Ph_3P promoted one-pot synthesis of dialkyl 2-(2-oxopyridin-1(2*H*)-yl)but-2-enedioates from a reaction of 2-hydroxypyridine and dialkyl acetylenedicarboxylates

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2-Hydroxypyridine undergoes a smooth reaction with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine (15 mol%) to produce the *E/Z* isomers of dialkyl 2-(2-oxopyridin-1(2*H*)-yl)but-2-enedioates in high yields.

Keywords: 2-hydroxypyridine; triphenylphosphine; acetylenic ester; 2-pyridone

Due to the environmental demand, there has been considerable interest in developing a new catalyst for organic reactions that would be mild, easily available at low-cost, high performance in transformation and wide applicability. Organophosphorus compounds are widely used in organic synthesis.[1-3] When they act as a catalyst, 'soft' nucleophilicity is one of their most characteristic features, as shown in the Michael addition, aldol condensation, isomerisation of C–C mutiple bonds,[4-8] silylcyanation of aldehydes,[9] alcohol addition to methyl propiolate,[10] carbonate formation from propargyl alcohol and carbon dioxide,[11,12] and cycloaddition of buta-2,3-dienoates or but-2-ynoates with electron-deficient olefins.[13]

The phosphine induced isomerisation of alkynoates and addition to the α-position of these substrates indicated the possibility of a new reactivity pattern for alkynoates-nucleophilic addition at the α-position as a new source of α-substituted alkyl acrylates. An important point is the ability of the nucleophile to undergo Michael addition in preference to the α–attack since phosphines could also serve as general base catalysts for conjugate additions.[14-16] In this regard, triphenylphosphine (Ph_3P) has received increasing attention as versatile and mild reagent in many occasions for various organic transformations under neutral conditions in recent years.[17-24]

The addition reaction between electron-deficient acetylenic compounds and nitrogen-containing hetrocycles has been extensively investigated.[25,26] We report here that dialkyl acetylenedicarboxylates **1** undergo addition reaction with 2-hydroxypyridine (**2**) in the presence of Ph_3P, yielding dialkyl (*Z*)- and (*E*)-2-(2-oxopyridin-1(2*H*)-yl)but-2-enedioates **3** in good yields.

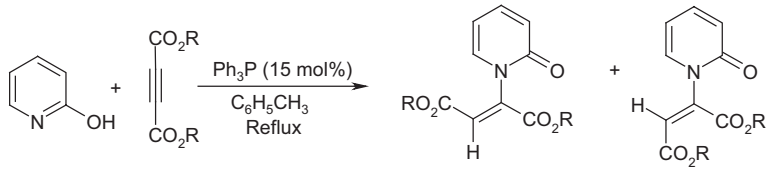
The reaction of Ph_3P with acetylenic ester **1** in the presence of **2** affords products **(*Z*)-3** and **(*E*)-3** in good yields (Scheme 1). The structures of **(*Z*)-3** and **(*E*)-3** were deduced from IR, ^1H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds are fairly similar and display molecular ion peaks at appropriate *m/z* values.

The ^1H NMR spectra of **3a** exhibited signals for methoxy and methine protons, together with characteristic multiplets for the aromatic protons. The ^{13}C NMR spectra of **(*Z*)-3a** or **(*E*)-3a** showed 11 distinct resonances in agreement with the proposed structures. Partial assignments of these resonances are given in the Experimental section. The structural assignments of compounds **(*Z*)-3** and **(*E*)-3** made on the basis of their ^1H- and ^{13}C NMR spectra were supported by their IR spectra. The carbonyl region of these compounds displayed characteristic absorption bands.

NMR spectroscopy was employed to distinguish between **(*Z*)-3** and **(*E*)-3**. The (*Z*) and (*E*) configurations of the carbon-carbon double bonds in **3** are based on the chemical shift of the olefinic proton.[27] The ^1H NMR spectra of **(*Z*)-3** showed olefinic proton at 6.98–7.06 ppm, while the **(*E*)-3** isomer exhibited the olefinic proton at 6.16–6.30 ppm.

