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Short Note

Benzyl {2-[(2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino]-2-oxoethyl} carbamate †

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Abstract: N-(Protected α-aminoacyl)benzotriazoles are powerful acylating agents, and they are used frequently for preparing peptides and their mimetics and conjugates. The present paper describes the synthesis and characterization of a new benzyl {2-[(2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino]-2-oxoethyl} carbamate.

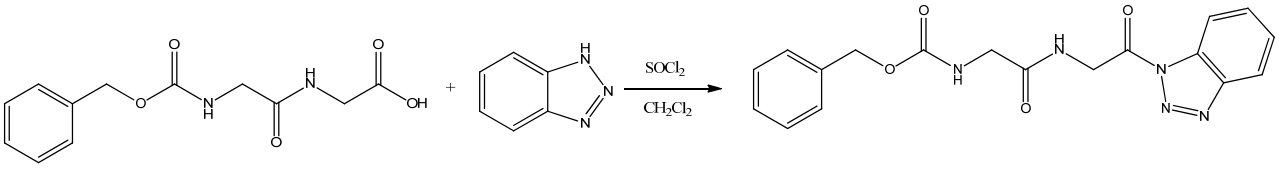
Keywords: peptide synthesis; amino acids; peptide-benzotriazole

N-(protected α-aminoacyl)benzotriazoles are powerful acylating agents, and they are used frequently for preparing peptides and their mimetics and conjugates [1]. Peptide-protein interactions are central to cell biology. It is also known that low molecular weight peptides can easily cross biological barriers and are less susceptible to protease attacks [2]. The synthesis of peptides and proteins is of great importance to the understanding of biological functions [3]. Although peptides and proteins mediate numerous biological processes, their use as therapeutic agents is often accompanied by several drawbacks, including poor bioavailability, low biostability and limited receptor subtype selectivity. Many of these drawbacks can be improved by the derivatization of the biomolecules [4]. Therefore, much effort has been expended on the design and synthesis of selective, high-affinity ligands by replacing portions of peptides with nonpeptide structures to obtain peptide derivatives. Due to the absence of a synthesis method of the title compound in the literature, we wish to report on the synthesis method and properties of benzyl {2-[(2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino]-2-oxoethyl} carbamate.

Results and Discussion

Benzyl {2-[(2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino]-2-oxoethyl}carbamate was synthesized from the reaction of 2-{2-[((benzyloxy)carbonyl)amino]acetamido}acetic acid and benzotriazole using the Katritzky method (Scheme 1).

Scheme 1. Synthesis equations of benzyl {2-[(2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino]-2-oxoethyl} carbamate.



N-(protected α-aminoacyl)benzotriazoles are efficient intermediates for N- and O-aminoacylation. These intermediates are very useful for synthesizing biologically relevant peptides and peptide conjugates in high yields and purity [5]. Contrary to many dipeptides and their benzotriazole derivatives found in the literature, the dipeptide-benzotriazole derivative synthesized in this work has not been reported in the literature according to the SciFinder and Web of Science databases. In order to fill the gap in the literature, the title compound was successfully synthesized in high yield, and its full characterization was made. The new compound is isolable at room temperature and can be handled without special procedures to exclude air and moisture. Since benzotriazoles offers an extremely useful alternative to synthesize peptides and their conjugates, the title compound may be used to obtain biologically relevant new dipeptide-heterocyclic conjugates.

Experimental Section

General Chemical Procedure

All of the chemicals used were supplied commercially by Merck, Fluka or Aldrich Chemical Co. Both ^{1}H-NMR (300.13 MHz) and ^{13}C-NMR (75.47 MHz) spectra were determined using a Bruker DPX-300 high-performance digital FT-NMR spectrometer. FT-IR spectra were recorded on a Perkin-Elmer spectrophotometer in the range 4,000–400 cm^{-1}. Elemental analysis was performed by a LECO CHNS-932 elemental analyzer. The melting point was recorded using an electrothermal 9200 melting point apparatus, and it was uncorrected.

2-{2-[((Benzyloxy)carbonyl)amino]acetamido}acetic acid [5–7] was synthesized from N-Cbz-Gly-Bt [8] and Gly-OH using literature methods.

Synthesis of the Benzyl {2-[(2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino]-2-oxoethyl}carbamate

To the solution of benzotriazole (3.58 g, 30.0 mmol, 4 equiv.) in CH_2Cl_2 (25 mL), thionyl chloride (9.65 mmol, 0.7 mL, 1.3 equiv.) was added, and the reaction mixture was stirred for 30 min at room temperature. The temperature of the reaction mixture was then lowered to 258 K, and Cbz-Gly-Gly-OH (2.00 g, 7.50 mmol, 1 equiv.) was added and stirred for 5 h at 258 K. Subsequently, all volatiles

were removed by vacuum and the obtained crude product was first washed with aqueous saturated sodium carbonate solution three times (3 × 30 mL) for the complete removal of benzotriazole, then washed with diethyl ether and dried to give the title compound as a white clear solid. (2.04 g, 74%). Mp: 438–439 K. $\upsilon_{(C=O,\ ester)}$: 1,766 cm^{-1}, $\upsilon_{(C=O,\ amides)}$: 1,698 and 1,655 cm^{-1}, $\upsilon_{(C\text{-}N,\ amides)}$): 1,518 and 1,573 cm^{-1}. Analysis found: C, 58.32; H, 4.83; N, 18.92%. Calcd. for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06%. ^{1}H-NMR (300 MHz, DMSO-d_6, 298 K): δ (ppm) 8.64 (t, 1H, N*H*, *J* = 5.7 Hz), 8.28 (d, 1H, Ar-*H*, *J* = 8.1 Hz), 8.21 (d, 1H, Ar-*H*, *J* = 8.1 Hz), 7.81 (t, 1H, Ar-*H*, *J* = 7.8 Hz), 7.66-7.58 (m, 2H, Ar-*H* + N*H*), 7.38–7.31 (m, 5H, Ar-*H*), 5.06 (s, 2H, CH_2-O), 4.99 (d, 2H, CH_2-N, *J* = 5.7 Hz), 3.80 (d, 2H, CH_2-N, *J* = 6 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6, 298 K): δ (ppm) 170.7 (*C*=O), 169.0 (*C*=O), 157.0 (*C*=O, ester), 145.7, 137.5, 131.5, 131.0, 128.8, 128.3, 127.6, 127.1, 120.6, 114.2, 66.0 (*C*H_2-O), 43.8 (*C*H_2), 43.0 (*C*H_2).

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Author Contributions

Hasan Küçükbay designed research, analyzed the data and wrote the paper. Nesrin Buğday performed the laboratory synthesis. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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