

Benzamidomethylation with (Benzamidomethyl)triethylammonium Chloride. 2. A Simple Method for Benzamidomethylation of Thiols, Amines and Carboxylic Acids*

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Abstract: Thiols and amines were benzamidomethylated in water solution at room temperature with (benzamidomethyl)triethylammonium chloride (**1**) in the presence of a small quantity of triethylamine (pH>9). Benzamidomethyl thioethers (**3a-d**) and (benzamidomethyl)amines or di(benzamidomethyl)amines (**5**) were obtained in high yields (>90%) as well as S(CH₂NHBz)₂ in a reaction of **1** with Na₂S. Benzamidomethyl esters RCOOCH₂NHBz were obtained (60-75%) in reactions of carboxylic acids with **1** in chloroform or dioxane.

Keywords: Benzamidomethylation, thiols, carboxylic acids, amines.

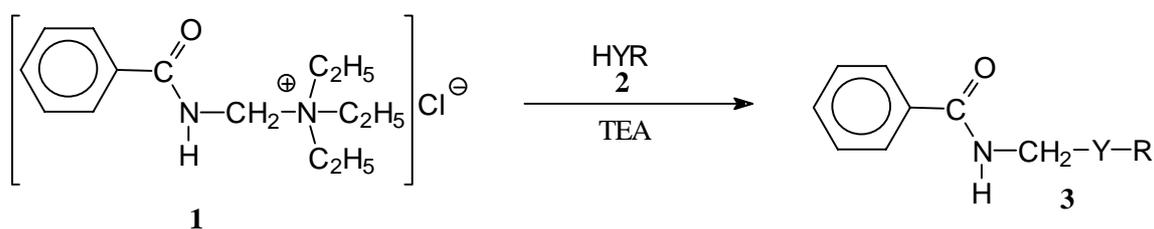
Introduction

In the past, a large number of benzamidomethyl compounds have been synthesized which have been used for different purposes. In the final decade, in the case of a thiol group, benzamidomethylation was used for synthesis of ligands for ⁹⁹Tc complexes, which have been utilized as radiolabels [2-4]. Also, benzamidomethylation was used to obtain some benzamidomethyl aryl thioethers as intermediates in the synthesis of benzothiazines [5-7]. Among the numerous S-benzamidomethyl derivatives there are

reports of a *S*-benzamidomethyl-L-cysteine, which was used in peptide synthesis [8-11] and some of them are useful for the treatment of glaucoma [12]. Also, wool proteins can be analyzed as the corresponding *S*-amidomethyl derivatives [13]. Amidomethyl and benzamidomethyl esters were synthesized and evaluated as potential prodrugs of carboxylic acid agents [14-17] or amide agents [18]. The benzamidomethyl esters of carboxylic acids were used as a benzamidomethylation reagent for compounds with a different nucleophilic group [19, 20]. In the case of an amine group, amidomethylation was used for synthesis of derivatives of some uracils or thiouracils that showed antitumor activity [21, 22]. Zlotin and coworkers [23] investigated some routes for the synthesis of *N*-benzamidomethyl derivatives of functional derivatives of α -aminoacids and peptides, etc. Our good results with the benzamidomethylation of phenols [1] using (benzamidomethyl)triethylammonium chloride (**1**), prompted us to investigate the reaction of this compound with thiols, carboxylic acids and amines.

Results and Discussion

Reactions with thiols were performed in very vigorously stirred aqueous mixtures of **1** and thiols **2(a, b, c and d)**, in the presence of a small quantity of triethylamine (TEA) to pH > 9 (Scheme 1). The reactions with liquid thiols (**2a,c,d**) in the first 5-10 minutes gave yellow oils which over the next 5-10 minutes are transformed to small white solid lumps. For best results, the lumps should be ground with a glass rod and the reaction mixture stirred over 1 hour, although in some cases the reaction is over in 30-40 minutes. The products were collected by filtration.



