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ORIGINAL PAPER

A facile approach to substituted acrylates by regioselective and stereoselective addition of thiols and amines to an alkynyl ester in water

Nitin A. Randive · Varun Kumar · Vipin A. Nair

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Abstract Water-promoted hydrothiolation and hydroamination of ethyl propiolate leading to highly regioselective and stereoselective formation of thioacrylates and β-enamino esters in excellent yields, by a simple, efficient, and environmentally friendly reaction procedure without employing any hazardous reagent or solvent is reported.

Keywords Water · Hydrothiolation · Hydroamination · Thioacrylate · β-Enamino ester

Introduction

Vinyl sulfides are an important class of intermediates that serve as auxiliaries in many synthetic sequences [1–5]. Among functionalized vinyl sulfides, those containing a Michael acceptor, for example thioacrylate esters, are of greatest interest, because they combine the chemical reactivity of the vinyl sulfides and vinyl esters [6, 7]. Thioacrylate esters can be synthesized by addition of thiols to propiolates by use of a Lewis acid [8–10] or by vinylic free radical substitution [11] but the disadvantages associated with these methods are poor yields, high cost, and long reaction time.

β-Enamino esters are important precursors for the synthesis of a variety of heterocycles [12] and natural products, for example alkaloids [13, 14]; some of these derivatives have anticonvulsant [15], anti-inflammatory [16], and antibacterial properties [17]. β-Enamino esters can be synthesized by direct condensation of β-ketoesters with amines [18–22], amine salts [23], alkyl azides [24], or ammonium salts [25]. Treatment of cyclic diazoamides and diazoamines in the presence of rhodium(II) acetate as catalyst will furnish cyclic enamides and enamines [26]. Reformatsky reaction has also been reported for the synthesis of various β-enamino esters with disubstituted formamides [27]. But most of the processes suffer from limitations such as long reaction time, unsatisfactory yields, drastic reaction conditions, tedious workup procedures, low selectivity, or use of toxic solvents. This prompted us to explore alternative methods which not only overcome these disadvantages but also enable direct addition of thiols and amines to alkynyl esters to give thioacrylate esters and β-enamino esters, respectively, in good yields, without using hazardous solvents, reagents, or catalyst, thereby providing an economic and environmentally friendly procedure.

With an ever interesting quest for greener synthetic approaches, reactions in water have attracted significant attention because of its advantages over other solvents [28, 29]; some recent additions to this venture include water-promoted addition of thiols to alkynes [30, 31], maleimides, and α,β-unsaturated carbonyl compounds [32].

Results and discussion

In this paper we discuss an efficient method for thiolation and amination of ethyl propiolate in water that afforded the desired products in excellent yields and short reaction time with high regioselectivity and stereoselectivity (Scheme 1). As a model reaction, equimolar amounts of ethyl propiolate and thiophenol were reacted in different solvents at room temperature (20 °C) and the progress of the reaction was monitored in each case. Upon completion of the reaction, the product was isolated and characterized as ethyl

N. A. Randive · V. Kumar · V. A. Nair (✉)
Department of Medicinal Chemistry,
National Institute of Pharmaceutical Education and Research,
Sector 67, Mohali, Punjab 160062, India
e-mail: vnair@niper.ac.in; vn74nr@yahoo.com

Scheme 1

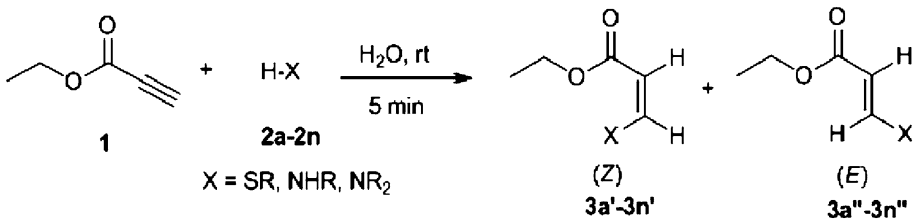

Table 1 Effect of solvents

Entry	Solvent	Time (min)	Yield (%)	(*Z*):(*E*) ratio[a]
1	H_2O	5	98	97:3
2	CH_3CN	15	90	87:13
3	CH_3OH	25	85	85:15
4	DMF	20	80	53:47
5	DCM	20	44	74:26
6	THF	30	30	68:32
7	EtOAc	25	12	83:17
8	Acetone	20	74	80:20
9	Toluene	40	18	75:25
10	*n*-Hexane	40	19	67:33

