Short Note

(Benzoylamino)methyl 4-[(Benzoylamino)methoxy]benzoate

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Abstract: In this note, two procedures for the synthesis of (benzoylamino)methyl 4-[(benzoylamino)methoxy]benzoate (3) are presented. The first procedure is carried out in dioxane/water using benzoylaminomethyl-4-hydroxybenzoate, while the second one employs a suspension of 4-hydroxybenzoic acid in dioxane. In both procedures, benzamidomethyl triethylammonium chloride is used for the benzamidomethylation reaction.

Keywords: benzamidomethyl ester; synthesis

Methyl 4-methoxybenzoate (also known as methyl anisate) is a white crystalline powder, soluble in alcohol and ether, but insoluble in water. In the nature, it occurs as a volatile compound in mushroom species and plants [1–5]. These types of esters are used as pharmaceutical intermediates and take part in many organic syntheses [6,7]. For example, a new imaging compound, [(125)I]iodoDPA-713, was synthesized in several steps from methyl 4-methoxybenzoate as a tool for quantification of inflammation in preclinical models [6]. Nowadays, methyl 4-methoxybenzoate has application in the flavor and perfume industry as synthetic flavoring substance due to its sweet herbal anis aroma, impressing lilac or magnolia [8,9].

In this note, the synthesis of a new compound, (benzoylamino)methyl 4-[(benzoylamino)methoxy]benzoate (3), similar to methyl anisate, is reported. The synthesis of 3 was carried out by using (benzamidomethyl)triethylammonium chloride (2) as a reagent for benzamidomethylation. Although 2 is an excellent reagent for benzamidomethylation of phenols [10], in our previous work [11] we demonstrated that the phenol group at 4-hydroxybenzoic acid (4) cannot be benzamidomethylated with
2 in aqueous media. The carboxylic group as a weak nucleophile in aqueous media does not react [12], but it deactivates the phenol group in the molecule of 4-hydroxybenzoic acid. However, once the carboxylic group is protected as in (benzoylamino)methyl 4-hydroxybenzoate (1), the hydroxyl group can be easily benzamidomethylated with 2 in aqueous media to obtain 3 (Scheme 1).

As presented in Scheme 1, the title compound can also be obtained directly from 4 in dioxane suspension of 2 at 50 °C.

**Scheme 1.** Synthetic routes to the title compound 3.

![Scheme 1](image)

**Experimental**

Compound 2 is not commercially available and it was synthesized as described previously [10].

**(Benzoylamino)methyl 4-[(benzoylamino)methoxy]benzoate (3)**

**Procedure A**

To a mixture of 1 (0.310 g, 1.14 mmol), well powdered 2 (0.334 g, 1.23 mmol), dioxane (25 mL) and triethylamine (0.1 mL) was added water drop by drop, until a clear solution was obtained. The mixture was stirred for 10 h at room temperature and subsequently water was added until occurrence of a precipitate. The maximal yield of crude colorless crystals was 70%. The purification was performed firstly by dissolving the product in dioxane and by precipitation with water and then by recrystallization from ethyl acetate.

**Procedure B**

To a suspension of 2 (0.529 g, 1.95 mmol) in dioxane (10 mL) were added 4 (0.108 g, 0.78 mmol) and TEA (0.1 mL). The mixture was stirred and heated at 50 °C for 24 h. After cooling, water was
added until a white precipitate occurred. The colorless crystals were filtered off and purified as described in Procedure A. Maximum yield was 56%.

Melting point of pure crystals: 176.5–177.5 °C (uncorrected).

FT-IR (KBr): 3,311 (νNH), 1,728 (νOC=O), 1,655 (Amide I), 1,536 cm$^{-1}$ (Amide II).

$^1$H-NMR (250 MHz, DMSO-$d_6$): δ/ppm 9.62 (t, $J = 6.7$ Hz, 2H, 2xNH); 7.95–7.15 (14H, Ar); 5.57 (d, $J = 6.7$ Hz, 2H, N-CH$_2$-O); 5.40 (d, $J = 6.7$ Hz, 2H, N-CH$_2$-O)

$^{13}$C-NMR (63 MHz, DMSO-$d_6$): δ/ppm 167.1 (C=O); 167.0 (C=O); 68.7 (CH$_2$); 65.5 (CH$_2$); Ar: 161.0, 133.3, 133.2, 132.1, 131.4, 128.5, 127.6, 127.5, 122.2, 115.3.

Anal. Calcd. (found) for C$_{23}$H$_{20}$N$_2$O$_5$: C, 68.31 (68.13); H, 4.98 (5.19); N, 6.93 (6.85).

References


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