SYNTHESIS OF BENZAMIDOMETHYL DERIVATIVES OF SOME AMINO ACIDS

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ABSTRACT

The benzamidomethyl derivatives, N,N-bis-(benzamidomethyl)glycine, N,N-bis-(benzamidomethyl)methionine, N-(benzamidomethyl)phenylalanine and N-(benzamidomethyl)leucine, were conveniently synthesised in good yields by a simple procedure in aqueous media using (benzamidomethyl)triethylammonum chloride as a reagent. The structure of all products was confirmed by the ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

Keywords: benzamidomethyl derivatives, amino acids, pro-drugs.

AIMS AND BACKGROUND

One of the well-known strategies for pro-drugs design is based on inherent hydrolysability of α-substituted derivatives of glycine[1]. These compounds are easily hydrolysable due to the participation of the glycine amino group lone pair in this process. An advantage of this approach is that the hydrolysis rate can be controlled by regulating the amino group basicity, e.g. conversion to amide function[2]. The same mechanism can be anticipated in the case of the benzamidomethyl derivatives. The amide nitrogen lone pair in the benzamidomethyl derivatives, similarly to the α-substituted derivatives of glycine, should also facilitate drug-releasing dissociations. Thus, the benzamidomethyl derivatives can be used as pro-drugs of biologically active amines, amino acids, alcohols, etc. In fact, these types of compounds have already been used as pro-drugs[3,4]. In this respect, it is noteworthy that the kinetics of dissociation in water of benzamidomethyl derivatives similar to the investigated here has recently been published[5].

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Synthesis of benzamidomethyl derivatives of amino acids utilising the Manich reaction has also been described[6,7]. In addition, Zlotin et al.[8–10] had performed similar reactions to obtain benzamidomethyl derivatives of amino acid esters, amino acid nitriles and some dipeptides. However, in the present paper an alternative one-step method is reported for the synthesis of benzamidomethyl derivatives of some amino acids using (benzamidomethyl)triethylammonium chloride (**1**). This reagent has been successfully used in the preparation of benzamidomethyl derivatives of amines, alcohols, thiols, carboxylic acids and inorganic nucleophiles[11–13]. The advantages of this reagent are high yields and easy isolation of the pure products.

EXPERIMENTAL

General experimental procedure. 2 mmol of **1** were added to a solution of 1 mmol amino acid **2** in 2 ml water. N-methylmorpholine was added for obtaining pH ≥ 9. The reaction mixture was stirred vigorously 1 h at room temperature. Next, few drops of diluted 1/1 hydrochloric acid were added. The colourless crystals were collected and washed with water on the Buchner funnel. The yields were about 70–77%.

The melting points were measured using a Kofler melting point apparatus. The IR spectra were taken on a Thermo Mattson IR300 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX250 instrument. The spectra are referred to the solvent signal. The chemical shifts are expressed in ppm and coupling constants in Hz. The precise assignments of the ^{1}H and ^{13}C NMR spectra were accomplished by measurement of 2D homonuclear correlation (COSY), DEPT-135 and 2D inverse detected heteronuclear (C–H) correlations (HMQC and HMBC).

The melting points and the spectral (IR, ^{1}H and ^{13}C NMR) data of some representative benzamidomethyl derivatives of amino acids are given below:

N,N-bis-(*benzamidomethyl*)*glycine* (***3a***):
Colourless crystals, m.p. 168–169 °C (Ref. 7 – 164–165°C)

IR (KBr; cm^{-1}): ν(N–H) 3295; ν(Ar–H) 3100–2100; ν(C(O)–O) 1679; Amide I 1640; Amide II 1544;

^{1}H NMR (250 MHz, DMSO-d6, 25 °C): δ = 3.458 (s, 2H, Gly-CH_2), 4.410 (d, J = 5.9, 4H, $NHCH_2$), 7.460 (t, J = 7.6, 4H, *m*-Ph), 7.540 (t, J = 7.4, 2H, *p*-Ph), 7.846 (d, J = 7.2, 4H, *o*-Ph), 8.821 (t, J = 5.9, 2H, CONH);

^{13}C NMR (69 MHz, DMSO-d6, 25°C): δ = 50.22 (Gly-CH_2), 57.24 ($NHCH_2$), 127.07 (*o*-Ph), 128.24 (*m*-Ph), 131.33(*p*-Ph), 166.90 (CONH), 172.25 (COOH).

