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Ph_3P Catalyzed Synthesis of Alkyl 2-(4-Oxopyridin-1(4*H*)-yl)acrylates by Nucleophilic Addition to Alkyl Propiolates

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ABSTRACT

4-Hydroxypyridine undergoes a smooth reaction with alkyl propiolates in the presence of triphenylphosphine to produce α and β-substituted alkyl acrylate products. When the reaction was performed with 4-hydroxyquinoline only α-substituted alkyl acrylates were obtained.

KEYWORDS

4-hydroxypyridine, 4-hydroxyquinoline, alkyl acrylates, alkyl propiolates, triphenylphosphine.

Organophosphorus compounds have often been used in organic synthesis as useful reagents, in addition to being utilized as ligands for a number of transition metal catalysts.[1–3] The phosphine-induced isomerization of alkynoates and subsequent addition to the α-position of these substrates has demonstrated the possibility of a new route to α-substituted alkyl acrylates by employing this alkynoate-nucleophilic addition at the α-position. In this regard, triphenylphosphine (Ph_3P) has received increasing attention as a versatile and mild reagent for various organic transformations under neutral conditions in recent years.[4–11]

In this work, we present the nucleophilic α and β-addition of 4-hydroxypyridine (**1**) to alkyl propiolates (**2**) in the presence of Ph_3P under neutral conditions to produce alkyl 2-(4-oxopyridin-1(4*H*)-yl)acrylate (**3**) and (2*E*)-alkyl 3-(4-oxopyridin-1(4*H*)-yl)acrylate (**4**) in good yields (Scheme 1).

The reaction proceeded at room temperature in CH_2Cl_2 and was finished within 24 h. The products were separated by column chromatography and identified as **3a** and **4a**, based on their elemental analyses and their IR, ^1H, and ^{13}C NMR spectral data. The ^1H NMR spectrum of **3a** exhibited a single resonance signal for the methyl group at δ = 3.90 ppm, together with two doublets at δ = 5.95 and 6.49 ppm with J = 1.4 Hz, which were readily assigned to the C=CH_2 group. The ^{13}C NMR spectrum of **3a** showed 7 distinct resonances in agreement with the structure of methyl 2-(4-oxopyridin-1(4*H*)-yl)acrylate. Similarly, the ^1H NMR spectrum of **4a** exhibited an AX system for the *trans*-olefinic protons at δ = 5.92 and 7.60 ppm with J = 14 Hz.

Mechanistically, it is conceivable that the reaction leading to **3** and **4** involves the initial formation of a zwitterionic 1:1 intermediate **5** of Ph_3P and the acetylenic compound (Scheme 2).[12] The intermediate **5** is then protonated by the OH-acidic **1** to afford **6**. Then the positively charged ion is attacked by the nitrogen atom of the conjugate base of the NH-acid **7** at the α-position. Compound **3** is subsequently formed by the elimination of Ph_3P. Attack of the conjugate base on the β-position of **6** ultimately leads to product **4**.

When the reaction is carried out using 4-hydroxyquinoline only the α-substituted alkyl acrylates (**11**) were obtained in excellent overall yields (Fig. 1). This selectivity is possibly due to the steric bulk of the triphenylphosphine employed in the reaction.

In conclusion, the functionalized acrylates reported here may be considered as potentially useful synthetic intermediates

