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## SHORT COMMUNICATIONS

# Catalyzed Synthesis of β-Amino Acids Esters

**T. V. Dokichev[a], D. R. Latypova[b], R. R. Shakirov[a], R. Z. Biglova[a], and R. F. Talipov[a]**

[a]*Bashkir State University, Ufa, 450074 Russia*
*e-mail: dokichev@anrb.ru*
[b]*Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, Russia*

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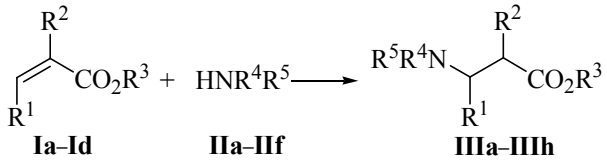
β-Aminoalcohols, β-amino acids, and their esters exhibit a wide range of biological action antitumor, immunostimulating, antiphlogistic). They are used as peptidomimetics and are precursors of many synthetic and natural compounds, in particular, of β-lactams [1–4]. For instance, bestatin, [(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine, is a specific inhibitor of the chemotoxic activity of the aminopeptidase possessing a low toxicity; it is used in medical practice as immunomodulator and antitumor drug [1].

The intense studies on the development of new methods for preparation the mentioned compounds are going on, and the substances as a rule are obtained by the nucleophilic Michael addition of primary or secondary amines to the activated C=C bond [5, 6]. The reaction is commonly performed in polar solvents (alcohols or carboxylic acids), the process is carried out in the presence of catalysts, Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$) that accelerate Michael reaction [2, 5–10]. Recently as catalysts triflates of lanthanides were suggested [6]. However even at the use of new more efficient catalysts the reaction often proceeds nonselectively and requires several hours at 50–100°C and the presence of organic solvents. Therefore the development of catalytic methods free of the mentioned drawbacks is an urgent task.

We report here on the new convenient catalytic procedure for one-stage preparation of β-amino acids esters by the reaction of esters of conjugated unsaturated acid with a series of primary and secondary amines in the presence of Kuganak montmorillonite $Al_2O_3 \cdot 4SiO_2 \cdot 2H_2O$ that contains relatively high amount of $TiO_2$. As esters of α,β-unsaturated acids we used methyl acrylate (**Ia**), allyl acrylate (**Ib**), methyl methacrylate (**Ic**), and dimethyl maleate (**Id**), and as amines, isopropylamine (**IIa**), butylamine (**IIb**), benzylamine (**IIc**), monoethanolamine (**IId**), diethylamine (**IIe**), and morpholine (**IIf**). The experiments were carried out at 20°C over 0.5 and 1.5 h at molar ratio of the α,β-un-saturated acid–amine 2 : 3.




**Ia–Id** **IIa–IIf** **IIIa–IIIh**

**I**, $R^1 = R_2 = H$, $R^3 = Me$ (**a**); $R^1 = R^2 = H$, $R^3 = All$ (**b**); $R^1 = H$, $R^2 = R^3 = Me$ (**c**); $R^1 = CO_2Me$, $R^2 = H$, $R^3 = Me$ (**d**); **II**, $R^4 = H$, $R^5 = i$-Pr (**a**); $R^4 = H$, $R^5 = Bu$ (**b**); $R^4 = H$, $R^5 = Bn$ (**c**); $R^4 = H$, $R^5 = CH_2CH_2OH$ (**d**); $R^4 = R^5 = Et$ (**e**); $R^4 + R^5 = CH_2CH_2OCH_2CH_2$ (**f**).

| **III** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (**III**), % | |
|---|---|---|---|---|---|---|---|
| | | | | | | 0.5 h | 1.5 h |
| **a** | H | H | Me | H | *i*-Pr | 78 | 98 |
| **b** | H | H | Me | H | Bn | 67 | 95 |
| **c** | H | H | Me | H | $CH_2CH_2OH$ | 75 | 99 |
| **d** | H | H | Me | Et | Et | 90 | 99 |
| **e** | H | H | Me | $-CH_2CH_2OCH_2CH_2-$ | | 52 | 97 |
| **f** | H | H | All | Et | Et | 59 | 95 |
| **g** | H | Me | Me | H | Bu | 38 | 96 |
| **h** | $CO_2Me$ | H | Me | Et | Et | 71 | 99 |

The reaction led to the formation of β-amino acids esters **IIIa–IIIh** in virtually quantitative yield within 1.5 h. The nucleophilic addition of butylamine to the C=C bond of methyl methacrylate (**Ic**) under the conditions we chose provided 38% of the product, and the diethyl- and isopropylamine did not react at all. The application of the chosen catalyst made it possible to synthesize selectively exclusively monoadducts of primary amines with methyl acrylate [11]. The reaction of diethylamine with allyl acrylate occurred regioselectively at the double bond of the acrylic system affording *N,N*-diethyl-β-alanine allyl ester (**IIIf**), yield 97%. In contrast to the noncatalytic method of preparation of β-substituted amino acids we did not detect in the reaction mixture products of amines addition to the ester group [12]. The preferable application of Kuganak montmorillonite as a catalyst of the conjugate Michael addition compared to the Lewis acids consists in the disability of the montmorillonite to form stable complexes with amines that suppress the reactivity of the amines.

