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SIMPLE METHOD FOR BENZAMIDOMETHYLATION OF PHENOLS IN WATER SOLUTION

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Benzamidomethyl ethers $ROCH_2NHBz$ **(5)** (R = aryl, cyclohexyl and benzyl) were obtained in high yields in reactions of ROH **(4)** with (benzamidomethyl)triethylammonium chloride **3** as a benzamidomethylation agent. Reactions occurred in water, except reactions of cyclohexyl and benzyl alcohol with **3** that occurred in $CHCl_3$.

Introduction

N-(Hydroxymethyl)benzamide **(1a)** and *N*-(chloromethyl)benzamide **(1b)** are reagents that have been widely used in reactions of benzamidomethylation. Also used, although more seldom, are *N*-(diethylaminomethyl)benzamide[1] **(1c)**, dibenzamidomethyl ether[2] **(1d)**, and *N*-(acetoxymethyl)benzamide[3] **(1e)**.

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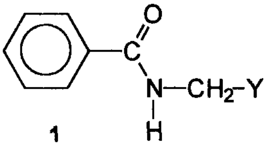


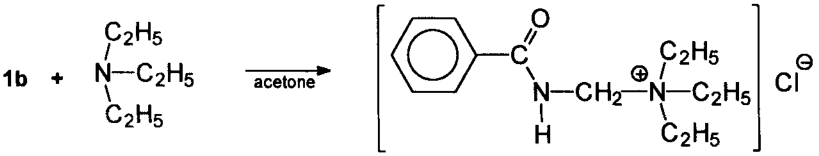
1

a) Y = OH
b) Y = Cl
c) Y = $N(C_2H_5)_2$
d) Y = OCH_2NHBz
e) Y = OAc

In the course of our studies in benzamidomethylation, we noticed the occurrence of a white precipitate, which appears immediately when triethylamine (TEA) is added into dioxane or acetone solution of **1b.** The investigation that we undertook, revealed eventually that the obtained precipitate is (benzamidomethyl)triethylammonium chloride **(3)** which was successfully used in the benzamidomethylation reaction of some phenols and alcohols.

Results and discussion

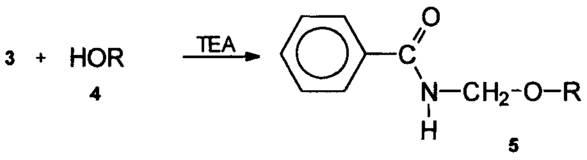
Compound **3** was obtained through several reaction steps. First **1a** was synthesized in a reaction of benzamide and a water solution of formaldehyde.[4] Having synthesized **1a**, its conversion into **1b** was performed by $SOCl_2$ in cooled dry CCl_4.[5] As mentioned earlier, **3** was obtained in a reaction of **1b** and TEA, according to FIG. 1. The crucial point in this synthesis was that the whole quantity of acetone solution of **1b** is to be added in a vigorously stirred acetone solution of TEA (otherwise, a branching reaction occurs, and large quantities of triethylamine hydrochloride and *N,N'*-methylenedibenzamide are also obtained).



3

FIG. 1

In dry media, compound **3** is a stable substance (after several months, no changes were detected in its IR spectrum). It is readily soluble in water (but this solution is stable only few days). Using **3** as a benzamidomethylation reagent, compounds **5** were synthesized (FIG. 2). First **5a** was synthesized in rather high yield (75 %) in the reaction of phenol and an acetone or dioxane suspension of **3**. However, if the reaction was performed in a water solution and in presence of a small quantity of TEA (pH > 9), it was much faster and also more efficient (the yield was over 95 %). The reactions of phenols **4(b-f)** were analogous to the one with **4a**; in water solutions they react with **3** giving **5(b-f)**. Alcohols **4g** and **4h** could not be benzamidomethylated with **3** in water solutions but **5g** and **5h** were obtained from the same reaction in $CHCl_3$.



a) R = Ph
b) R = p-C_6H_5-NO_2
c) R = p-C_6H_5-OH
d) R = p-C_6H_5-O-CH_2-NH-Bz
e) R = p-C_6H_5-NH-Ac
f) R = 2-naphthyl
g) R = cyclohexyl
h) R = CH_2-C_6H_5

FIG. 2

As conclusion, benzamidomethylation with compound **3** is a simple method, which gave excellent results for preparation of benzamidomethyl aryl ethers. Reactions occurred fast, in mild conditions and in always-easy accessible solvent - water. The products (most of them almost pure) are easily isolated from reaction mixture by simple filtration. Also, compound **3** gave good results in benzamidomethylation of alcohols.

