

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 benzoylamino-methyl-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

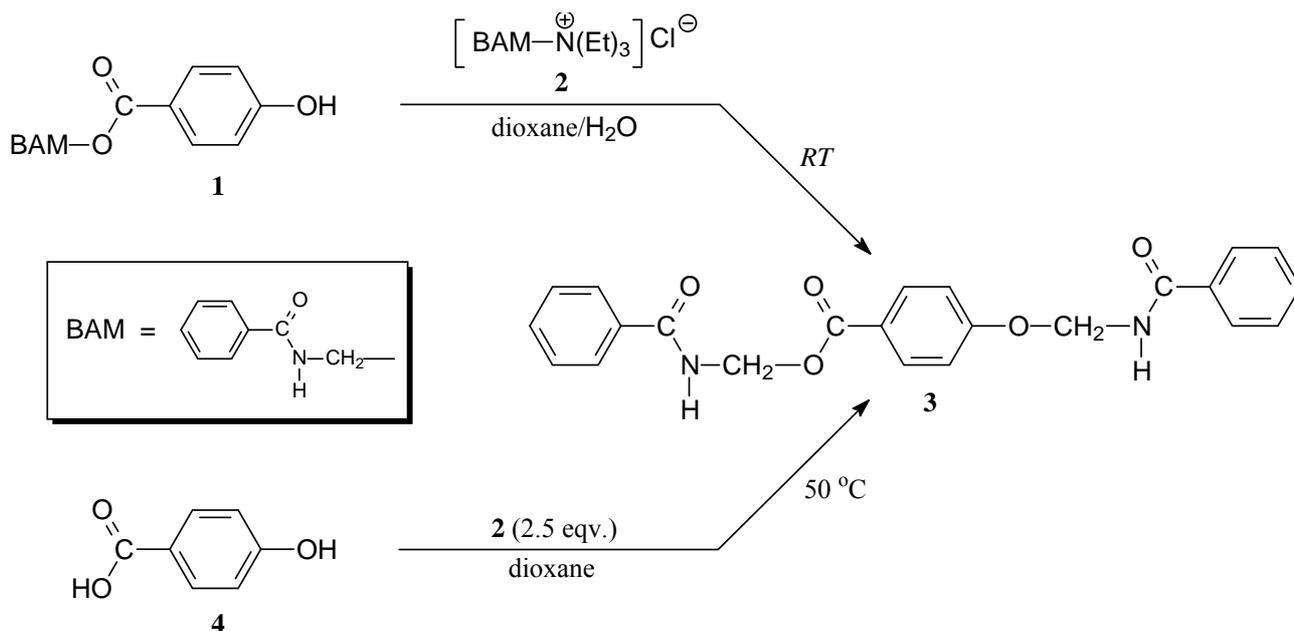
Methyl 4-methoxybenzoate (also known as methyl anisate) is a white crystalline powder, soluble in alcohol and ether, but insoluble in water. In the nature, it occurs as a volatile compound in mushroom species and plants [1–5]. These types of esters are used as pharmaceutical intermediates and take part in many organic syntheses [6,7]. For example, a new imaging compound, [(125I)]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**.



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).

¹H-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-CH₂-O); 5.40 (d, *J* = 6.7 Hz, 2H, N-CH₂-O)

¹³C-NMR (63 MHz, DMSO-*d*₆): δ/ppm 167.1 (C=O); 167.0 (C=O); 68.7 (CH₂); 65.5 (CH₂); 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 C₂₃H₂₀N₂O₅: C, 68.31 (68.13); H, 4.98 (5.19); N, 6.93 (6.85).

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