N,N-bis-(*benzamidomethyl*)*methionine* (***3b***):
Colourless crystals, m.p. 139–141°C

IR (KBr; cm^{-1}): ν(O–H; N–H,) 3550–3300; ν(Ar–H) 3100–2100; ν(C(O)–O) 1670; Amide I 1635; Amide II 1545;

^{1}H NMR (250 MHz, DMSO-d6, 25 °C): δ = 1.896–1.755 (m, 1H, β-CH_2) and 1.829–1.899 (m, 1H, β-CH_2), 2.016 (s, 3H, CH_3), 2.465–2.510 (m, 1H, γ-CH_2) and

2.528–2.576 (m, 1H, γ-CH_2), 3.405 (dd, J = 4.9, 7.6, 1H, CH), 4.132 (dd, J = 5.8, 13.0, 2H, NHCH_2) and 4.241 (dd, J = 5.6, 13.0, 2H, NHCH_2), 7.436–4.474 (m, 4H, m-Ph), 7.504–7.538 (m, 2H, *p*-Ph), 7.821 (d, J = 7.1, 4H, *o*-Ph), 8.830 (t, J = 5.6, 2H, CON*H*);

^{13}C NMR (69 MHz, DMSO-d6, 25°C): δ = 14.44 (CH_3), 29.51 (β-CH_2), 31.96 (γ-CH_2), 53.12 ($NHCH_2$), 56.680 (α-CH), 127.08 (*o*-Ph), 128.16 (*m*-Ph), 131.14 (*p*-Ph), 167.75 (CONH), 175.24 (COOH).

N-(*benzamidomethyl*)*phenylalanine* (***3c***):
Colourless crystals, m.p. 171–174 °C (Ref. 7 – 157–159 °C)

IR (KBr; cm^{-1}): ν(N-H) 3403; ν(Ar-H) 3200–2900; ν(C(O)–O) 1663; Amide I 1621; Amide II 1517;

^{1}H NMR (250 MHz, DMSO-d6, 25 °C): δ = 2.824 (dd, J = 13.7, J = 7.0, 1H, Phe-β-CH_2) and 2.912 (dd, J = 13.7 Hz, J = 5.9, 1H, Phe-β-CH_2), 3.587 (dd, J = 7.0, J = 5.9, 1H, Phe-α-CH), 4.117 (dd, J = 13.0, J = 5.9, 1H, $NHCH_2$) and 4.183 (dd, J = 13.0, J = 5.5, 1H, $NHCH_2$), 7.166–7.254 (m, 5H, Phe-Ph), 7.460 (t, J = 7.5, 2H, *m*-Ar), 7.530 (t, J = 7.3, 1H, *p*-Ar), 7.784 (d, J = 7.5, 2H, *o*-Ar), 8.809 (t, J = 5.5, 1H, CON*H*);

^{13}C NMR (69 MHz, DMSO-d6, 25 °C): δ = 38.38 (Phe-β-CH_2), 53.05 ($NHCH_2$), 59.12 (Phe-α-CH), 126.11 (*p*-PhCH_2), 127.05 (*o*-PhCO), 127.94 (*m*-PhCH_2), 128.18 (*m*-PhCO), 129.15 (*o*-PhCH_2), 131.19 (*p*-PhCO), 134.10 (*i*-PhCO), 137.84 (*i*-PhCH_2), 166.69 (CONH), 174.89 (COOH).

