

Short Note

Methyl 2-Benzamido-2-(1*H*-benzimidazol-1-ylmethoxy)acetate

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Abstract: The heterocyclic carboxylic α -aminoester methyl 2-benzamido-2-(1*H*-benzimidazol-1-ylmethoxy)acetate is obtained by *O*-alkylation of methyl α -azido glycinate *N*-benzoylated with 1*H*-benzimidazol-1-ylmethanol.

Keywords: α -aminoesters; *O*-alkylation; methyl α -azidoglycinate

1. Introduction

It is interesting to note that amino acids are components of living organisms and are precursors for protein formation. Several researchers have investigated the inhibitory potential of some amino acids and the results obtained from such studies have given some hope for the use of amino acids as green corrosion inhibitors [1–4].

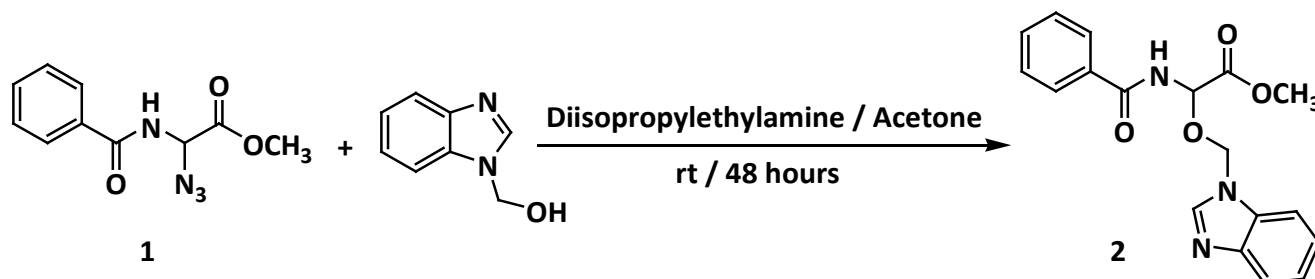
Recently, benzimidazole derivatives are a key part of many drugs [5] for their potency and activation [6–8]. Both telmisartan (TST) and candesartan (CST) are potent angiotensin II type 1 (AT1) receptor blockers (ARBs), which have been widely used in the treatment of hypertension and also found to display some other pharmacologic effects in treating diabetes [9] and heart disease [10], while DB921 with diamidine in terminal can strongly bind to the DNA groove and cause rapid destruction of the mitochondrial kinetoplast [11].

For this reason, we considered it interesting to synthesize new compounds containing 1*H*-benzimidazol-1-ylmethanol fused with a derivative of amino acid, in order to study their biological activities.

Following the research done on the synthesis of new α -carboxylic aminoesters [12] and in the synthesis of heterocyclic systems of benzimidazole derivatives, we reported in this paper another part

of our investigations concerning the preparation of methyl 2-benzamido-2-(1*H*-benzimidazol-1-ylmethoxy)acetate. Our strategy is based on the *O*-alkylation of methyl α -azido glycinate *N*-benzoylated with 1*H*-benzimidazol-1-ylmethanol. The product synthesized with a satisfactory yield was characterized by nuclear magnetic resonance and mass spectrometry (Scheme 1).

Scheme 1. *O*-alkylation of 1*H*-benzimidazol-1-ylmethanol with methyl α -azidoglycinate.



2. Results and Discussion

Our strategy is based on the *O*-alkylation of alcohol 1*H*-benzimidazol-1-ylmethanol with methyl α -azidoglycinate **1** (scheme 1). Azide derivative **1** was prepared using Steglich method [13] and Achamlale's procedure [14].

Methyl α -azido glycinate *N*-benzoylated **1** was obtained by the reaction [14] of sodium azide with the methyl α -bromo glycinate. The title compound is stable and can be stored for an unlimited time without any signs of decomposition. The methyl α -bromo glycinate also can be used and gives satisfactory results; the azide **1** is used especially for its stability.

As shown in Scheme 1, the reaction of 1*H*-benzimidazol-1-ylmethanol on azide **1** results in formation of the new racemic α -heterocyclic α -carboxylic aminoester **2** carrying 1*H*-benzimidazol-1-ylmethoxy group or substituent in position α .

As a first step and to optimize the different reaction conditions (choice of base, solvent ...), we conducted several test reactions. For all these tests, the reactions were followed by TLC and ^1H -NMR. Yields are given as pure product after column chromatography on silica gel.

After several attempts of reactions without base or in the presence of bases such as triethylamine, reaction with diisopropylethylamine (DIPEA) gave the best results. The reaction was carried out in dry acetone at room temperature for 48 h. Results are summarized in Table 1.

Table 1. Synthesis of Methyl 2-benzamido-2-(1*H*-benzimidazol-1-ylmethoxy)acetate **2**.

Nu-H	Product	M.P. (°C)	Reaction Time (h)	-	Et ₃ N	Et ₃ N	DIPEA	DIPEA
				DCM	DCM	Acetone	DCM	Acetone
				Yield (%)	Yield (%)	Yield (%)	Yield (%)	Yield (%)
1 <i>H</i> -benzimidazol-1-ylmethanol	Methyl 2-benzamido-2-(1 <i>H</i> -benzimidazol-1-ylmethoxy)acetate 2	116–118	48	0	10	15	22	30

The product **2** was obtained in 30% overall yield from **1** and was characterized by MS, ^1H -NMR and ^{13}C -NMR spectroscopy.

Comparing these results with the work done by our team [12,15,16], we see that we have obtained almost the same results.

3. Experimental

To a stirred solution of 2.86 mmol of alcohol (oxygen compound) and 3.12 mmol of diisopropylethylamine in 10 mL of dry acetone, 2.6 mmol of α -azido glycinate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kiesegel Merck 60F254). The solvent was evaporated under reduced pressure. The residue was quenched with saturated aqueous solution of ammonium chloride (20 mL) and extracted with dichloromethane (20 mL $\times$ 3). The organic phase was dried in sodium sulfate (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel using ether/hexane as eluant to afford pure *O*-alkylated product.

White solide: yield = 30%; Melting point (ether/hexane): 116–118 °C; R_f = 0.60 (ether).

^1H -NMR (Bruker, 300.13 MHz, CDCl_3): δ (ppm) = 3.87 (s, 3H, OCH_3), 5.37 (s_{br} , 1H, H_a), 5.81 (s, 2H, OCH_2), 7.00–7.82 (m, 9H, H_{arom}), 8.02 (s_{br} , 1H, NH_{amid}), 8.35 (s, 1H, H_{imid}).

^{13}C -NMR (75.47 MHz; CDCl_3): δ (ppm) = 54.2 (OCH_3), 60.8 (OCH_2N), 84.1 ($-\text{CH}-$), 110.0 (2C), 123.2 (2C), 124.05 (2C), 127.4 (2C), 128.8, 132.7 (C_6H_5 aromatic carbons), 134.1 ($=\text{C}_q\text{N}-$), 138.2 ($=\text{C}_q\text{N}-$), 143.0 ($-\text{CH}_{\text{imid}}$), 167.3 (CO), 171.4 (CO).

MS (electrospray) m/z : 362 ($\text{M}+\text{H}^++\text{Na}^+$, 19%), 340 ($\text{M}+\text{H}^+$, 100%), 296 (11%), 221 (20%), 219 (9%), 192 (33%).

Anal Calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$: C, 63.71%; H, 5.05%; N, 12.38%. Found: C, 63.68%; H, 5.01%; N, 12.31%.

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