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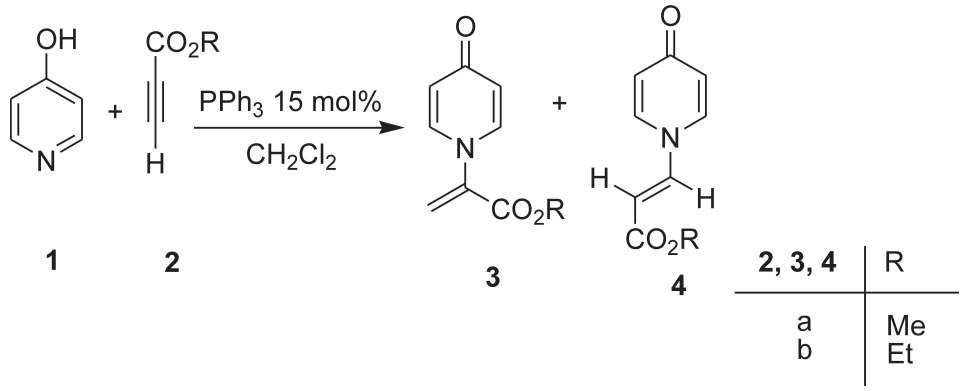
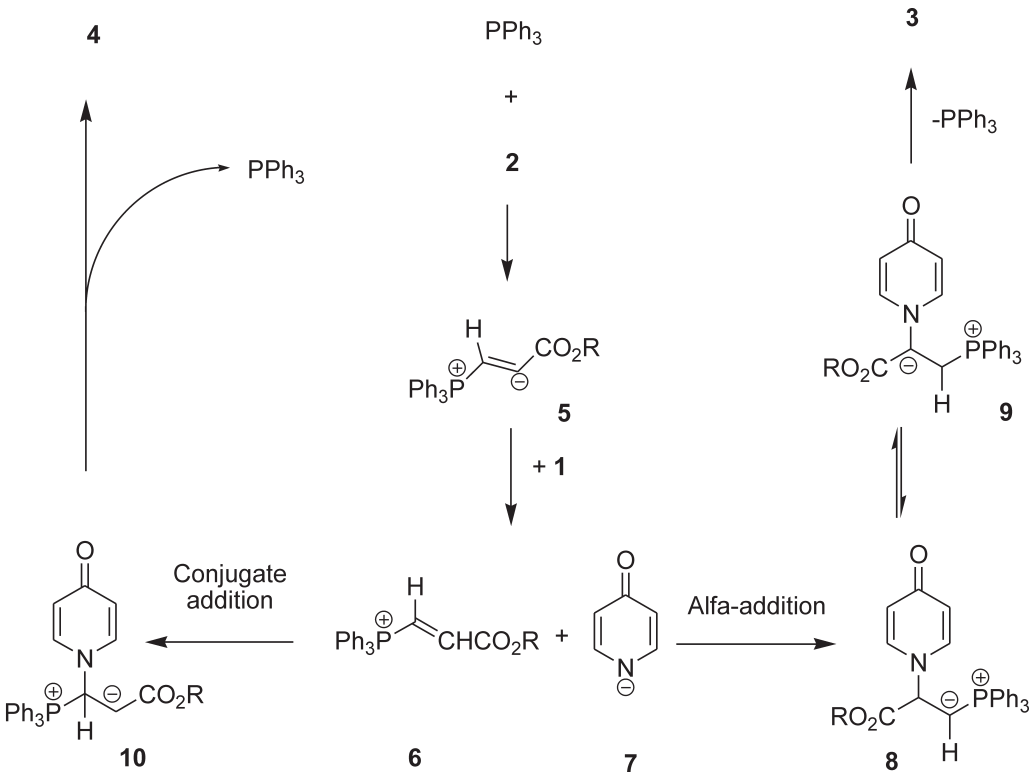
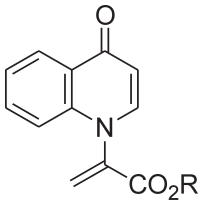


Scheme 1.
Typical procedure for compounds **3** and **4**.



Scheme 2.
A possible mechanism for preparation of **3** and **4**.



11	R	yield %
a	Me	77
b	Et	71

Figure 1.

because they possess variable functionality. Advantages of the present method include the application of the reaction under neutral conditions and the fact that the transformation involves a one pot reaction.