N-(*benzamido*)*methylleucine* (***3d***):
Colourless crystals, m.p. 135–138°C (Ref. 7 – 164–166°C)

IR (KBr; cm^{-1}): ν(N–H) 3320; ν(Ar–H) 3150–2100; ν(C(O)–O) 1665; Amide I 1635; Amide II 1550–1540;

^{1}H NMR (250 MHz, DMSO-d6, 25 °C): δ = 0.867 (d, J = 6.6, 3H) and 0.886 (d, J = 6.6, 3H, CH_3), 1.546 (t, J = 7.0, 2H, β-CH_2), 1.764 (m, 1H, γ-$CH(CH_3)_2$), 3.610 (m, J = 6.9, 1H, α-CH), 4.380 (doublet AB, J = 5.6, J = 12.9, 2H, N–CH_2–N), 7.496 (t, J = 7.1, 2H, *m*-Ph), 7.570 (t, J = 7.1, 1H, *p*-Ph), 7.878 (d, J = 7.1, 2H, *o*-Ph), 9.209 (t, J = 5.6, 1H, CONH);

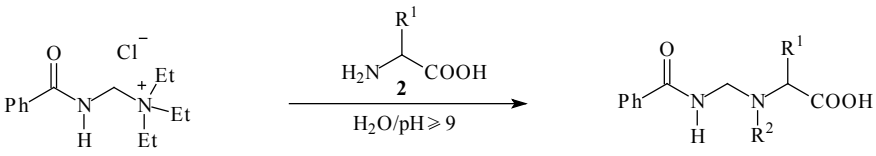
^{13}C NMR (69 MHz, DMSO-d6, 25°C): δ = 22.10 (CH_3), 24.10 (CH), 40.10 (CH_2), 52.24 ($NHCH_2$), 56.02 (CH), 127.34(*o*-Ph), 128.08 (*m*-Ph), 131.09 (*p*-Ph), 134.14 (*i*-Ph), 166.88 (CONH), 171.36 (COOH).

RESULTS AND DISCUSSION

The procedure used in this paper is shown in Scheme 1. Glycine (**2a**), methionine (**2b**), phenylalanine (**2c**) and leucine (**2d**) were conveniently benzamidomethylated in aqueous media using **1** as a reagent. The reactions were carried out at room temperature and pH ≥ 9. The benzamidomethyl derivatives: N,N-bis-(benzamidomethyl)glycine (**3a**), N,N-bis-(benzamidomethyl)methionine (**3b**), N-(benzamidomethyl)phenylalanine

(**3c**) and N-(benzamidomethyl)leucine (**3d**), were easily isolated in pure state as a colourless crystals from the reaction mixture by simple filtration and washing over the Buchner funnel. The yields exceed 70%. It should be mentioned that in these conditions the carboxylic group in the amino acids can not be benzamidomethylated by (**1**) in aqueous media as it has been previously found in Ref. 12.

Scheme 1



1 **3**

(**a**) $R^1 = H$; $R^2 = CH_2NHCOPh$
(**b**) $R^1 = CH_2CH_2SCH_3$; $R^2 = CH_2NHCOPh$
(**c**) $R^1 = CH_2Ph$; $R^2 = H$
(**d**) $R^1 = CH_2CH(CH_3)_2$; $R^2 = H$

In the case of benzamidomethylation of amino groups, it is typically very difficult to stop the reaction at the stage of mono-substituted products. Thus dibenzamidomethyl derivatives **3a** and **3b** were obtained. However, in the reactions of **1** with **2c** and **2d**, the corresponding mono-benzamidomethyl derivatives **3c** and **3d** were obtained. This is probably due to the steric hindrance of the benzyl and isobutyl residue in these amino acids.

Compound **3b** is newly synthesised and has not been described in literature. The structures of all products were confirmed by ^1H NMR, ^{13}C NMR and IR spectroscopy. Previous spectroscopic data for these compounds were not found in literature.

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Received 27 August 2008
Revised 17 September 2008