Hence we developed a convenient preparation method for β-amino acids.

**Reaction of esters of α,β-unsaturated acids with amines in the presence of Kuganak montmorillonite.** ***General procedure.*** To a mixture of 5.8 mmol of an ester of α,β-unsaturated acid **Ia–Id** and 0.29 g of the catalyst was added 8.7 mmol of amine **IIa**–**IIf**, and the mixture was stirred at room temperature for 0.5 or 1.5 h. The catalyst was filtered off, washed with 20 ml of dichloromethane, the solvent was removed at a reduced pressure. The structure of compounds **IIIb, IIId, IIIe** was established by comparison of their spectral characteristics ($^1$H, $^{13}$C, NMR, and IR spectra) with the published data [11, 13].

***N*-Isopropyl-β-alanine methyl ester (IIIa)**. IR spectrum, ν, cm$^{-1}$: 3412–3258 (NH), 1735 ($CO_2$), 1337. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.04 d (6H, 2Me, $^2J$ 6.2 Hz), 1.32 s (1H, NH), 2.50 t (2H, $CH_2$, $^2J$ 6.6 Hz), 2.77 septet (1H, NCH, $^2J$ 6.2 Hz), 2.86 t (2H, $CH_2$, $^2J$ 6.6 Hz), 3.67 s (3H, OMe). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 22.22 (2Me), 34.46 ($CH_2$), 42.23 ($CH_2$), 48.15 (NCH), 51.23 ($OCH_3$), 172.97 (C=O). Mass spectrum, *m/z*: 146 [$M$ + H]$^+$. Found, %: C 57.66; H 10.42; N 9.82. $C_7H_{15}NO_2$. Calculated, %: C 57.90; H 10.41; N9.65.

***N*-(2-Hydroxyethyl)-β-alanine methyl ester (IIIc)**. Colorless crystals, mp 40.5°C (40°C [14]).

***N,N*-Diethyl-β-alanine allyl ester (IIIf)**. $n_D^{20}$ 1.4665 (1.4662 [15]). IR spectrum, ν, cm$^{-1}$: 1738 ($CO_2$), 991, 929 ($CH=CH_2$). $^1$H NMR spectrum ($CDCl_3$) δ, ppm: 1.02 t (6H, 2Me, $^2J$ 7.2 Hz), 2.45–2.55 m (6H, 3$CH_2$), 2.80 t (2H, $CH_2$, $^2J$ 7.5 Hz), 4.57 d (2H, $OCH_2$, $^2J$ 5.7 Hz), 5.22 d (1H, $=CH_2$, $^3J$ 10.5 Hz), 5.31 d (1H, $=CH_2$, $^3J$ 17.2 Hz), 5.85–5.98 m (1H, =CH). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 11.72 (Me), 32.17 ($CH_2$), 46.69 ($CH_2$), 47.95 ($CH_2$), 64.37 ($OCH_2$), 117.9 ($=CH_2$), 132.12 (=CH), 172.26 (C=O). Mass spectrum, *m/z*: 186 [$M$ + H]$^+$.

***N*-Butyl-2-methyl-β-alanine methyl ester (IIIg)**. IR spectrum, ν, cm$^{-1}$: 3450–3241 (NH), 1740 ($CO_2$), 1325. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 t (3H, Me, $^2J$ 7.3 Hz), 1.11 d (3H, Me, $^2J$ 6.5 Hz), 1.27–1.53 m (4H, $CH_2CH_2$), 1.95 s (1H, NH), 2.43 m (1H, CH), 2.48 m (4H, $NCH_2$), 3.56 s (3H, OMe). Mass spectrum, *m/z*: 174 [$M$ + H]$^+$. Found, %: C 62.48; H 11.21; N 8.04. $C_9H_{19}NO_2$. Calculated, %: C 62.39; H 11.05; N 8.08.

***N,N*-Diethyl-D,L-aspartic acid dimethyl ester (IIIh)**. IR spectrum, ν, cm$^{-1}$: 1740, 1737 ($CO_2$), 1212, 1033. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.06 t (6H, 2Me, $^2J$ 6.2 Hz), 2.44 m (2H, $CH_2$), 2.86 q (4H, 2$NCH_2$, $^2J$ 6.4 Hz), 3.70 m (1H, NCH), 3.67 s (3H, OMe), 3.72 s (3H, OMe). Mass spectrum, *m/z*: 218 [$M$ + H]$^+$. Found, %: C 55.17; H 8.90; N 6.42. $C_{10}H_{19}NO_4$. Calculated, %: C 55.28; H 8.81; N 6.45.

$^1$H and $^{13}$C NMR spectra were registered on a spectrometer Bruker AM-300 (300.13 and 75.47 MHz respectively), internal reference $Me_4Si$. IR spectra were recorded on a spectrophotometer UR-20 from thin films. Mass spectra were measured on a liquid chromato mass spectrometer LCMS-2010EV Shimadzu in the chemical ionization mode at the atmospheric pressure.

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