[a] (*Z*):(*E*) ratio is based on ^{1}H NMR

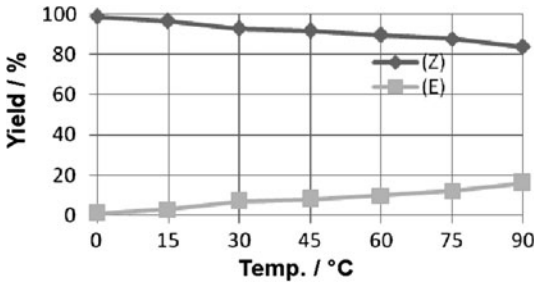

Fig. 1 Effect of temperature

Table 2 Isomerization under reflux conditions

Entry	Thiol	12 h (*Z*):(*E*) ratio[a]	24 h (*Z*):(*E*) ratio[a]
1	**2a**	26:74	21:79
2	**2b**	25:75	27:73
3	**2c**	44:56	42:58
4	**2d**	30:70	25:75
5	**2e**	96:4	92:8
6	**2f**	90:10	90:10
7	**2g**	85:15	84:16

[a] (*Z*):(*E*) ratio is based on ^{1}H NMR

3-(phenylthio)acrylate, formed by the *β*-addition of thiophenol to the alkynyl ester. From the results obtained (Table 1) it could be inferred that increasing the polarity of the solvents led to high yields of the product, with water being the ideal solvent for the reaction, affording 98% yield of the product in 5 min with diastereoselectivity of 97% in favor of the (*Z*) isomer. With non-polar solvents the yields were relatively poor.

From the remarkable success of the reaction in aqueous medium, water was chosen as the solvent for further studies. The effect of temperature on diastereoselectivity was then examined by carrying out the reaction at different temperatures. We observed a decrease in selectivity with increasing temperature, as indicated in Fig. 1; maximum selectivity was observed at 0 °C.

To determine the possibility of isomerization at room temperature, the reaction mixture was stirred continuously for 4 h, but no change in the ratio of isomers was observed. Nevertheless as the reaction temperature was increased, the ratio of (*Z*):(*E*) changed as expected, possibly as a result of thermally induced isomerization. To ascertain the extent of isomerization a mixture of (*Z*) and (*E*) isomers of ethyl 3-(phenylthio)acrylate in the ratio of 99:1, formed by reaction of ethyl propiolate with thiophenol at 0 °C in 5 min, was refluxed continuously for 48 h. The ratio of the isomers at different time intervals was determined in samples withdrawn at regular intervals from the reaction mixture. We observed that the product was substantially isomerized to the thermodynamically more stable (*E*) isomer in 24 h (Table 2).

To investigate the scope of the reaction, ethyl propiolate was treated with various thiols **2a**–**2g** in water at room temperature. All reactions afforded the *β*-addition products in excellent yields (entries 1–7, Table 3) with (*Z*) isomer as the major product; its exclusive formation was observed for pyrimidine-2-thiol.

To understand the effect of steric and nucleophilic factors on selectivity, the reaction was further explored for addition of amines **2h**–**2n** to ethyl propiolate (entries 8–14, Table 3). In these reactions *trans* *β*-addition afforded the (*E*) isomer, but a mixture of (*E*) and (*Z*) isomers was obtained from the sterically less demanding primary amines with the (*Z*) isomer as the major diastereomer.

To conclude, we report an efficient method for formation of thioacrylates and aminoacrylates by water-mediated addition of thiols and amines to ethyl propiolate. The environmentally benign experimental conditions affording