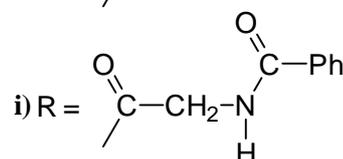
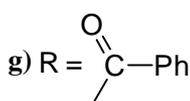
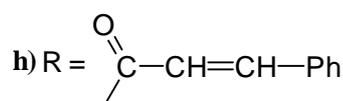
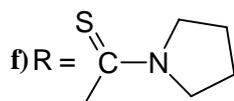
For **a, b, c, d** and **f**, Y = S (only for **2f** HY = NH₄S); for **g, h** and **i**, Y = O

a) R = Ph

b) R = 2-naphthyl

c) R = CH₂-C₆H₅

d) R = cyclohexyl



Scheme 1.

Table 1. NMR data of compounds 3a-i.

Compound	¹ H-NMR (300 MHz; DMSO-d ₆ ; δ in ppm)				¹³ C-NMR (75 MHz; δ in ppm)
	CONHCH ₂	Aromatic	NHCH ₂	Other	
3a	t, 9.33 1H, <i>J</i> 5.9	m, 7.86-7.21 10H	d, 4.84 2H, <i>J</i> 5.9	-	166.53 C=O; 43.91 CH ₂ ; Ar: 135.56, 134.02, 131.84, 129.9, 129.3, 128.64, 127.54, 126.68
3b	t, 9.41 1H, <i>J</i> 5.9	m, 8.05-7.44 12H	d, 4.97 2H, <i>J</i> 6.2	-	166.37 C=O; 43.63 CH ₂ ; Ar: 133.79, 133.39, 132.85, 131.6, 131.48, 128.39, 127.78, 127.59, 127.51, 127.3, 127.1, 126.64, 125.88
3c	t, 9.22 1H, <i>J</i> 5.9	m, 7.9-7.21 10H	d, 4.42 2H, <i>J</i> 5.9	s, 3.9 2H, PhCH ₂	166.68 C=O; 41.08 CH ₂ ; 34.66 PhCH ₂ Ar: 139.2, 134.36, 131.73, 129.13, 128.61, 127.56, 127.01,
3d	9.13 1H broad s(t)	m, 7.88-7.46 5H	d, 4.46 2H, <i>J</i> 6.2	2.89 1H, SCH broad s(quin) m, 1.98-1.24 10H, 5 × CH ₂	166.27 C=O; 42.28 CH ₂ ; 39.68 SCH; 33.54, 25.62, 25.41 5 × CH ₂ ; Ar: 134.31, 131.65, 128.61, 127.48
3e	t, 9.2 2H, <i>J</i> 6.2	m, 7.89-7.46 10H	d, 4.65 4H, <i>J</i> 6.2	-	166.6 C=O; 41.57 CH ₂ ; Ar: 134.05, 131.91, 128.73, 127.48
3f	t, 9.28 1H, <i>J</i> 6.0	m, 7.89-7.46 5H	d, 5.19 2H, <i>J</i> 6.3	t, 3.79, 2H NCH ₂ C t, 3.59, 2H NCH ₂ C quin, 2.00, 2H CCH ₂ C quin, 1.91, 2H CCH ₂ C	190.18 C=S; 166.74 C=O; 46.71 CH ₂ ; 54.88 and 50.70, 2 × N-CH ₂ -C; 25.64 and 23.81, 2 × C-CH ₂ -C; Ar: 133.31, 131.83, 128.48, 127.44
3g^a		m, 8.08-7.41 11H ^b	d, 5.73 2H, <i>J</i> 7.3	-	167.57 C=O; 167.48 C=O; 65.2 CH ₂ ; Ar: 133.51, 133.22, 132.29, 129.87, 129.39, 128.70, 128.45, 127.29
3h^c	t, 9.61 1H, <i>J</i> 6.7	m, 7.96-7.4 11H ^d	d, 5.50 2H, <i>J</i> 6.7	d, 6.66 1H, <i>J</i> 16.1 =CHCOO	167.12 C=O; 166.0 C=O; 65.18 CH ₂ ; Ar and HC=CH: 145.06, 134.01, 133.24, 132.08, 130.63, 129.0, 128.55 127.62, 117.92
3i	t, 9.63 1H, <i>J</i> 6.5 t, 9.02 1H, <i>J</i> 5.6	m, 7.96-7.49 10H	d, 4.44 2H, <i>J</i> 6.5 d, 4.07 2H, <i>J</i> 5.9	-	170.08 C=O; 167.40 C=O; 167.1 C=O 65.62 O-CH ₂ ; 41.44 C-CH ₂ ; Ar: 133.95, 133.39, 132.36, 131.85, 128.79, 128.7, 127.85, 127.58

