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Synthesis of Dialkyl 2-(4-oxopyridin-1(4*H*)-yl)dicarboxylates Through the Reaction of 4-hydroxypyridine and Dialkyl Acetylenedicarboxylate in the Presence of Triphenylphosphine

Bita Mohtat,[1]* Zohre Najafi Azar,[1] Semiramis Nahavandian,[1] Hoorieh Djahaniani,[2] and Abbas Ahmadi[1]

[1] Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran
[2] Department of Chemistry, East Tehran Branch, Islamic Azad University, Qiamdasht, Tehran, Iran
b.mohtat@jooyan.org

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Abstract. 4-Hydroxypyridine undergoes a smooth reaction with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine (15 mol %) to produce the *E*/*Z* isomers of dialkyl 2-(4-oxopyridin-1(4*H*)-yl)but-2-enedioates in high yields.

Keywords: 4-Hydroxypyridine, dialkyl acetylenedicarboxylates, triphenylphosphine, dialkyl 2-(4-oxopyridin-1(4*H*)-yl)but-2-enedioates.

Resumen. 4-Hidroxipiridina reacciona bajo condiciones suaves con acetilencarboxilatos de dialquilo en presencia de trietilfosfina (15% molar) para producer los isómeros *E*/*Z* de los 2-(4-oxopiridin-1(4*H*)-il)but-2-endioatos de dialquilo en rendimientos elevados.

Palabras clave: 4-Hidroxipiridina, acetilendicarboxilatos de dialquilo, trifenilfosfina, 2-(4-oxopiridin-1(4*H*)-il)but-2-endioatos de dialquilo.

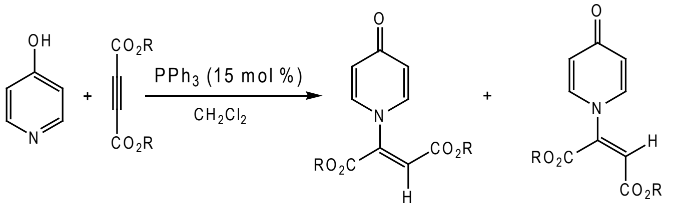
Introduction

The fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. Usually, the addition of nucleophiles devoid of an acidic hydrogen atom leads to a 1:1 zwitterionic intermediate that can undergo further transformations culminating in a stabilized product [1]. It is known that compounds such as triphenylphosphine, pyridine, amines and isocyanides can invoke zwitterion formation [2-5].

In this regard, triphenylphosphine (Ph_3P) has received increasing attention as versatile and mild reagent, for various organic transformations under neutral conditions, in recent years [6-9]. The addition reaction between electron-deficient acetylenic compounds and nitrogen containing hetrocycles has been extensively investigated [10, 11]. Recently, we reported the synthesis of the **E/Z** isomers of dialkyl 2-(2-oxopyridin-1(2H)-yl)but-2-enedioates, through the reaction of 2-hydroxypyridine with dialkyl acetylenedicarboxylates, in the presence of triphenylphosphine (Ph_3P) [12]. In continuation of our current interest in the application of triphenylphosphine and activated acetylenes in organic synthesis [13-15], we extend this methodology to the 4-hydroxypyridine (**1**) (Scheme 1).

Result and discussion

The reaction of Ph_3P with acetylenic ester **2** in the presence of 4-hydroxypyridine affords products (*Z*)-**3** and (*E*)-**3** in good yields (Scheme 1). The structures of (*Z*)-**3** and (*E*)-**3** were deduced from IR, ^{1}H 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 ^{1}H NMR spectra of **3a** exhibited signals for methoxy and vinyl protons, together with characteristic doublets for the aromatic protons. The ^{13}C NMR spectra of (*Z*)-**3a** or (*E*)-**3a** showed 9 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 ^{1}H 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 [16]. The ^{1}H NMR spectra of (*Z*)-**3** showed an olefinic proton at 6.93-7.05 ppm, while the (*E*)-**3** isomer exhibited the olefinic proton at 6.35-6.54 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 [17]. The intermediate **4** is then protonated by the acidic OH of **1** to afford **5**. The latter might be attacked by the