Mechanistically, it is conceivable that the reaction leading to **3** involves the initial formation of a zwitterionic 1:1 intermediate **4** of Ph_3P and the acetylenic compound (Scheme 2).[28-30] The intermediate **4** is then protonated by the OH-acidic **1** to afford **5**. The latter might be attacked by the N-atom of the bidentate anion **6** to afford the ylide **7**. This intermediate undergoes a proton transfer to furnish the 1,3-diionic structure **8,** which is converted to the final product by loss of Ph_3P (Scheme 2).

In conclusion, the reaction of 2-hydroxypyridine with dialkyl acetylenedicarboxylates in the presence of Ph_3P provides a simple one-pot entry into the synthesis of stable compounds of potential interest. This method offers advantages such as mild reaction conditions faster reaction rates, high yields, readily availability of the catalyst and cleaner reaction profiles.



1 **2** **(*Z*)-3** **(*E*)-3**

2, 3	R	Yield of 3 (%)	*Z/E*
a	Me	98	7.5
b	Et	96	5.0
c	^{i}Pr	85	4.5
d	^{t}Bu	88	3.1

Scheme 1

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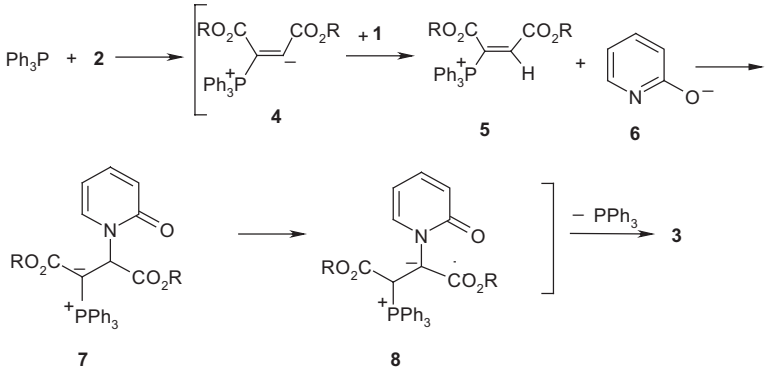

Scheme 2

The experimental procedure is convenient and avoids tedious work-up procedure for the isolation of the products.

Experimental

General

Compounds **1**, **2** and Ph_3P were obtained from *Fluka* and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m*/*z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

Typical procedure for preparation of compounds **3**:

To a stirred solution of **2** (2 mmol) and Ph_3P (15 mol%) in toluene (10 ml) was added drop wise a mixture of **1** (0.190 g, 2 mmol) in toluene (2 ml) at room temperature over 5 min. The reaction mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography (SiO_2; hexane/AcOEt 4:1) to afford the pure adducts.

(*Z*)-3a: *Dimethyl (Z)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Brown oil, yield: 0.35 g (75%). IR (KBr): 1731, 1675 (C=O). ^1H NMR: 3.71, 3.85 (6 H, 2 *s*, 2 MeO), 6.26 (1 H, *t*, ^3J = 6.8, CH), 6.59 (1 H, *d*, ^3J = 9.3, CH), 7.06 (1 H, s, CH), 7.10 (1 H, *d*, ^3J = 6.7, CH), 7.43 (1 H, t, ^3J = 9.3, CH). ^{13}C NMR: 52.9, 53.9 (2 MeO), 106.2, 121.7, 126.2, 138.0, 141.4 (5 CH), 141.5 (C), 162.3, 162.8, 163.3 (3 C=O). EI-MS: 237 (M^+, 11), 206 (50), 178 (100), 83 (87), 59 (40), 39 (75). Anal. Calcd for $C_{11}H_{11}NO_5$ (237.21): C, 55.70; H, 4.67; N, 5.90; found: C, 55.62; H, 4.69; N, 5.96%.

