for the preparation of **10** and **12** (examplified by **10a** and **12**)*
To a magnetically stirred solution of 0.34 g ethyl acetamidocyanoacetate (2 mmol) and 0.168 g methyl propiolate (2 mmol) in 10 cm^3 dry dichloromethane, a solution of 0.52 g triphenylphosphine (2 mmol) in 2 cm^3 dry dichloromethane was added dropwise at room temperature over 10 min. The reaction mixture was stirred for 1 day. The solvent was removed under reduced pressure and the residue was purified by column chromatography using *n*-hexane ethyl acetate (60:40) as eluent.

5-Ethyl 1-methyl (E)-4-(acetyl amino)-4-cyano-2-pentenedionate (**10a**, $C_{11}H_{14}N_2O_5$)
Yellow oil, yield: 61%; $R_f = 0.5$ (*n*-hexane/ethyl acetate 60/40, *v*/*v*); IR (KBr): $\bar{\nu}_{max} = 3307$ (NH), 3025 (CH), 2405 (CN), 1737, 1725, and 1677 (C=O), 1627 (C=C) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 2.1 (3H, s, CH_3CO), 3.70 (3H, s, CH_3O), 4.26–4.36 (2H, m, OCH_2), 6.46 (1H, d, $^3J_{HH} = 15.5$ Hz, =CH), 6.74 (1H, d, $^3J_{HH} = 15.5$ Hz, =CH), 6.9 (1H, bs, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.82$ (CH_3), 23.28 (CH_3CO), 52.29 (OCH_3), 64.05 (OCH_2), 57.72 (C), 114.10 (CN), 127.00 (=CH), 137.27 (=CH), 163.67 (CONH), 164.76 (CO_2Me), 169.76 (CO_2Et) ppm; MS: m/z(%) = 254 (M^+, 5), 229 ($M^+ - CN + 1$, 8), 223 ($M^+ - OCH_3$), 170 [$M^+ - (CH_3CONH + CN)$, 12), 108 [$M^+ - (CO_2Me + CO_2 + C_2H_4 + CH_3)$, 100], 43 ($CH_3CO^+$, 100).

Diethyl (E)-4-(acetylamino)-4-cyano-2-pentenedionate (**10b**, $C_{12}H_{16}N_2O_5$)
White powder, mp 92–95°C, yield: 65%; $R_f = 0.5$ (*n*-hexane/ethylacetate 60/40, *v*/*v*); IR (KBr): $\bar{\nu}_{max} = 3237$ (NH), 2395 (CN), 1740, 1726, and 1659 (C=O), 1635 (C=C) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.28$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 1.33 (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 2.08 (3H, s, CH_3), 4.2 (2H, t, $^3J_{HH} = 7.1$ Hz, OCH_2), 4.27–4.38 (2H, m, OCH_2), 6.48 (1H, d, $^3J_{HH} = 15.5$ Hz, =CH), 6.73 (1H, d, $^3J_{HH} =$ 15.5 Hz, =CH), 6.82 (1H, bs, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.76$ (CH_3), 14.06 (CH_3), 22.4 (CH_3CO), 57.6 (C), 61.4 (OCH_2), 64.91 (OCH_2), 114.09 (CN), 127.56 (=CH), 136.90 (=CH), 163.70 (CO_2Et), 164.37 (CO_2Et), 169.38 (CONH) ppm; MS: m/z(%) = 268 (M^+, 3), 223 ($M^+ - OEt$, 6), 181 [$M^+ - (CH_3CONH + Et)$, 38], 156 [$M^+ - (C_2H_4 + CH_3CONH + CN)$, 81], 108 [$M^+ - (CO_2Et + CO_2 + C_2H_4 + CH_3)$, 100], 43 ($CH_3CO^+$, 100).

Ethyl 1-acetyl-2-cyano-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxylate (**12**, $C_{10}H_{10}N_2O_4$)
Yellow oil, yield: 30–35%; $R_f = 0.7$ (*n*-hexane/ethyl acetate 60/40, *v*/*v*); IR (KBr): $\bar{\nu}_{max} = 2371$ (CN), 1725, 1690, and 1675 (C=O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.3$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 2.55 (3H, s, CH_3), 4.31 (2H, q, $^3J_{HH} = 7.1$ Hz, OCH_2), 6.44 (1H, d, $^3J_{HH} = 5.8$ Hz,

=CH), 7.17 (1H, d, $^3J_{HH} = 5.8$ Hz, =CH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.83$ (CH_3), 23.92 (CH_3CO), 65.08 (OCH_2), 68.14 (C), 111.77 (CN), 130.43 (=CH), 141.85 (=CH), 161.28 (CO), 166.25 (CO), 168.35 (CO) ppm; MS: $m/z(\%) = 222$ (M^+, 3), 150 [$M^+ - (CO_2 + C_2H_4)$, 57], 136 [$M^+ - (OEt + CN + CH_3)$, 73], 108 [$M^+ - (CO_2Et + CN + CH_3)$, 81 [$M^+ - (CH_3CO + CN + CO2 + C_2H_4)$, 100], 43 ($CH_3CO^+$, 100].

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