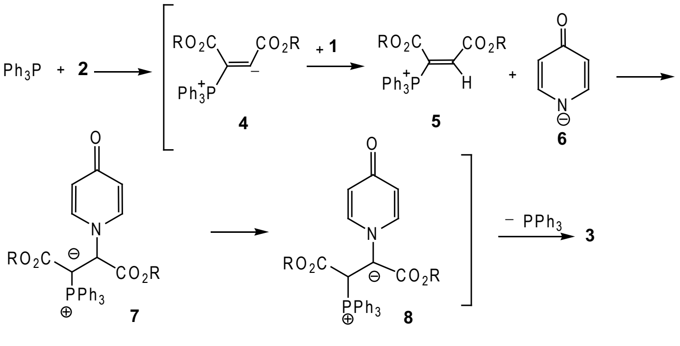


1 2 (Z)-3 (E)-3

2, 3	R	yield of 3 (%)	Z/E
a	Me	93	2.25
b	Et	86	2.54
c	*t*-Bu	87	6

Scheme 1.

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).



Scheme 2.

Conclusion

In conclusion, the reaction of 4-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, easy availability of the catalyst and cleaner reaction profiles. The experimental procedure is convenient and avoids tedious work up for the isolation of the products.

Experimental

General

Compounds **1**, **2** and Ph_3P were obtained from Fluka and were used without further purification. IR Spectra were measured in a Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra were determined in a Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ is expressed in ppm and *J* in Hz. The EI-MS (70 eV) were recorded in a 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 0.52 g of Ph_3P (2 mmol) and 0.19 g of **1** (2 mmol) in CH_2Cl_2 (10 mL) was added, drop wise, a mixture of **2** (2 mmol) in CH_2Cl_2 (4 mL) at −5 °C over 10 min. The mixture was then allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was separated by column chromatography (SiO_2; n-hexane: EtOAc : 1:1) to afford the pure title compounds.

***Dimethyl 2-(4-oxopyridin-1(4H)-yl)maleate* (Z)-3a:**

Brown oil, yield: 0.27 g (58%). IR (KBr): 1732, 1637 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (2H, d, *J* = 7.9 Hz, 2CH), 7.05 (1H, s), 6.14 (2H, d, *J* = 7.9 Hz, 2CH), 3.88 (3H, s, CH_3-O), 3.73 (3H, s, CH_3-O). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.7 (C=O), 163.5 (C=O), 163.2 (C=O), 141.5 (C), 141.2 (2CH), 126.1 (CH), 117.9 (2CH), 54.0 (CH_3-O), 52.8 (CH_3-O). EI-MS *m/z* (rel.int.): 237 [M^+] (100), 209 (39), 179 (30), 150 (30), 95 (65), 67 (61), 59 (73), 41 (59). *Anal.* C 55.66 %, H 4.65 %, N 5.93%, Calcd for $C_{11}H_{11}NO_5$, C 55.70 %, H 4.67 %, N, 5.90 %.

***Dimethyl 2-(4-oxopyridin-1(4H)-yl)fumarate* (E)-3a:**

Brown oil, yield: 0.12 g (35%) IR (KBr): 1713, 1635 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.0 Hz, 2CH), 6.54 (1H, s, CH), 6.21 (2H, d, *J* = 8.0 Hz, 2CH), 3.94 (3H, s, CH_3-O), 3.77 (3H, s, CH_3-O). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.7 (C=O), 165.3 (C=O), 163.5 (C=O), 144.7 (C), 138.2 (2CH), 119.5 (CH), 114.1 (2CH), 54.1 (CH_3-O), 52.6 (CH_3-O). EI-MS *m/z* (rel.int.): 237 [M^+] (45), 209 (15), 179 (100), 150 (61), 95 (65), 67 (32), 59 (55), 41 (24). *Anal.* C 55.62 %, H 4.69 %, N 5.96 %, Calcd for $C_{11}H_{11}NO_5$, C 55.70 %, H 4.67 %, N 5.90 %.