(*E*)-3a: *Dimethyl (E)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Brown oil, yield: 0.05 g (10%). IR (KBr): ^1H NMR: 3.78, 3.82 (6 H, 2 s, 2 MeO), 6.25 (1 H, t, ^3J = 6.8, CH), 6.30 (1 H, s, CH), 6.60 (1 H, d, ^3J = 9.2, CH), 7.10 (1 H, d, ^3J = 6.8, CH), 7.42 (1 H, *t*, ^3J = 9.2, CH). ^{13}C NMR: 52.8, 52.9 (2 MeO), 107.3, 122.5, 129.1, 133.7, 137.6 (5 CH), 141.7 (C), 162.4, 163.0, 163.8 (3 C=O). EI-MS: 237 (M^+, 8), 206 (38), 178 (100), 83 (69), 59 (48), 39 (80). Anal. Calcd for $C_{11}H_{11}NO_5$ (237.21): C, 55.70; H, 4.67; N, 5.90; found: C, 55.82; H, 4.71; N, 5.98%.

(*Z*)-3b: *Diethyl (Z)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Brown oil, yield: 0.37 g (70%). IR (KBr): 1671 and 1727 (C=O). ^1H NMR: 1.20 (3 H, *t*, ^3J = 7.1, Me), 1.31 (3 H, t, ^3J = 7.1, Me), 4.17 (2 H, q, ^3J = 7.1 Hz, CH_2O), 4.28 (2 H, q, ^3J = 7.1, CH_2O), 6.24 (1 H, *t*, ^3J = 6.7, CH), 6.58 (1 H, *d*, ^3J = 9.2, CH), 7.04 (1 H, *s*, CH), 7.11 (*d*, ^3J = 6.7, CH), 7.46 (1 H, *t*, ^3J = 9.2, CH). ^{13}C NMR: 14.3, 14.4 (2 Me), 62.0, 63.2 (2 CH_2O), 106.0, 121.7, 126.5, 138.0, 141.3 (5 CH), 141.3 (C), 162.3, 162.4, 163.0 (3 C=O). EI-MS: 265 (M^+, 4), 192 (83), 164 (100), 120 (25), 96 (23), 51 (25). Anal. Calcd for $C_{13}H_{15}NO_5$ (265.26): C, 58.86; H, 5.70; N, 5.28; found: C, 59.02; H, 5.78; N, 5.37%.

(*E*)-3b: *Diethyl (E)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Brown oil, yield: 0.08 g (14%). IR (KBr): ^1H NMR: 1.21 (3 H, *t*, ^3J = 7.1, Me), 1.33 (3 H, *t*, ^3J = 7.1, Me), 4.19 (2 H, *q*, ^3J = 7.1 Hz CH_2), 4.21 (2 H, *q*, ^3J = 7.1 Hz CH_2), 6.26 (1 H, *t*, ^3J = 6.8, CH), 6.28 (1 H, *s*, CH) 6.59 (1 H, *d*, ^3J = 9.1, CH), 7.06 (1 H, *d*, ^3J = 6.7, CH), 7.47 (1 H, *t*, ^3J = 9.1, CH). ^{13}C NMR: 14.3, 14.4 (2 Me), 62.0, 63.2 (2 CH_2O), 107.5, 122.0, 122.9, 132.3, 136.8 (5 CH), 143.0 (C), 162.2, 162.4, 164.0 (3 C=O). EI-MS: 265 (M^+, 6), 192 (80), 164 (100), 120 (32), 96 (29), 51 (34). Anal. Calcd for $C_{13}H_{15}NO_5$ (265.26): C, 58.86; H, 5.70; N, 5.28; found: C, 59.11; H, 5.80; N, 5.39%.

(*Z*)-3c: *Di-isopropyl (Z)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Brown oil, yield: 0.41 g (54%). IR (KBr): 1671 and 1727 (C=O). ^1H NMR: 1.18 (6 H, *d*, ^3J = 6.2, 2 Me), 1.29 (1 H, *d*, ^3J = 6.3, 2 Me), 5.00 (1 H, *sept*, ^3J = 6.2, CH), 5.14 (1 H, *sept*, ^3J = 6.2, CH), 6.24 (1 H, *t*, ^3J = 6.7, CH), 6.58 (1 H, *d*, ^3J = 9.3, CH), 6.98 (1 H, *s*, CH), 7.09 (1 H, *d*, ^3J = 6.7, CH), 7.41 (1 H, *t*, ^3J = 9.3, CH). ^{13}C NMR: 21.9, 22.0 (2 $CHMe_2$), 69.9, 71.3 (2 $CHMe_2$), 105.9, 121.8, 126.7, 138.1, 141.3 (5 CH), 143.1 (C), 161.9, 162.2, 162.6 (3 C=O). EI-MS: 293 (M^+, 5), 220 (100), 192 (62), 148 (58), 124 (71), 79 (67), 59 (83). Anal. Calcd for $C_{15}H_{19}NO_5$ (293.32): C, 61.42; H, 6.53; N, 4.78; found: C, 61.57; H, 6.61; N, 4.83%.