Table 3 Reactions of thiols and amines with ethyl propiolate

Entry	Reactant	Products[a]	Total yield (%)	(*Z*):(*E*) ratio[b]	Ref.
1	Benzenethiol (**2a**)	**3a′ + 3a″**	98	97:3	[33]
2	4-Chlorobenzenethiol (**2b**)	**3b′ + 3b″**	95	92:8	[34]
3	4-Bromobenzenethiol (**2c**)	**3c′ + 3c″**	94	86:14	[34]
4	4-Fluorobenzenethiol (**2d**)	**3d′ + 3d″**	96	80:20	–
5	Pyrimidine-2-thiol (**2e**)	**3e′**	95	100:0	–
6	2-Mercaptoethanol (**2f**)	**3f′ + 3f″**	95	90:10	–
7	2-Aminobenzenethiol (**2g**)	**3g′ + 3g″**	94	88:12	[35]
8	Dimethylamine (**2h**)	**3h″**	88	0:100	[27]
9	Diisopropylamine (**2i**)	**3i″**	86	0:100	[36]
10	Pyrrolidine (**2j**)	**3j″**	91	0:100	[26]
11	Piperidine (**2k**)	**3k″**	96	0:100	[26, 27]
12	Morpholine (**2l**)	**3l″**	94	0:100	[26, 27]
13	Phenylmethanamine (**2m**)	**3m′ + 3m″**	87	69:31	–
14	1-Phenylethanamine (**2n**)	**3n′ + 3n″**	86	80:20	–

[a] Reaction time 5 min

[b] (*Z*):(*E*) ratio is based on ^{1}H NMR

products in good yields and high stereoselectivity within short reaction time make this method economical, efficient, and further adds to on-going efforts to use eco-friendly greener approaches for organic reactions.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Avance 400 (400 MHz) spectrometer, in $CDCl_3$, using TMS as internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Mass spectra were recorded on a Finnigan Mat LCQ LCMS. The reactions were monitored by TLC (Merck). Evaporation of solvents was performed under reduced pressure using a Büchi rotary evaporator. Commercial grade reagents and solvents were used without further purification.

General procedure for the synthesis of ethyl 3-(arylthio)acrylates

To 0.1 g ethyl propiolate (1 mmol) in an RB flask was added 5 cm^3 demineralized water followed by thiol (1 mmol). The reaction mixture was stirred for 5 min at room temperature. Workup of the reaction was carried out by extracting the product with ethyl acetate, drying over sodium sulfate, and evaporating under reduced pressure to afford the crude product. The crude product was purified using column chromatography on 60–120 mesh silica gel using EtOAc–*n*-hexane as eluent (1:99). The spectroscopic data for the known products (**3a′–3c″**, **3a″–3c″**, **3g′**, **3g″**) were in agreement with the reported data.

Ethyl (E + Z)-3-(4-fluorophenylthio)acrylate (**3d′ + 3d″**, $C_{11}H_{11}FO_2S$)

Yield 0.21 g (96%); slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.27 (t, J = 7.1 Hz, 3H), 1.31–1.34 (t, J = 7.1 Hz, 3H), 4.13–4.18 (q, J = 7.1 Hz, 2H), 4.22–4.28 (q, J = 7.1 Hz, 2H), 5.53–5.57 (d, J = 15.0 Hz, 1H, *E* vinylic H), 5.88–5.91 (d, J = 10.0 Hz, 1H, *Z* vinylic H), 7.04–7.14 (4H, aromatic), 7.15–7.17 (d, J = 10.0 Hz, 1H, *Z* vinylic H), 7.42–7.50 (4H, aromatic), 7.69–7.73 (d, J = 15.0 Hz, 1H, *E* vinylic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.23, 14.30, 60.30, 60.34, 113.40, 115.51, 116.36, 116.85, 131.47, 133.49, 133.57, 135.65, 146.77, 149.96, 161.59, 164.07, 165.07, 166.44 ppm; MS (APCI): m/z = 226.87 (M + 1).

Ethyl (Z)-3-(pyrimidine-2-ylthio)acrylate (**3e′**, $C_9H_{10}N_2O_2S$)

Yield 0.20 g (95%); off-white solid; m.p.: 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32−1.36 (t, J = 7.1 Hz, 3H), 4.25–4.30 (q, J = 7.1 Hz, 2H), 6.10–6.12 (d, J = 10.3 Hz, 1H, vinylic H), 7.10–7.12 (t, J = 4.8 Hz, 1H, aromatic), 8.51–8.54 (d, J = 10.4 Hz, 1H, vinylic H), 8.62–8.63 (d, J = 4.8 Hz, 2H, aromatic) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.33, 60.60, 114.98, 118.08, 141.52, 157.59, 166.53, 168.92 ppm; MS (APCI): m/z = 211.00 (M + 1).

