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CHEMISTRY

Synthesis of *N*-(2-Hydroxyethyl) Derivatives of β-Alanine

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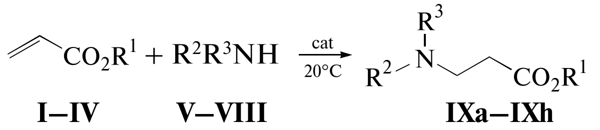
It was previously shown that ethanolamines react with acrylic acid and its esters via the Michael reaction on heating to form *N*-(2-hydroxyethyl)-substituted derivatives of β-alanine. These derivatives are antagonists of γ-aminobutyric and glycine receptors and are of interest as complex-forming agents for metals [1–6]. The nucleophilic addition of amines to the activated C=C bond is known to be catalyzed by Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$) and rare earth triflates [7–9]. The aim of this study is to establish the direction and product composition of the catalytic reaction of acids and esters of conjugated unsaturated acids with ethanolamines in the presence of heterogeneous catalysts.

We have found that bentonite and activated Al_2O_3 are efficient and regioselective catalysts of the Michael reaction, which make it possible to obtain β-amino acid derivatives under mild conditions and in high yields. The reaction results in formation of esters of *N*-(2-hydroxyethyl)-β-alanines (**IXa–IXh**, **XII**, Schemes 1 and 2) in 80–98% yields over 1 h at 20°C without solvent (Table 1).



I: $R^1 = H$; **II**: $R^1 = Me$; **III**: $R^1 = CH_2CH = CH_2$; **IV**: $R^1 = CH_2Ph$;
V: $R^2 = H$, $R^3 = CH_2CH_2OH$; **VI**: $R^2 = CH_2CH_2OH$, $R^3 = CH_2CH_2OH$;
VII: $R^2 = H$, $R^3 = CH(CH_2OH)_2$; **VIII**: $R^2 = H$, $R^3 = C(CH_2OH)_3$.

Scheme 1

The nucleophilic addition of monoethanolamine (**V**) and diethanolamine (**VI**) to the C=C bond of acrylic acid (**I**) proceeds under these conditions much more difficult than the addition of compounds **VII** and **VIII** and the yield of reaction products is not higher than 60%.

It should be noted that the use of bentonite and activated Al_2O_3 enables selective synthesis of monoadducts of monoethanolamines with methyl acrylate (Scheme 2). It was shown by the example of the reaction of monoethanolamine (**V**) and methyl acrylate (**II**) that methyl ester of *N*-(2-hydroxyethyl)-N-(3-methoxy-3-oxopropyl)-β-alanine (**X**) formed in 25% yield along with methyl ester of *N*-(2-hydroxyethyl)-β-alanine (**IXc**) (70%) only at 75°C for 3 h [10].

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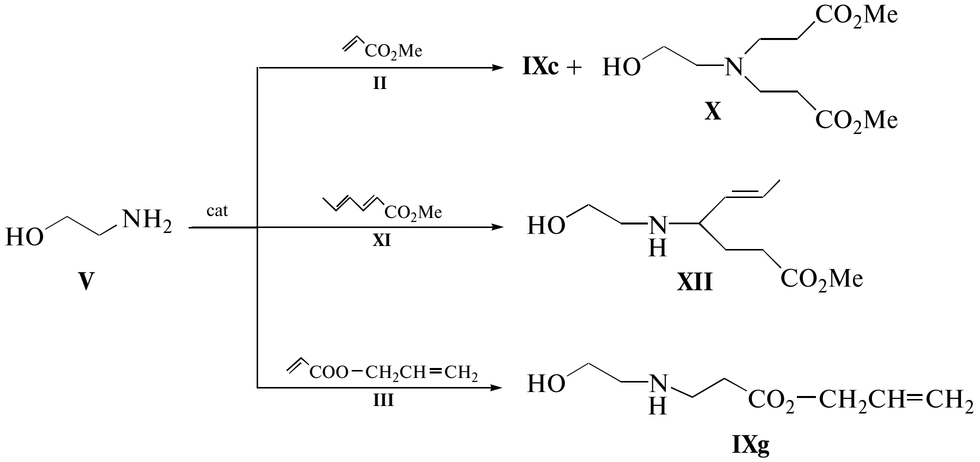

Scheme 2.

The bentonite-catalyzed reaction of monoethanolamine (**V**) with allyl acrylate (**III**) and methyl sorbinate (**XI**) proceeds regioselectively at the C=C bond in the α, β-position to the carboxy group to form allyl ester of *N*-(2-hydroxyethyl)-β-alanine (**IXg**) and methyl ester of 3-(2-hydroxyethylamino)hex-4-enoic acid (**XII**) in 92 and 78% yields, respectively. It should be noted that transesterification and polymerization products and amides of acrylic acid and β-alanine derivatives were not detected in the reaction mixture [11].

Thus, we have established for the first time that the reaction of acrylic acid or esters of conjugated unsaturated acids with ethanolamines in the presence of bentonite and activated Al_2O_3 proceeds selectively at the C=C bond to form monoadducts with retention of the ester group.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300.13 and 75.47 MHz, respectively, with Me_4Si as an internal reference. IR spectra were recorded on an UR-20 spectrometer in a thin film. Mass spectra were obtained with a Thermo Finnigan MAT 95 XP high-resolution mass spectrometer at the ionizing voltage 70 eV (ionizing chamber temperature of 250°C, direct injection temperature of 50–270°C, heating rate of 10 K/min). Bentonite was purchased from Idzhevanskii bentonit kombinat OAO (Armenia).

General Procedure for the Catalytic Reaction of α,β-Unsaturated Acids and Their Esters with Ethanolamines

Ethanolamine (**V–VIII**) (8.7 mmol) was added to a mixture of 5.8 mmol of α,β-unsaturated acid **I** or ester **II–IV** or **XI**, and 0.29 g of the catalyst, and the mix was stirred at ambient temperature for 1 h. The catalyst was separated by filtration, washed with 20 mL of methylene chloride or methanol, the solvent was removed under reduced pressure. The structure of compounds **IXa–IXh** and **XII** was established by the comparison of their physicochemical characteristics

Effect of the catalyst nature and reagent structures on the yield of *N*-(2-hydroxyethyl) derivatives of β-alanine **IXa–IXh**

IX	R^1	R^2	R^3	Yield of **IX**, %	
				bentonite	Al_2O_3
a	H	H	CH_2CH_2OH	60	54
b	H	CH_2CH_2OH	CH_2CH_2OH	52	49
c	Me	H	CH_2CH_2OH	97	90
d	Me	CH_2CH_2OH	CH_2CH_2OH	91	95
e	Me	H	$CH(CH_2OH)_2$	88	89
f	Me	H	$C(CH_2OH)_3$	81	80
g	$CH_2CH=CH_2$	H	CH_2CH_2OH	92	93
h	CH_2Ph	H	CH_2CH_2OH	98	81

Note: Experiments were carried out at 20°C for 1 h at the molar ratio ester of α,β-unsaturated acid : ethanolamine = 2 : 3.

(^{1}H and ^{13}C NMR and IR spectra) with literature data [1, 3–9].

Allyl ester of N-(2-hydroxyethyl)-β-alanine (IXg). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.59–2.94 (m, 6H, $3CH_2$), 3.56 (s, 1H, OH), 3.69 (t, 2H, CH_2O), 4.57 (d, 2H, CO_2CH_2), 5.01 (s, 1H, NH), 5.23 (d, 1H, CH_2=), 5.33 (d, 1H, CH_2=), 5.81–5.98 (m, 1H, HC=). MS (*m/z*): 173.21 [MH^+].

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