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Preparative Synthesis of β-Amino Alcohols from α-Amino Dicarboxylic Acid Derivatives

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Abstract—A low-expensive preparative procedure has been developed for the synthesis of protected β-amino alcohols from α-amino dicarboxylic acid derivatives.

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Reduction of N-protected α-amino acids to the corresponding β-amino alcohols is the key step in the synthesis of many analogs of biologically active peptides, in particular caspase [1] and cathepsin inhibitors [2], peptide analogs with ether bonds [3, 4], and neuroprotectors [5]. β-Amino alcohols are also used as starting compounds in the synthesis of such chemically important intermediate products as α,α′-diamino dicarboxylic acids [6], (3*S*)-amino-γ-butyrolactone [7], (*S*)-γ-fluoroleucine [8], and various β-amino acids through β-iodo amines [9].

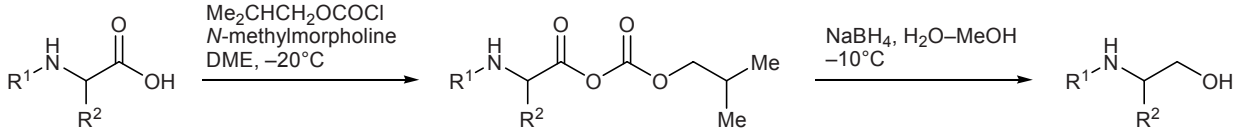
Amino dicarboxylic acids could give rise to trifunctional amino-, carboxy-, and hydroxy-containing chiral synthons with selectively removable protective groups, which can be used, e.g., for the preparation of monomers of negatively charged peptidonucleic acids [10, 11].

A standard procedure for selective reduction of α-carboxy group to hydroxymethyl involves treatment with a 1 M solution of BH_3 in THF. Protected β-amino alcohols are thus obtained in moderate yields (~50%), the reaction should be carried out at –78°C, and the reducing agent is toxic and expensive. Therefore, we tried to develop a less expensive and reproducible method of synthesis of β-amino alcohols **II** from amino dicarboxylic acid derivatives **Ia**–**Ic**.

Sodium (or lithium) tetrahydridoborate in water or aqueous alcohol is frequently used as a cheap and selective reducing agent capable of converting a carboxy group into hydroxymethyl. Hydrolysis of tetrahydridoborate ion gives a complex of borane with water, which is analogous to the complex formed by borane with tetrahydrofuran molecule [12]. However, the reduction of *N*-acyl amino acids with $NaBH_4$ is often accompanied by cleavage of the amide bond [13]. Therefore, the carboxy group should preliminarily be activated via conversion into ester or mixed anhydride moiety [5, 6, 14]. Thus one-step reduction with borane–THF becomes a two-step process: in the first step, activated derivative of N-protected amino acid is obtained, and in the second step it is reduced *in situ* with a solution of $NaBH_4$ (Scheme 1).

The transformation of protected amino acids into the corresponding amino alcohols through mixed carboxylic acid anhydrides is performed according to the procedures reported in [3, 15] with insignificant modifications [1, 4, 8, 16]. Using various combinations of tertiary amines as bases (triethylamine and *N*-methyl-

Scheme 1.



R^1 = Boc, R^2 = $(CH_2)_2CO_2Bzl$ (**a**), CH_2CO_2Bzl (**b**); R^1 = Cbz, R^2 = $(CH_2)_2CO_2Bu$-*t* (**c**).

morpholine), solvents (tetrahydrofuran and 1,1-dimethoxyethane), and isobutyl chloroformate as activating agent, we obtained salt of the amino acid with tertiary amine as a sticky material which hampered stirring of the reaction mixture and reduced the conversion of initial compound **I** even under relatively strong dilution. The best results were obtained with dimethoxyethane as solvent and *N*-methylmorpholine as base; therefore, all subsequent experiments were performed using the same substances.

As shown in [17], in the synthesis of mixed anhydrides excess isobutyl chloroformate with respect to amino acid should be maintained to avoid formation of the corresponding amino acid anhydride. We proposed to add equimolar solutions of amino acid and tertiary amine simultaneously at similar rates from two dropping funnels to a cold solution of isobutyl chloroformate in THF. In such a way we succeeded in attaining complete conversion of initial amino acids **Ia**–**Ic** into mixed anhydrides **IIIa**–**IIIc**.

While optimizing the conditions for the reduction of intermediate **IIIa** (without isolation), we found that the best results are obtained using 3 equiv of the reducing agent. The order of mixing of the reactants is also important. A solution of $NaBH_4$ should be added in portions to a cold solution of mixed anhydride **III**; otherwise, the reaction may be accompanied by deprotection of the amino group. Sodium tetrahydridoborate was dissolved in aqueous methanol (1:1) which ensured better results as compared to aqueous solution of $NaBH_4$. The structure of compounds **IIa**–**IIc** was confirmed by ^{1}H NMR spectroscopy. Their purity was evaluated by measuring their melting points which in all cases coincided with published data. The enantiomeric purity of amino alcohols **IIa** and **IIb** was determined from the optical rotation values which coincided with the data reported for analogous compounds prepared by reduction with borane in THF [7, 11].

We planned to use β-amino alcohols **IIa** and **IIc** in the Mitsunobu condensation with *o*-nitrobenzylsulfonyl (Ns) derivatives of various amino acids to obtain protected pseudopeptides BocGlu(γ-OBzl)-ψ(Ns)-GlyOAll and CbzGlu(γ-OBu-*t*)-ψ(Ns)-His(Ns)OMe. For this purpose, compounds **IIa** and **IIc** were dissolved in ethyl acetate, and the solutions were filtered through a layer of aluminum oxide to remove impurities. Otherwise, compounds **IIa** and **IIc** failed to react. The Mitsunobu reactions with purified amino alcohols **IIa** and **IIc** gave the target condensation products in 65 and 30% yield, respectively.