^a¹H-NMR (360 MHz; CDCl₃), ¹³C-NMR (90 MHz);^bone of the 11H is from NH;^c¹H-NMR (250 MHz), ¹³C-NMR (63 MHz);^done of the 11H is from PhCH=.

Table 2. Physicochemical data of compounds **3a-i** and **5a-h**.

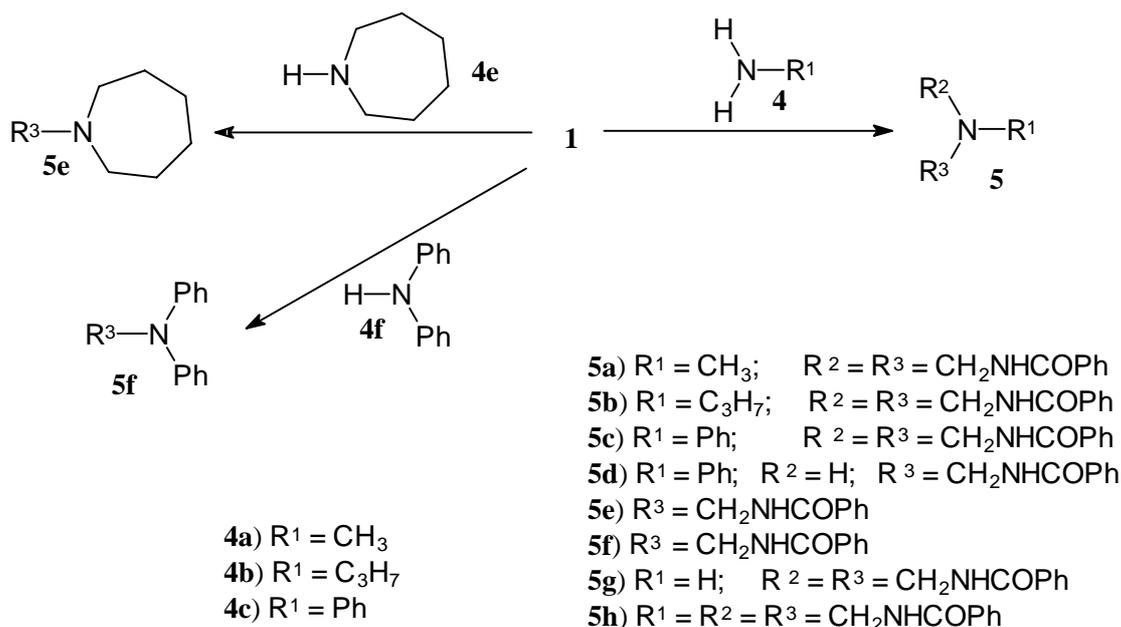
Compound	Yield %	M.p. °C	Calc/found			FTIR (KBr) / cm ⁻¹			
			C	H	N	vNH	Amide I	Amide II	Other
3a	99.3	64 ^e	69.1 69.3	5.4 5.7	5.8 5.6	3306.5	1630.0	1531.7	
3b	98.8	127-30	73.7 74.0	5.1 4.9	4.8 4.8	3242.4	1638.9	1542.7	
3c	93.6	79-80 ^f	70.0 69.9	5.9 5.7	5.4 5.5	3354.1	1638.9	1539.7	
3d	94.6	67-8	67.4 67.3	7.6 7.7	5.6 5.6	3313.4	1639.3	1540.0	
3e	96.3	179	64.0 63.7	5.4 5.7	9.3 9.2	3311.4	1658.6 1644.0	1531.7	
3f	95.7	119-20	55.7 55.4	5.7 6.0	10.0 9.8	3397.1	1673.9	1507.0	
3g	73.0	95-96 ^g	70.6 70.7	5.1 5.4	5.5 5.4	3311.8	1655.5	1534.8	1723.7 CH ₂ O-C=O
3h	62.3	111-12	72.6 72.2	5.4 5.2	5.0 5.0	3344.6	1657.8	1536.5	1709.1 CH ₂ O-C=O
3i	74.4	171	65.4 65.1	5.2 5.2	9.0 8.9	3372.5 3320.1	1663.5 1648.1	1533.5	1745.7 CH ₂ O-C=O
5a	97.3	119-21	68.7 68.8	6.4 6.4	14.1 14.1	3350.9	1645.6	1536.9	
5b	90.9	119-20	70.1 69.8	7.1 7.4	12.9 12.7	3319.5	1641.4	1538.5	
5c	91.7	181-3	73.5 73.4	5.9 6.1	11.7 11.5	3340.5 3298.6	1640.7	1537.4	
5d	100	116-7	74.3 74.6	6.2 6.4	12.3 12.5	3418.1 3340.4	1662.6	1507.6	
5e	92.9	93-4	72.4 72.0	8.7 8.9	12.1 12.3	3333.8	1636.7	1538.5	
5f	88.2	116-7	79.4 79.5	6.0 6.4	9.3 9.0	3379.3 3365.3	1645.1 1636.8	1537.0 1529.5	
5g	50-70	179	67.8 67.8	6.0 6.3	14.8 14.6	3360.4 3263.9	1642.9	1551.5	
5h		191-2	69.2 69.5	5.8 6.0	13.4 13.3	3317.7	1642.3	1541.3	