Experimental Section

3. (Benzamidomethyl)triethylammonium chloride. Freshly synthesized **1b** (13.57 g, 0.08 mol) was dissolved in dry acetone (70 cm^3) and solution the whole was at once added to a very vigorously mixed solution of TEA (14 cm^3, 0.1 mol) in the same solvent (130 cm^3). A white precipitate was immediately formed. An additional 100 cm^3 of acetone was added and the mixture was stirred for 30 min. A thick suspension was filtered off using a sintered-glass funnel, while the precipitate was washed with the same solvent. A typical yield of crude product was 17.968 g (0.066 mol; 82.93 %). Recrystallization was performed from $CHCl_3$, mp above 125 °C (decomp): (Found: C, 62.3; H, 8.6; N, 10.2; Cl, 12.9; $C_{14}H_{23}ClN_2O$ requires C, 62.1; H, 8.6; N, 10.3; Cl, 13.1 %); IR(Nujol)/cm^{-1} 1660 Amide I; 1545 Amide II; ^1H-NMR(300 MHz; DMSO-d_6)/ppm 9.93 (1H, t, *J* 6.3, NH); 8.10-7.51 (5 H, m, Ph); 4.76 (2H, d, *J* 6.7, NCH_2N); 3.25 (6H, q, *J* 6.4, $3CH_2CH_3$); 1.28 (9H, t, *J* 6.4, $3CH_3$); ^{13}C-NMR(75 MHz; DMSO-d_6)/ppm 168.90 C=O, 132.75 and 128.62 Ar, 60.07 NCH_2N, 50.33 CH_2CH_3, 7.52 CH_3.

5a. Benzamidomethyl phenyl ether. A solution of **3** (1.896 g, 7.0 mmol) in water (30 cm^3) was added to the water (40 cm^3) solution of phenol (0.538 g, 5.7 mmol) and TEA (0.3 cm^3). The mixture was stirred for 2-3 h at room temperature. This was followed by formation of colourless crystals, which were filtered. The purification was done by dissolving the product in dioxane (or acetone) and precipitation with water. The typical yield of colourless crystals with a mp of 123-125 °C (lit.[6] 120-122 °C) was 1.252 g (5.5 mmol; 96.38 %): (Found: C, 73.5; H, 5.7; N, 6.3; $C_{14}H_{13}NO_2$ requires C 74.0; H 5.8; N 6.2 %); FTIR(KBr)/cm^{-1} 3325.9 (NH); 1650.6 Amide I; 1531.5 Amide II: ^1H-NMR(300 MHz; DMSO-d_6)/ppm 9.60 (1H, t, *J* 6.2, NH); 7.94-6.94 (10 H, m, 2Ph); 5.34 (2H, d, *J* 6.5, N-CH_2-O);

^{13}C-NMR(75 MHz; DMSO-d_6)/ppm 167.16 C=O, 68.49 CH_2, *Aromatic*:157.13, 133.71, 132.16, 129.79, 128.73, 127.71, 121.29 and 115.49.

