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Triphenylphosphine-promoted α-vinylation of 4-hydroxyquinazoline

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Abstract: 4-Hydroxyquinazoline undergoes a smooth reaction with alkyl acetylenecarboxylates in the presence of triphenylphosphine (15 mol%) to produce the isomers of α-alkyl acrylates in good yields.

Keywords: 4-Hydroxyquinazoline, Triphenylphosphine, Acetylenic ester, Alkyl actylates.

Introduction

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, silylcyanation of aldehydes, alcohol addition to methyl propiolate, carbonate formation from propargyl alcohol and carbon dioxide and cycloaddition of buta-2,3-dienoates or but-2-ynoates with electron-deficient olefins [4-13]. 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 α-position as a new source of a substituted alkyl acrylates. An important point is the ability of the nucleophile to undergo Michael addition in preference to α–attack since phosphines could also serve as general base catalysts for conjugate additions [14-16].

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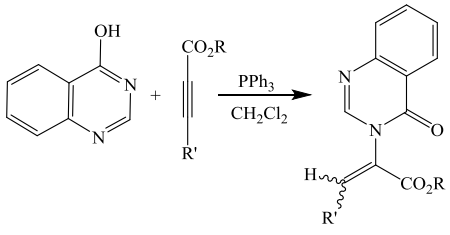
Previously, we described a convenient method for the preparation of α-alkyl acrylates by a three-component reaction of alkyl acetylenecarboxylates triphenylphosphine (Ph_3P) and some NH acids [17, 18]. Here, we extend this methodology using 4-hydroxyquinazoline **1** (Scheme **1**).



1 **2** **3**

2, 3	R	R'	yeild %
a	Me	H	75
b	Et	H	88
c	Et	Ph	72

Scheme 1: Typical procedure for compound **3**.

Results and discussion

The reaction proceeded at room temperature in CH_2Cl_2 and was finished within 24 h. The products were separated by TLC chromatography and identified as **3** and **4**, based on their elemental analyses and their IR, ^1H, and ^{13}C NMR spectral data. The ^1H NMR

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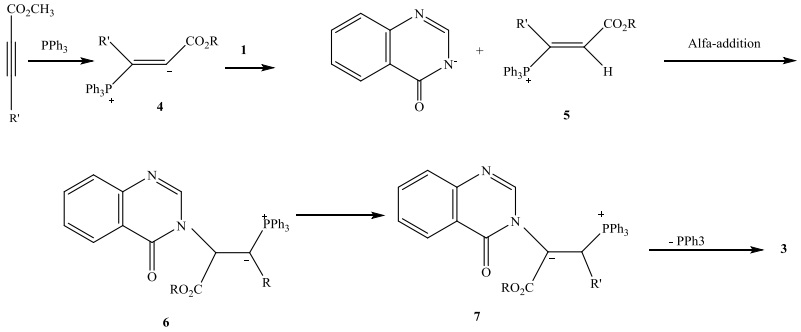
spectrum of **3a** exhibited three single resonance signals for the methyl group at δ = 3.86, ppm, and δ = 5.95 and 6.49 ppm which were readily assigned to the C=CH_2 group. The ^{13}CNMRspectrum of **3a** showed 12 distinct resonances in agreement with the structure of methyl 2-(4-oxoquinazolin-3(4H)-yl)acrylate.

NMR spectroscopy was employed to distinguish between (*Z*)-**3c** and (*E*)-**3c**. The (*Z*) and (*E*) configurations of the carbon–carbon double bonds in 3c are based on the chemicalshift of the olefinic proton [19]. The ^{1}H NMR spectra of (*Z*)-**3c** showed olefinic proton at 6.6-7.00 ppm, while the (*E*)-**3c** isomer exhibited the olefinic proton at 7.72 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**). The intermediate **5** is then protonated by the NH-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.



Scheme 2: Proposed mechanism for the synthesis of compound **3**.

Conclusion

In conclusion, the reaction of 4-hydroxyquinazoline with alkyl acetylenecarboxylates 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. 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. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-300 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 4-hydroxyquinazoline (0.28 gr, 2 mmol) and Ph_3P (15 mol%) in in 10 mL of CH_2Cl_2 was added drop wise a mixture of **2** (0.190 g, 2 mmol) in CH_2Cl_2 (2 ml) at room temperature over 5 min. The reaction mixture was at room temperature and stand for 24 h. The solvent was removed under reduced pressure and oil products were purified by preparative TLC on silica gel (Merck silica gel DCFertigplatten 60/Kieselgur F_{254}) 20*20 cm plates using nhexane- EtOAc (2:1) as eluent.