^elit. [25], M.p. = 67°C; lit [26], M.p. = 65-6°C; ^flit. [25], M.p. = 82°C; ^glit. [27], M.p. = 92°C

The sparingly water soluble 2-thionaphtole (**2b**) was also benzamidomethylated with **1**, but the reaction mixture was stirred over 3 hours. Reactions of **1** with aqueous solutions of Na₂S always gave dibenzamidomethyl sulphide (**3e**; R = CH₂NHBz, Y = S), regardless of the mole ratio of reactants (compound **1** : Na₂S = 1:0.5; 1:1; 1:2 or 1:5). An attempt to synthesize *N*-(sulphonylmethyl)benzamide

(PhCONHCH₂SH) at pH = 9 (where the concentration of S²⁻ ions is minimal and concentration of SH⁻ ions is maximal [24]) failed. Under these conditions the reaction did not occur. An experiment with an aqueous solution of H₂S and controlled increase of pH failed, too. The reaction started and occurred rapidly only when the pH of the mixture was ~10 and higher; however only **3e** was obtained. Product **3e** was also obtained in the reactions of **1** with thioacetic acid and thioacetamide. However, in a reaction of ammonium pyrrolidinedithiocarbamate (**2f**) with **1**, performed in aqueous solution (at room temperature), benzamidomethyl pyrrolidinedithiocarbamate (**3f**) was obtained.