***Diethyl 2-(4-oxopyridin-1(4H)-yl)maleate* (Z)-3b:**

Brown oil, yield: 0.33 g (62%). IR (KBr): 1730, 1635 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 7.5 Hz, 2CH), 7.07 (1H, s, CH), 6.24 (2H, d, *J* = 7.5 Hz, 2CH), 4.34 (2H, q, *J* = 7.1 Hz, CH_2-O), 4.17 (2H, q, *J* = 7.1 Hz, CH_2-O), 1.32 (3H, t, J = 7.1 Hz, CH_3), 1.19 (3H, t, *J* = 7.1 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.5 (C=O), 163.1 (C=O), 162.7 (C=O), 141.6 (2CH), 141.3(C), 126.8(CH), 117.8(2CH), 63.8 (CH_2-O), 62.3 (CH_2-O), 14.3 (CH_3), 14.2 (CH_3). EI-MS *m/z* (rel.int.): 265 [M^+] (46), 237 (14), 220 (100), 192 (18), 164 (34), 121 (17). *Anal.* C 58.97 %, H 5.73 %, N 5.31 %, Calcd for $C_{13}H_{15}NO_5$, C 58.86 %, H 5.70 %, N 5.28 %.

***Diethyl 2-(4-oxopyridin-1(4H)-yl)fumarate* (E)-3b:**

Brown oil, yield: 0.13 g (24%). IR (KBr): 1730, 1634 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 7.9 Hz, 2CH), 6.55 (1H, s, CH), 6.28 (2H, d, *J* = 7.9 Hz, 2CH), 4.40 (2H, q, *J* = 7.1 Hz, CH_2-O), 4.23 (2H, q, *J* = 7.1 Hz, CH_2-O), 1.29 (3H, t, *J* = 7.1 Hz, CH_3), 1.18 (3H, t, *J* = 7.1 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.9 (C=O), 164.8 (C=O), 162.9 (C=O), 144.3 (C), 138.5 (2CH), 119.4 (CH), 115.2 (2CH), 63.8 (CH_2-O), 62.3 (CH_2-O), 14.3 (CH_3), 14.2 (CH_3). EI-MS *m/z* (rel.int.): 265 [M^+] (100), 237 (42), 220 (38), 192 (29), 164 (30), 121 (26). *Anal.* C 59.02 %, H 5.78 %, N 5.37 %, Calcd for $C_{13}H_{15}NO_5$, C 58.86 %, H 5.70 %, N 5.28 %.

***Di-tert -butyl 2-(4-oxopyridin-1(4H)-yl)maleate* (Z)-3c:**

Brown oil, yield: 0.48 g (75%). IR (KBr): 1720, 1637 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 7.9 Hz, 2CH), 6.93 (1H, s, CH), 6.15 (2H, d, *J* = 7.9 Hz, 2CH), 1.53 (9H, s, $3CH_3$), 1.40 (9H, s, $3CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.4 (C=O), 162.7 (C=O), 161.8 (C=O), 141.3 (2CH), 141.1 (C), 128.3 (CH), 117.9 (2CH), 84.8 (C-O), 83.7 (C-O), 30.6 ($3CH_3$), 29.0 ($3CH_3$). EI-MS *m/z* (rel.int.): 321 [M$^+$] (10), 220 (38), 192 (46), 164 (70), 120 (60), 83 (80), 57 (100). *Anal.* C 63.66 %, H 7.35 %, N 4.44 %, Calcd for $C_{17}H_{23}NO_5$, C 63.54 %, H 7.21 %, N 4.36 %.

***Di-tert-butyl 2-(4-oxopyridin-1(4H)-yl)fumarate* (E)-3c:**

Brown oil, yield: 0.08 g (12%). IR (KBr): 1720, 1637 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* = 8.0 Hz, 2CH), 6.35 (1H, s, CH), 6.21 (2H, d, *J* = 8.0 Hz, 2CH), 1.57 (9H, s, $3CH_3$), 1.49 (9H, s, $3CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.6 (C=O), 160.9 (C=O), 141.8 (C), 138.3 (2CH), 119.4 (CH), 116.2 (2CH), 85.4 (C-O), 82.5 (C-O), 28.0 ($3CH_3$), 27.9 ($3CH_3$). EI-MS *m/z* (rel.int.): 321 [M+] (10), 220 (38), 192 (46), 164 (70), 120 (60), 83 (80), 57 (100). Anal. C 63.62 %, H 7.37 %, N 4.40 %, Calcd for $C_{17}H_{23}NO_5$, C 63.54 %, H 7.21 %, N 4.36 %.

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