Experimental

Typical Procedure for Preparation of (3)

To a stirred solution of Ph_3P (0.52 g, 2 mmol) and **1** (0.19 g, 2 mmol) in CH_2Cl_2 (10 mL) was added, drop-wise, to a mixture of **2** (2 mmol) in CH_2Cl_2 (4 mL) over 10 min. The reaction mixture was then 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.

*Methyl 2-(4-oxopyridin-1(4*H*)-yl)acrylate* (**3a**)

Yellow powder; yield: 0.21 g (58 %); m.p.: 90–92 °C; δ_H (300 MHz, $CDCl_3$): 3.90 (3H, s, OCH_3), 5.95 (1H, d, *J* 1.4 Hz, CH), 6.40 (2H, d, *J* 6.1 Hz, 2 CH), 6.49 (1H, d, *J* 1.4 Hz, CH), and 7.32 ppm (2H, d, *J* 6.1 Hz, 2 CH); δ_c (75 MHz, $CDCl_3$): 53.4 (OCH_3), 118.3 (2 CH), 123.4 (CH_2), 139.4 (2 CH), 140.2 (C), 162.1 (C=O), and 179.1 ppm (C=O); ν_{max} ($CHCl_3$): 1733 cm^{-1} (C=O); *m/z*: 179 (M+, 20), 83 (75), 59 (40) and 39 (64); (Found: C, 60.42; H, 5.01; N, 7.77 %. Calc. for $C_9H_9NO_3$ (179.17): C, 60.33; H, 5.06; N, 7.82).

*(2*E*)-Methyl 3-(4-oxopyridin-1(4*H*)-yl)acrylate late* (**4a**)

Yellow powder; yield: 0.07 g (21 %); m.p.: 97–100 °C; δ_H (300 MHz, $CDCl_3$): 3.82 (3H, s, OCH_3), 5.92 (1H, d, *J* 14.1 Hz, CH), 6.22 (2H, d, *J* 8.0 Hz, 2 CH), 7.54 (2H, d, *J* 8.0 Hz, 2 CH), and 7.60 ppm (H, d, *J* 14.1 Hz, CH); δ_c (75 MHz, $CDCl_3$): 52.2 (OCH_3), 105.2 (CH), 119.8 (2 CH), 136.3 (2 CH), 142.4 (CH), 165.9 (C=O), and 179.6 ppm (C=O); ν_{max} ($CHCl_3$): 1713 cm^{-1} (C=O); (Found: C, 60.24; H, 5.10; N, 7.79 %. Calc. for $C_9H_9NO_3$ (179.17): C, 60.33; H, 5.06; N, 7.82).

*Ethyl 2-(4-oxopyridin-1(4*H*)-yl)acrylate* (**3b**)

Yellow powder; yield: 0.24 g (62 %); m.p.: 93–95 °C; δ_H (300 MHz, $CDCl_3$): 1.28 (3H, t, *J* 7.1 Hz, CH_3), 4.30 (2H, q, *J* 7.1Hz, OCH_2), 6.11 (2H, d, *J* 7.9 Hz, 2 CH), 6.14 (1H, d, *J* 1.5 Hz, CH), 6.44 (1H, d, *J* 1.5 Hz, CH), and 7.59 ppm (2 H, d, *J* 7.9 Hz, 2 CH); δ_c (75 MHz, $CDCl_3$): 14.2 (CH_3), 62.9 (OCH_2), 118.1 (2 CH), 123.1 (CH_2), 140.9 (2 CH), 141.5 (C), 162.7 (C=O), and 178.5 ppm (C=O); ν_{max} ($CHCl_3$): 1737 cm^{-1} (C=O); *m/z*: 193 (M+, 4), 164 (96), 120 (20) and 96 (32); (Found: C, 62.54; H, 5.57; N, 7.68 %. Calc. for $C_{10}H_{11}NO_3$ (193.2): C, 62.17; H, 5.74; N, 7.25).