EXPERIMENTAL

All operations in the synthesis of mixed anhydrides **IIIa**–**IIIc** were performed under dry argon with protection from moisture. Dimethoxyethane was dehydrated by double distillation over KOH and distillation over $LiAlH_4$ just before use. Isobutyl chloroformate was purified by vacuum distillation. *N*-Methylmorpholine was dehydrated by distillation first over ninhydrin and then over BaO. The ^{1}H NMR spectra were recorded at 25°C on a Bruker MSL-200 spectrometer (Germany) with Fourier transform at a frequency of 200 MHz using tetramethylsilane as internal reference. The optical rotations were measured on a Perkin–Elmer 241 polarimeter at 19–22°C. The progress of reactions was monitored by TLC on Silica gel 60 F_{254} plates (Merck, Germany); the solvents were removed under reduced pressure (20 mm); the products were dried at a residual pressure of 0.5 mm.

Benzyl 4-(*tert*-butyloxycarbonylamino)-5-hydroxypentanoate (IIa). A solution of 0.68 g (0.62 ml, 4.2 mmol, 1.2 equiv) of isobutyl chloroformate in 7 ml of dimethoxyethane was cooled to –30°C, and solutions of 0.42 g (0.46 ml, 4.2 mmol, 1 equiv) of *N*-methylmorpholine in 7 ml of dimethoxyethane and of 1.4 g (4.2 mmol, 1 equiv) of 5-benzyloxy-2-(*tert*-butoxycarbonylamino)-5-oxopentanoic acid (**Ia**) in 7 ml of dimethoxyethane were added dropwise at equal rates simultaneously from two dropping funnels under stirring in an argon atmosphere. When the addition was complete, the mixture was stirred for 5 min at –30°C, allowed to warm up to –15°C, and filtered, and the precipitate was washed on a filter with 3 ml of dimethoxyethane. The filtrate was transferred into a 250-ml flask and cooled to –15°C, and a freshly distilled solution of 0.47 g (12.5 mmol, 3 equiv) of $NaBH_4$ in 10 ml of aqueous methanol (1:1) was added in several portions. The mixture was then stirred for 5 min, 12 ml of water and 25 ml of ethyl acetate were added, the organic phase was separated, the aqueous phase was additionally extracted with ethyl acetate (2×25 ml; gas evolution was observed), and the extracts were combined with the organic phase, washed in succession with a 1.5 M solution of citric acid (5 ml), a saturated solution of $NaHCO_3$ (2×15 ml), and a saturated solution of NaCl (20 ml), dried over Na_2SO_4, filtered, and evaporated. The precipitate was treated with 20 ml of hexane at 4°C. After 10 h, the colorless crystals were filtered off and dried under reduced pressure (0.5 mm). Yield 1.2 g (90%), R_f 0.35 (ethyl acetate–hexane,

1:1), mp 76–77°C, $[\alpha]_D^{20}$ = –6.2 (*c* = 1, MeOH); published data: mp 76–77°C [4], $[\alpha]_D^{20}$ = –6.0 [7]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 s (9H, *t*-Bu), 1.79 m (1H, β-CH), 1.90 m (1H, β-CH), 2.45 m (2H, γ-CH_2), 3.55 m (1H, α-CH), 3.62 d (2H, C**H**$_2$OH, *J* = 4.65 Hz), 4.71 s (1H, OH), 4.79 m (1H, N**H**), 5.11 s (2H, C**H**$_2$Ph), 7.35 s (5H, C_6H_5).

Benzyl 3-(*tert*-butyloxycarbonylamino)-4-hydroxybutanoate (IIb) was synthesized in a similar way from 1 g of 4-benzyloxy-2-(*tert*-butoxycarbonylamino)-4-oxobutanoic acid (**Ib**). Yield 0.68 g (71%), R_f = 0.75 (ethyl acetate), mp 61–62°C, $[\alpha]_D^{20}$ = –2.8 (*c* = 1, methanol); published data: mp 62–63.8°C [7], $[\alpha]_D^{20}$ = –2.7 [11]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 s (9H, *t*-Bu), 2.71 d (2H, β-CH_2, *J* = 6.0 Hz), 3.70 d (2H, C**H**$_2$OH, *J* = 4.8 Hz), 4.02 m (1H, α-CH), 4.72 s (1H, OH), 5.15 s (2H, C**H**$_2$Ph), 5.24 d (1H, N**H**), 7.37 s (5H, C_6H_5).

***tert*-Butyl 4-(benzyloxycarbonylamino)-5-hydroxypentanoate (IIc)** was synthesized from 1 g of 5-*tert*-butoxy-2-(benzyloxycarbonylamino)-5-oxopentanoic acid (**Ic**). Yield 0.8 g (83%), oily substance, R_f 0.3 (ethyl acetate–hexane, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.43 s (9H, *t*-Bu), 1.59 s (1H, OH), 1.83 m (2H, β-CH_2), 2.34 m (2H, γ-CH_2), 3.58 m (1H, α-CH), 3.68 m (2H, C**H**$_2$OH), 5.09 s (2H, C**H**$_2$Ph), 5.14 d (1H, NH), 7.35 s (5H, C_6H_5).

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