The benzamidomethylation reactions of carboxylic acids with **1** did not take place in aqueous solutions. Benzamidomethyl esters **3(g,h)** were obtained in the reactions of carboxylic acids **2(g,h)** and **1**, performed for 20 min in boiling chloroform in the presence of a small quantity of TEA. Benzamidomethylation of **2i** (which is sparingly soluble in chloroform) under the same conditions did not give good results. But, when the reaction was performed in a dioxane suspension of **1**, benzamidomethyl hippurate (**3i**) was obtained in more than a 70% yield. The temperature of the mixture had to be higher than 40°C (at lower temperatures, the reaction does not occur or is very slow) and lower than 60°C (otherwise, a branching reaction occurs, and *N,N'*-methylenedibenzamide is obtained). Under the same conditions **3f** and **3g** were also obtained. ¹H-NMR and ¹³C-NMR data of compounds **3a-i** are given in Table 1, and physicochemical data are given in Table 2.



Scheme 2.

Benzamidomethylation of amines in the aqueous solutions occurred immediately (Scheme 2). At room temperature **1** reacts very quickly with the primary amines (**4a-c**) as well as with the secondary amine (**4e**). Because of that, dibenzamidomethyl derivatives of primary amines (**5a-c**) were obtained regardless of whether the reaction mixture had a larger quantity of primary amine than of **1**. For the synthesis of monobenzamidomethyl derivative of aniline (**5d**), drops of a very dispersed water solution of **1** had to be added to a very concentrated and vigorously stirred aqueous solution of aniline (**4c**). Benzamidomethylation of sparingly water soluble diphenylamine (**4f**) was performed in dioxane-water mixture as a solvent.

Table 3. NMR data of compounds 5.

Compound	¹ H-NMR (300 MHz; DMSO-d ₆ ; δ in ppm)				¹³ C-NMR (75 MHz; δ in ppm)
	CONHCH ₂	Aromatic	NHCH ₂ N	Other	
5a	t, 8.78 2H, <i>J</i> 5.7	m, 7.9-7.46 10H	d, 4.29 4H, <i>J</i> 6.0	s, 2.31 3H, CH ₃	167.12 C=O; 58.59 CH ₂ ; 37.03 CH ₃ ; Ar: 134.25, 131.48, 128.44, 127.25
5b	t, 8.74 2H, <i>J</i> 5.4	m, 7.88-7.45 10H	d, 4.36 4H, <i>J</i> 5.8	t, 2.54, 2H <i>J</i> 7.2, NCH ₂ C sex, 1.56, 2H <i>J</i> 7.2, CCH ₂ C t, 0.95, 3H <i>J</i> 7.2, CH ₃	167.1 C=O; 57.0 NCH ₂ N; 49.94, 20.36, 11.90 propyl Ar: 134.27, 131.49, 128.45, 127.22
5c	t, 9.12 2H, <i>J</i> 4.9	m, 7.91-6.71 15H	d, 5.16 4H, <i>J</i> 5.2	-	166.83 C=O; 56.50 CH ₂ ; Ar: 145.35, 133.99, 131.64, 129.11, 128.49, 127.31, 117.69, 112.89
5d	t, 8.98 1H, <i>J</i> 4.4	m, 7.90-6.57 10H	t, 4.73 2H, <i>J</i> 6.0	t, 6.31, 1H <i>J</i> 6.6, NHPH	166.64 C=O; 48.71 CH ₂ ; Ar: 147.20, 134.34, 131.41, 128.97, 128.37, 127.39, 116.61, 112.65
5e	t, 8.73 2H, <i>J</i> 5.7	m, 7.90-7.44 5H	d, 4.24 2H, <i>J</i> 5.9	t, 2.73, 4H 2 × NCH ₂ C m, 1.57-1.53, 8H 4 × CCH ₂ C	166.98 C=O; 61.98 NCH ₂ N; 52.53 NCH ₂ C; 28.47, 26.72 CCH ₂ C; Ar: 134.72, 131.16, 128.26, 127.38
5f	t, 9.01 1H, <i>J</i> 4.9	m, 7.85-6.96 15H	d, 5.27 2H, <i>J</i> 5.4	-	166.87 C=O; 57.05 CH ₂ ; Ar: 146.83, 134.25, 131.43, 129.26, 128.28, 127.54, 121.81, 121.24
5g	t, 8.80 2H, <i>J</i> 5.4	m, 7.84-7.41 10H	d, 4.27 4H, <i>J</i> 5.7	broad s, 2.93, 1H	166.61 C=O; 53.10 CH ₂ ; Ar: 134.34, 131.31, 128.31, 127.17
5h	t, 8.82 3H, <i>J</i> 5.8	m, 7.90-7.46 15H	d, 4.45 6H, <i>J</i> 6.0	-	167.14 C=O; 55.56 CH ₂ ; Ar: 134.09, 131.61, 128.50, 127.23

