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

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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(4H)-yl)but-2-enedioates in high yields.

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

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 (Ph3P) 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 heterocycles 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 (Ph3P) [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 Ph3P 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, 1H NMR, and 13C 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 vinyl protons, together with characteristic doublets for the aromatic protons. The 13C

Scheme 1.
Synthesis of Dialkyl 2-(4-oxopyridin-1(4H)-yl)dicarboxylates

N-atom of the bidentate anion 6 to afford the ylide 7. This intermediate undergoes a proton transfer to furnish the 1,3-dionic structure 8, which is converted to the final product by loss of Ph₃P (Scheme 2).

Conclusion

In conclusion, the reaction of 4-hydroxy pyridine with dialkyl acetylenedicarboxylates in the presence of Ph₃P, 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 Ph₃P were obtained from Fluka and were used without further purification. IR Spectra were measured in a Shimadzu IR-460 spectrometer. ¹H and ¹³C NMR spectra were determined in a Bruker DRX-300 AVANCE instrument; in CDCl₃ 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 Ph₃P (2 mmol) and 0.19 g of 1 (2 mmol) in CH₂Cl₂ (10 mL) was added, drop wise, a mixture of 2 (2 mmol) in CH₂Cl₂ (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 (SiO₂; 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, CDCl₃) 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, CH₃-O), 3.73 (3H, s, CH₃-O). ¹³C NMR (75.5 MHz, CDCl₃) 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 (CH₃-O), 52.8 (CH₂-O).

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, CDCl₃) 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, CH₃-O), 3.77 (3H, s, CH₃-O). ¹³C NMR (75.5 MHz, CDCl₃) δ 178.7 (C=O), 165.3 (C=O), 165.5 (C=O), 144.7 (C), 138.2 (2CH), 119.5 (CH), 114.1 (2CH), 54.1 (CH₃-O), 52.6 (CH₂-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 C₁₁H₁₅NO₃, C 55.70 %, H 4.67 %, N, 5.90 %.

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

Brown oil, yield: 0.33 g (62%) IR (KBr): 1730, 1635 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃) 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, CH₂-O), 4.17 (2H, q, J = 7.1 Hz, CH₂-O), 1.32 (3H, t, J = 7.1 Hz, CH₃), 1.19 (3H, t, J = 7.1 Hz, CH₃). ¹³C NMR (75.5 MHz, CDCl₃) δ 178.5 (C=O), 163.1 (C=O), 162.7 (C=O), 141.6 (2CH), 141.3(C), 126.8(CH), 117.8 (C=O), 63.8 (CH₂-O), 62.3 (CH₂-O), 14.3 (CH₃), 14.2 (CH₃). 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 C₁₃H₁₈NO₃, C 58.86 %, H 5.70 %, N 5.28 %.

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

Brown oil, yield: 0.13 g (24%) IR (KBr): 1730, 1634 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃) 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, CH₂-O), 4.23 (2H, q, J = 7.1 Hz, CH₂-O), 1.29 (3H, t, J = 7.1 Hz, CH₃), 1.18 (3H, t, J = 7.1 Hz, CH₃). ¹³C NMR (75.5 MHz, CDCl₃) 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 (CH₂-O), 62.3 (CH₂-O), 14.3 (CH₃), 14.2 (CH₃). 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 C₁₃H₁₈NO₃, C 58.86 %, H 5.70 %, N 5.28 %.

Scheme 2.
**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\(_3\)) \(\delta 7.45 (2H, d, J = 7.9\) 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\(_3\)). \(^1\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta 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\(_3\)) \(\delta 7.68 (2H, d, J = 8.0\) 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\(_3\)). \(^1\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta 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 %.

**References**