(*E*)-3c: *Di-isopropyl (E)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Brown oil, yield: 0.09 g (12%). IR (KBr): ^1H NMR: 1.29 (6 H, *d*, ^3J = 6.2, 2 Me), 1.31 (6 H, *d*, ^3J = 6.2, 2 Me), 5.03 (1 H, *d*, ^3J = 6.7, CH), 5.13 (1 H, *d*, ^3J = 6.7, CH), 6.23 (1 H, *t*, ^3J = 6.8, CH), 6.24 (1 H, *s*, CH) 6.56 (1 H, *d*, ^3J = 9.4, CH), 7.10 (1 H, *d*, ^3J = 6.7, CH), 7.43 (1 H, *t*, ^3J = 9.3, CH). ^{13}C NMR: 21.7, 22.1 (2 $CHMe_2$), 69.8, 70.8 (2 $CHMe_2$), 107.4, 123.1, 126.9, 132.4, 136.9 (5 CH), 143.2 (C), 161.6, 162.2, 163.4 (3 C=O). EI-MS: 293 (M^+, 7), 220 (100), 192 (78), 148 (39), 124 (64), 79 (79), 59 (76). Anal. Calcd for $C_{15}H_{19}NO_5$ (293.32): C, 61.42; H, 6.53; N, 4.78; found: C, 61.54; H, 6.60; N, 4.84%.

(*Z*)-3d: *Di-tert-butyl (Z)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Green oil, yield: 0.45 g (63%). IR (KBr): 1672 and 1722 (C=O). ^1H NMR: 1.38, 1.51 (18 H, 2 *s*, 2 CMe_3); 6.23 (1 H, *t*, ^3J = 6.7, CH); 6.57 (1 H, *d*, ^3J = 9.1, CH); 6.89 (1 H, *s*, CH); 7.10 (1 H, *d*, ^3J = 6.7, CH); 7.40 (1 H, *t*, ^3J = 9.1, CH). ^{13}C NMR: 28.2, 28.7 (2 CMe_3); 83.2, 84.2 (2 CMe_3); 105.8, 121.7, 127.7, 138.2, 141.1 (5 CH); 141.3 (C); 161.5, 162.2, 162.5 (3 C=O). EI-MS: 321 (M^+, 10), 220 (38), 192 (46), 164 (70), 120 (60), 83 (80), 57 (100). Anal. Calcd for $C_{17}H_{23}NO_5$ (321.37): C, 63.54; H, 7.21; N, 4.36; found: C, 63.66; H, 7.35; N, 4.44%.

(*E*)-3d: *Di-tert-butyl (E)-2-(2-oxopyridin-1(2H)-yl)but-2-enedioate*: Green oil, yield: 0.19 g (35%). IR (KBr): 1671 and 1724 (C=O). ^1H NMR: 1.53, 1.55 (18 H, 2 *s*, 2 CMe_3); 6.16 (1 H, *s*, CH); 6.22 (1 H, *t*, ^3J = 6.7, CH); 6.54 (1 H, *d*, ^3J = 9.3, CH); 7.24 (1 H, *d*, ^3J = 6.8, CH); 7.38 (1 H, *t*, ^3J = 9.3, CH). ^{13}C NMR: 28.0, 28.2 (2 CMe_3); 82.9, 83.8 (2 CMe_3); 107.1, 121.9, 123.8, 137.2, 141.1 (5 CH); 143.6 (C); 161.1, 162.2, 163.0 (3 C=O). EI-MS: 321 (M^+, 7), 220 (41), 192 (54), 164 (59), 120 (66), 83 (69), 57 (100). Anal. Calcd for $C_{17}H_{23}NO_5$ (321.37): C, 63.54; H, 7.21; N, 4.36; found: C, 63.66; H, 7.35; N, 4.44%.

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