5d. Benzamidomethyl 4-(benzamidometoxy)phenyl ether

A solution of **5c** (1.351 g, 5.5 mmol) in acetone (30 cm^3) was mixed with water (30 cm^3) solution of **3** (1.844 g, 6.8 mmol) and TEA (0.2 cm^3). The mixture was stirred for 6-8 h at room temperature and then was filtered. The yield of pale rose crystals was 82.39 %; mp 197-8 °C (from EtOH); (Found: C, 70.6; H, 5.4; N, 7.5; $C_{22}H_{20}N_2O_4$ requires C 70.2; H 5.4; N 7.4 %); FTIR(KBr)/cm^{-1} 3351.5 and 3314.7 (2 × NH); 1653.7 Amide I; 1547.2 Amide II: ^{1}H-NMR(300 MHz; DMSO-d_6)/ppm 9.55 (2H, t, *J* 6.4, 2 × NH); 7.92-7.01 (14 H, m, Ar); 5.28 (4H, d, *J* 6.4, 2 × N-CH_2-O); ^{13}C-NMR(75 MHz; DMSO-d_6)/ppm 167.12 C=O, 69.10 CH_2, *Aromatic*: 151.56, 133.77, 132.13, 128.73, 127.69, 116.74.

5g. Benzamidomethyl cyclohexyl ether

A solution of **4g** (0.758 g, 7.6 mmol), **3** (2.412 g, 8.9 mmol) and TEA (0.15 cm^3) was heated under reflux for 45 min. After cooling, solvent was evaporated at 30 °C. Precipitate formed was washed with H_2O (15 cm^3) and dissolved in EtOH (10 cm^3). Colourless crystals of **5g** were obtained when cold water was slowly dropped in to cooled and vigorously stirred ethanole solution. Yield 1.184 g (5.1 mmol; 67.04 %); mp 95 °C; (Found: C, 71.6; H, 8.4; N, 5.8; $C_{14}H_{19}NO_2$ requires C 72.0; H 8.2; N 6.0 %); FTIR(KBr)/cm^{-1} 3293.4 (NH); 1645.8 Amide I; 1541.3 Amide II; ^{1}H-NMR(250 MHz; DMSO-d_6)/ppm 9.19 (1H, t, *J* 6.3, NH); 7.92-7.43 (5H, m, Ph); 4.78 (2H, d, *J* 6.4, CH_2N); 3.47 (1H, br s(quintet), $CH_2CH(O)CH_2$); 1.57-1.15 (10H, m, 5 × CH_2 from Cy); ^{13}C-NMR(63 MHz; DMSO-d_6)/ppm 166.67 C=O, 73.89 NCH_2; 67.38 CH; 32.14, 25.39 and 23.58 CH_2(from Cy); *Aromatic*: 134.06, 131.53, 128.57 and 127.39.

5h. Benzamidomethyl benzyl ether was synthesized in a similar manner as **5g**. Colourless crystals; yield 62.77 %; mp 77-78 °C (lit.[7] 77-78 °C); (Found: C, 75.1; H, 6.1; N, 5.8; $C_{15}H_{15}NO_2$ requires C 74.7; H 6.3; N 5.8 %); FTIR(KBr)/cm^{-1} 3335.1 (NH); 1650.0 Amide I; 1538.2 Amide II; ^{1}H-NMR(250 MHz; DMSO-d_6)/ppm 9.36 (1H, t, *J* 6.4, NH); 7.94-7.30 (10H, m, 2Ph); 4.85 (2H, d, *J* 6.5, NCH_2); 4.57 (2H, s, $PhCH_2$); ^{13}C-NMR(63 MHz; DMSO-d_6)/ppm 167.05 C=O, 69.69 and 69.31 $2CH_2$; *Aromatic*: 138.50, 133.95, 131.68, 128.43, 128.24, 127.53, 127.46 and 127.38.

5b, 5c, 5e, 5f, was synthesized in a similar manner as 5a (*Method A*), and small differences are noted for each product.