Methyl 2-(4-oxoquinazolin-3(4H)-yl)acrylate (**3a**):

Yellow oil, yield: 0.34 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1737 and 16745 (C=O). ^{1}H-NMR: δ = 3.85 (3 H, *s*, CH_3), 6.07 (1 H, s, CH), 6.73 (1 H, s, CH), 7.58 (1 H, *t*, $^3J_{HH}$ = 8.1 Hz, CH), 7.75 (1 H, d, $^3J_{HH}$ = 7.1 Hz, CH), 7.83 (1 H, *t*, $^3J_{HH}$ = 6.9 Hz, CH), 8.26 (1 H, s, CH), 8.36 (1 H, d, $^3J_{HH}$ = 7.9 Hz, CH), ^{13}C-NMR: δ = 52.1, (CH_3), 109.7 (CH), 121.4 (C), 127.6 (CH), 130.9 (CH), 132.4 (CH), 135.3 (CH), 136.8 (CH), 141.6 (CH), 146.6 (C), 159.3, (C=O), 166.2, (C=O). EI-MS: 230 (M^+, 20), 171 (50), 154 (100), 145 (87), 85 (40), 59 (75). Anal. Calcd for $C_{12}H_{10}N_2O_3$ (230.22): C, 62.61; H, 4.38; N, 12.17; found: C, 62.66; H, 4.30; N, 12.18.

Ethyl 2-(4-oxoquinazolin-3(4H)-yl)acrylate (**3b**):

Yellow oil, yield: 0.43 g (88%). IR (KBr) (ν_{max}/cm^{-1}): 1737 and 1683 (C=O). ^{1}H-NMR: δ = 1.31 (3 H, t, $^3J_{HH}$ = 7.1, CH_3, 4.31 (2 H, q, $^3J_{HH}$ = 7.1, OCH_2), 6.00

(1 H, s, CH), 6.62 (1 H, s, CH), 7.53 (1 H, *t*, $^3J_{HH}$ = 6.9, CH), 7.75 (1 H, t, $^3J_{HH}$ = 7.3, CH), 7.81 (1 H, d, $^3J_{HH}$ = 7.0, CH), 7.95 (1 H, s, CH), 8.31 (1 H, t, $^3J_{HH}$ = 7.8, CH). ^{13}C-NMR: δ = 14.0, (CH_3), 62.3, (OCH_2), 121.9 (C), 125.5 (CH), 126.9 (CH), 127.6 (C), 127.7 (CH_2), 134.8 (CH), 137.0 (CH), 145.2 (CH), 147.9 (C), 160.4 (C=O), 162.0, (C=O). EI-MS: 244 (M^+, 4), 171 (100), 168 (100), 145 (25), 99 (23), 76 (25). Anal. Calcd for $C_{13}H_{12}N_2O_3$ (244.25): C, 63.93; H, 4.95; N, 11.47; found: C, 63.87; H, 4.95; N, 11.51.

Eethyl (*E*)*-2-(4-oxo quinazolin-3(4H)-yl)-3-phenyl acrylate* (**3c**):

Yellow oil, yield: 0.10 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 1721 and 1668 (C=O). ^{1}H-NMR: δ = 1.33 (3 H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 4.34 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2), 7.20-7.35 (5 H, m, 5 CH) 7.58 (1 H, *t*, $^3J_{HH}$ = 7.6, CH), 7.72 (1 H, s, CH), 7.78 (1 H, t, $^3J_{HH}$ = 7.3, CH), 7.85 (1 H, d, $^3J_{HH}$ = 8.1, CH), 8.0 (1 H, s, CH), 8.39 (1 H, t, $^3J_{HH}$ = 7.8, CH). ^{13}C-NMR: δ = 14.1 (CH3), 62.0, (CH_2), 106.8 (CH), 121.9 (2CH), 123.2 (CH), 137.3 (2CH), 140.5 (C), 140.6 (CH), 161.9 (C=O), 162.2, (C=O). EI-MS: 320 (M^+, 4), 247 (65), 175 (100), 145 (42), 77 (39), 51 (25). Anal. Calcd for Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.35): C, 71.24; H, 5.03; N, 8.74; found: C, 71.31; H, 5.09; N, 8.72.

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