Ethyl (E + Z)-3-(2-hydroxyethylthio)acrylate (**3f′ + 3f″**, $C_7H_{12}O_3S$)

Yield 0.17 g (95%); slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.29 (t, J = 7.1 Hz, 6H), 2.55–2.58 (bs, OH), 2.91–2.94 (t, J = 6.0 Hz, 4H),

3.81–3.85 (t, $J = 6.0$ Hz, 4H), 4.15–4.21 (q, $J = 7.1$ Hz, 4H), 5.78–5.82 (d, $J = 15.1$ Hz, 1H, *E* vinylic H), 5.84–5.87 (d, $J = 10.1$ Hz, 1H, *Z* vinylic H), 7.09–7.11 (d, $J = 10.1$ Hz, 1H, *Z* vinylic H), 7.63–7.66 (d, $J = 15.2$ Hz, 1H, *E* vinylic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.28$, 34.78, 38.58, 60.26, 60.40, 60.55, 61.96, 113.71, 114.42, 146.52, 150.05, 165.47, 166.82 ppm; MS (APCI): $m/z = 177.07$ (M + 1).

General procedure for the synthesis of ethyl 3-(substituted amino)acrylates

To 0.1 g ethyl propiolate (1 mmol) in an RB flask was added 5 cm^3 demineralized water followed by amine (1 mmol). The reaction mixture was stirred for 5 min at room temperature. Workup of the reaction was carried out by extracting the product with ethyl acetate, drying over sodium sulfate, and evaporating under reduced pressure to afford the crude product. The crude product was purified by column chromatography on 60–120 mesh silica gel using a mixture of EtOAc–*n*-hexane (12:88) as eluent. The spectroscopic data for the known products (**3h″**–**3l″**) were in agreement with the reported data.

Ethyl (E + Z)-3-(benzylamino)acrylate
(**3m′** + **3m″**, $C_{12}H_{15}NO_2$)
Yield 0.18 g (87%); slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.28 (t, $J = 7.1$ Hz, 3H), 1.25–1.29 (t, $J = 7.1$ Hz, 3H), 4.09–4.15 (q, $J = 7.1$ Hz, 2H), 4.10–4.16 (q, $J = 7.1$ Hz, 2H), 4.19–4.20 (d, $J = 5.4$ Hz, 2H), 4.33–4.34 (d, $J = 6.0$ Hz, 2H), 4.54–4.56 (d, $J = 8.0$ Hz, 1H, *Z* vinylic H), 4.78–4.81 (d, $J = 13.2$ Hz, 1H, *E* vinylic H), 5.05 (bs, NH, *E* isomer), 6.66–6.71 (m, 1H, *Z* vinylic H), 7.25–7.37 (10H, aromatic), 7.56–7.61 (m, 1H, *E* vinylic H), 8.14 (bs, NH, *Z* isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.55$, 14.57, 52.14, 58.72, 59.02, 82.94, 86.85, 127.35, 127.57, 127.81, 127.91, 128.49, 128.65, 137.10, 138.58, 152.07, 169.55, 170.80 ppm; MS (APCI): $m/z = 206.27$ (M + 1).

Ethyl (E + Z)-3-(1-phenylethylamino)acrylate
(**3n′** + **3n″**, $C_{13}H_{17}NO_2$)
Yield 0.19 g (86%); slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$–1.22 (t, $J = 7.1$ Hz, 3H), 1.24–1.28 (t, $J = 7.1$ Hz, 3H), 1.46–1.48 (d, $J = 6.8$ Hz, 3H), 1.51–1.53 (d, $J = 6.8$ Hz, 3H), 4.04–4.09 (q, $J = 7.1$ Hz, 2H), 4.09–4.14 (q, $J = 7.1$ Hz, 2H), 4.35–4.43 (m, 2H), 4.48–4.50 (d, $J = 8.1$ Hz, 1H, *Z* vinylic H), 4.61–4.65 (d, $J = 13.3$ Hz, 1H, *E* vinylic H), 4.84 (bs, NH, *E* isomer), 6.57–6.62 (m, 1H, *Z* vinylic H), 7.23–7.35 (10H, aromatic), 7.46–7.51 (m, 1H, *E* vinylic H), 8.16 (bs, NH, *Z* isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.48$, 14.57, 23. 28, 23.32, 57.04, 58.01, 58.70, 58.99, 82.94, 87.68, 125.69, 125.80, 128.49, 128.77, 128.80, 129.06, 142.81, 143.91, 147.84, 150.72, 169.46, 170.78 ppm; MS (APCI): $m/z = 220.20$ (M + 1).

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