5b. Benzamidomethyl 4-nitrophenyl ether

Stirring time 5 h; colourless crystals; yield 61.24 %; mp 148 °C (lit.[6] 142-44 °C); (Found: C, 61.8; H, 4.6; N, 10.4; $C_{14}H_{12}N_2O_4$ requires C 61.8; H 4.4; N 10.3 %); FTIR(KBr)/cm^{-1} 3294.7 (NH); 1663.2 Amide I; 1554.5 Amide II; 1542.2 and 1351.4 (NO_2); ^{1}H-NMR(250 MHz; DMSO-d_6)/ppm 9.71 (1H, t, *J* 6.6, NH); 8.23-7.27 (9 H, m, 2Ph); 5.47 (2H, d, *J* 6.6, N-CH_2-O); ^{13}C-NMR(63 MHz; DMSO-d_6)/ppm 167.06 C=O; 69.28 CH_2; *Aromatic*: 162.30, 141.218, 133.17, 132.16, 128.60, 127.55, 125.90 and 115.74.

5c. Benzamidomethyl 4-hidroxyphenyl ether, was synthesized in a similar manner as **5a** (*Method A*) with a small distinction. In the reaction mixture, reactants **3** and **4c** were in ratio 1:2. Yield 91.28 %; purification was done by dissolving the product in cold EtOH and precipitation with water. Pale rose crystals had a mp of 182 °C; (Found: C, 69.0; H, 5.5; N, 5.7; $C_{14}H_{13}NO_3$ requires C 69.1; H 5.4; N 5.8 %); FTIR(KBr)/cm^{-1} 3561.5 and 3481.5 (OH); 3300.9 and 3236.3 (NH); 1654.1 Amide I; 1542.2 Amide II; ^{1}H-NMR(300 MHz; DMSO-d_6)/ppm 9.50 (1H, t, *J* 6.6, NH); 9.01 (1H, s, OH); 7.99-6.67 (9 H, m, 2Ph); 5.21 (2H, d, *J* 6.5, N-CH_2-O); ^{13}C-NMR(75 MHz; DMSO-d_6)/ppm 167.07 C=O; 69.31 CH_2; *Aromatic*: 152.07, 149.79, 133.83, 132.09, 128.71, 127.67, 117.06 and 115.95.

5e. 4-Acetanilidyl benzamidomethyl ether

Colourless crystals; yield 84.16 %; mp 176 °C from dioxane (lit.[6] 169-72 °C); (Found: C, 68.0; H, 5.8; N, 9.8; $C_{16}H_{16}N_2O_3$ requires C 67.6; H 5.7; N 9.8 %); FTIR(KBr)/cm^{-1} 3310.3 and 3258.8 (2 × NH); 1662.3 and 1651.4 (2 × Amide I); 1549.5 Amide II; ^{1}H-NMR(300 MHz; DMSO-d_6)/ppm 9.82 (1H, s, PhN*H*CO); 9.56 (1H, t, *J* 6.4, CON*H*CH_2); 7.92-6.98 (9 H, m, 2Ph); 5.29 (2H, d, *J* 6.4, N-CH_2-O); 2.02 (3H, s, CH_3); ^{13}C-NMR(75 MHz; DMSO-d_6)/ppm 168.11 and 167.14 (2 × C=O), 68.82 CH_2, 23.88 CH_3; *Aromatic*: 152.80, 133.76, 133.37, 132.13, 128.73, 127.68, 120.72 and 115.73.

5f. Benzamidomethyl 2-naphthyl ether

Stirring time 10-12 h; colourless crystals; yield 80.46 %; mp 173 °C (from toluene); (Found: C, 77.8; H, 5.7; N, 5.2; $C_{18}H_{15}NO_2$ requires C 78.0; H 5.4; N 5.0 %); FTIR(KBr)/cm^{-1} 3314.2 (NH); 1653.9 Amide I; 1532.3 Amide II: ^{1}H-NMR(250 MHz; DMSO-d_6)/ppm 9.68 (1H, t, *J* 6.4, NH); 7.97-7.79 (5H, m, Ph); 7.58-7.25 (7H, m, naphtyl); 5.48 (2H, d, *J* 6.5, N-CH_2-O); ^{13}C-NMR(63 MHz; DMSO-d_6)/ppm 167.08 C=O, 68.66 CH_2, *Aromatic*: 154.76, 134.29, 133.56, 132.02, 129.51, 128.73, 128.59, 127.58, 126.81, 126.52, 123.87, 118.98 and 108.21.

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