*(2*E*)-Ethyl 3-(4-oxopyridin-1(4*H*)-yl)acrylate* (**4b**)

Yellow powder; yield: 0.09 g (24 %); m.p.: 105–107 °C; δ_H (300 MHz, $CDCl_3$): 1.26 (3H, t, *J* 7.1 Hz, CH_3), 4.20 (2H, q, *J* 7.1Hz, OCH_2), 6.18 (1H, d, *J* 14.1 Hz, CH), 6.22 (2H, d, *J* 7.9 Hz, 2 CH), 7.83 (1H, d, *J* 14.1 Hz, CH), and 8.01 ppm (2 H, d, *J* 7.9 Hz, 2 CH); δ_c (75 MHz, $CDCl_3$): 14.5 (CH_3), 61.0 (OCH_2), 105.4 (CH), 119.5 (2 CH), 138.1 (2 CH), 144.0 (CH), 166.4 (C=O), and 178.8 ppm (C=O); ν_{max} ($CHCl_3$): 1713 cm^{-1} (C=O); (Found: C, 62.62; H, 5.47; N, 7.60 %. Calc. for $C_{10}H_{11}NO_3$ (193.2): C, 62.17; H, 5.74; N, 7.25).

*Methyl2-(4-oxoquinolin(4*H*)-yl)acrylate* (**11a**)

Yellow oil; yield: 0.35 g (77 %); δ_H (300 MHz, $CDCl_3$): 3.78 (3 H, s, OCH_3), 6.16 (1H, s, CH), 6.30 (1H, d, *J* 7.8 Hz, CH), 6.85 (1H, s, CH), 7.10 (1H, d, *J* 8.5 Hz, CH), 7.37 (1H, t, *J* 7.2 Hz, CH), 7.43 (1H, d, *J* 7.8 Hz, CH), 7.58 (1H, t, *J* 7.2 Hz, CH), and 8.41 ppm (1H, d, *J* 8.5 Hz, CH); δ_c (75 MHz, $CDCl_3$): 53.4 (OCH_3) 110.7 (CH), 116.2 (CH), 124.1 (CH_2), 126.4 (C), 126.8 (CH), 129.1 (CH), 132.2 (CH), 139.3 (C), 140 4 (C), 142.2 (CH), 162.9 (C=O), and 178.4 ppm (C=O); ν_{max} ($CHCl_3$): 1741 cm^{-1} (C=O); *m/z*: 229 (M+, 23), 201 (44), 170 (75), 115 (40); (Found: C, 68.31; H, 4.95; N, 6.24 %. Calc. for $C_{13}H_{11}NO_3$ (229.23): C, 68.11; H, 4.84; N, 6.11).

*Ethyl2-(4-oxoquinolin(4*H*)-yl)acrylate* (**11b**)

Yellow oil; yield: 0.34 g (71 %). δ_H (300 MHz, $CDCl_3$): 1.24 (3H, t, *J* 7.1 Hz, CH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2), 6.14 (1H, s, CH), 6.33 (1H, d, *J* 7.8 Hz, CH), 6.84 (1H, s, CH), 7.12 (1H, d, *J* 8.5 Hz, CH), 7.38 (1H, t, *J* 7.3 Hz, CH), 7.44 (1H, d, *J* 7.8 Hz, CH), 7.59 (1H, t, *J* 7.3 Hz, CH), and 8.43 ppm (1H, d, *J* 8.5 Hz, CH); 14.0 (CH_3), 62.0 (OCH2) 110.7 (CH), 116.2 (CH), 124.8 (CH_2), 125.9 (C), 126.3 (CH), 128.7 (CH), 132.5 (CH), 139.0 (C), 141 7 (C), 142.1 (CH), 162.3 (C=O), and 178.6 ppm (C=O); ν_{max} ($CHCl_3$): 1729 cm^{-1} (C=O); *m/z*: 243 (M+, 38), 229 (71), 214 (20), 170 (34), (C, 69.34; H, 5.33; N, 5.84 %. Calc. for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76).

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