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CATALYTIC SYNTHESIS OF 3-ALKOXYACRYLIC ACID ESTERS UNDER NEAT CONDITIONS

Junhua Wang,[1] Honglin Wang,[2] and Hongmin Ren[1]
[1]*Institute of Marine Material Science and Engineering, Shanghai Maritime University, Shanghai, China*
[2]*School of Chemistry, Yunnan University, Kunming, China*

Triethylamine or Ph$_3$P (0.05 eq.) was found to catalyze the addition of alcohols to alkyl propiolates. The reaction occurred much more rapidly without solvent than in solvent. The E/Z ratio was relative to the reaction temperature. Water was found to inhibit the reaction.

Keywords: 3-Alkoxyacrylic acid ester; catalytic; neat conditions

3-Alkoxyacrylic acid esters, in particular, methyl 3-methoxyacrylate[1] and ethyl 3-ethoxyacrylate,[2] are valuable building blocks for the synthesis of many important compounds, for example, 2-aminothiozole-5-carboxylates,[3] an intermediate of ceftibuten. Furthermore, many useful compounds contain the structural unit of 3-alkoxyacrylic acid ester.[4]

The general synthetic route to 3-alkoxyacrylic acid esters involves the addition of the relevant alcohols to alkyl propiolates in the presence of solvents and stoichiometric amines.[5] Herein, we report a catalytic synthesis of 3-alkoxyacrylic acid esters under neat conditions (Scheme 1).

We studied the reaction between ethanol and ethyl propiolate as a model (Table 1). The addition of alkyl propiolate to a mixture of the catalyst and alcohol was essential: alternative orders of addition afforded poor conversion (<20%). Triethylamine (0.05 eq.) catalyzed the reaction to completion, but 0.01 eq. of triethylamine almost did not work (Table 1, entry 3).

Generally a mixture of (E)- and (Z)-isomers was obtained. The E/Z ratio was relative to the reaction temperature. The greater the reaction temperature, the more (E)-isomer was afforded (entries 4 and 5). The reaction was exothermic. Water was found to inhibit the reaction, and 95% EtOH did not add to alkyl propiolate under such conditions (entry 6).

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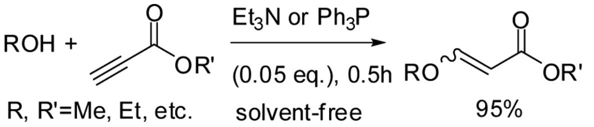
Address correspondence to Junhua Wang, Mailbox A25, Shanghai Maritime University, 1550 Haigang Avenue, Lingang New Town, Shanghai 201306, China. E-mail: chemwoods@yahoo.com.cn

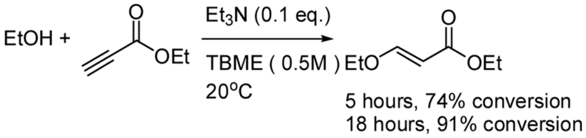


Scheme 1. The catalyzed addition of alcohols to alkyl propiolates under neat conditions.

Table 1. Screening of reaction conditions of the solvent-free addition of ethanol to ethyl propiolate

Entry	Ratio of EtOH/propiolate	Et_3N (eq.)	Temperature (°C)	Reaction time (h)	Yield (%)	Ratio of E/Z[a]
1	2	0.1	0–24	3	94	6.3
2	2	0.05	0–8	0.5	95	2.3
3	2	0.01	8–10	1	<10	—
4	1.2	0.05	24–40	0.5	94	>20
5	1.2	0.05	30–64	0.5	93	>20
6	1.2 (95% EtOH)	0.05	0–8	1	<10	—

[a] Determined by ^1H NMR.



Scheme 2. As a comparison, the reaction was run in TBME (0.5 M).

Under neat conditions, the reaction occurred rapidly and usually completed within 30 min. As a comparison, the reaction in tert-butyl methyl ether (TBME) (0.5 M) took much longer than in neat conditions (Scheme 2).

Phosphines also catalyze the addition of alcohols to alkyl propiolates.[6] To our knowledge, these reported procedures use additional solvents except for one case involving fluorous phosphines.[7] We found that Ph_3P can also catalyze this reaction in neat conditions, affording similar results.

In conclusion, 0.05 eq. of triethylamine or Ph_3P catalyzed the addition of alcohols to alkyl propiolates. Under neat conditions, the reaction occurred much more rapidly than in solvent. Our procedure minimizes the waste and labor and shortened the reaction time dramatically. These advantages could be significant in the case of large-scale synthesis.

EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used as received. NMR spectra were recorded on a Varian 300 instrument. The ^1H chemical shifts were obtained in $CDCl_3$ with tetramethylsilane (TMS) as standard.

Typical Procedure

Ethyl propiolate (4.90 g, 50.00 mmol) was added dropwise to a stirred solution of triethylamine (0.25 g, 2.50 mmol, 0.05 eq.) in absolute ethanol (2.76 g, 60.00 mmol, 1.2 eq.) in a water bath. The temperature of the reaction mixture rose to 40°C gradually. After the addition completed, the resulting mixture was stirred for 30 min. Triethylamine and slightly excessive ethanol were removed on a rotarator. The residual was (E)-ethyl 3-ethoxyacrylate, which was pure enough for many purposes. Further purification by distillation afforded a colorless liquid. Yield: 94%.

(E)-Ethyl 3-ethoxyacrylate[8]

Colorless liquid, bp 36–38°C/3 mmHg. ^{1}H NMR: δ 7.60 (d, $J = 12.3$ Hz, 1H), 5.19 (d, $J = 12.6$ Hz, 1H), 4.17 (q, $J = 6.9$ Hz, 2H), 3.91 (q, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 6.9$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H).

(E)-Methyl 3-methoxyacrylate[9]

Colorless liquid, bp 161–162°C. ^{1}H NMR: δ 7.64 (d, $J = 12.6$ Hz, 1H), 5.20 (d, $J = 12.6$ Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H).

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