The reaction of **1** with an aqueous solution of NH₃ gave a mixture of di(benzamidomethyl)amine (**5g**) and tri(benzamidomethyl)amine (**5h**). The major component (**5g**; 50-70%) was obtained when small quantities of **1** in powder form were added to a vigorously stirred large volume of 37% aqueous solution of NH₃. Compound **5h** was obtained without admixture of **5g** when aqueous NH₃ was dropped into a concentrated aqueous solution of **1**. Also, **5g** formed when a large quantity of TEA was added to the aqueous reaction mixture of **1** or an aqueous mixture of **1** and any other nucleophilic substrate (phenols, thiols, etc). A possible explanation for this phenomena is that pure TEA (98%) contains some quantity of NH₃. The physicochemical data of compounds **5a-h** are given in Table 2, and their ¹H-NMR and ¹³C-NMR data are given in Table 3.

Conclusions

In conclusion, compound **1** is an excellent benzamidomethylation agent for thiols and amines and a good agent for carboxylic acids. Reactions of **1** with thiols and amines occurred faster and with higher yields (>90%) than the reactions of **1** with phenols, at room temperature. The products are easily isolated from reaction mixture by simple filtration.

Experimental

Compound **1** was synthesized as described previously [1].

Benzamidomethyl phenyl sulphide (3a)

A solution of **1** (2.8611 g, 10.59 mmol) in water (40 cm³) was added to the water (40 cm³) mixture of **2a** (0.538 g, 5.7 mmol) and TEA (0.3-0.5 cm³). The mixture was stirred for 1h at room temperature. White lumps formed, which were ground with a glass rod. Colorless crystals were collected by filtration. Purification was performed by dissolving the product in cold EtOH (the smallest quantity possible) and precipitating with drops of cold water.

Dibenzamidomethyl sulphide (3e)

A solution of Na₂S · 7-9H₂O (3 g) in water (20 mL) was mixed with an aqueous (20 mL) solution of **1** (3.981 g, 14.7 mmol). The mixture was stirred for 30 min at room temperature and then was filtered. Colorless crystals (from acetone).

3b, **3c**, **3d** and **3f** were synthesized in a similar manner as **3a**, and only the differences are noted for each product.

Benzamidomethyl 2-naphthyl sulphide (3b)

Stirring time 3 h; colorless crystals; recrystallization from acetone.

Benzamidomethyl benzyl sulphide (3c)

Colorless crystals; Purification was performed by dissolving the product in cold acetone (smallest quantity possible) and precipitating with drops of cold water.

Benzamidomethyl cyclohexyl sulphide (3d)

Colorless crystals; purification as for **3a**.

Benzamidomethyl pyrrolidinedithiocarbamate (3f)

Gray-white crystals; The purification was performed by dissolving the product in dioxane and precipitating with drops of cold water.

Benzamidomethyl benzoate (3g)

Mixture of **1** (2.5633 g, 9.46 mmol), **2g** (0.9758 g, 7.99 mmol) and TEA (0.2-0.4 cm³) in CHCl₃ (40 cm³) was refluxed for 20-30 min. The solvent was removed under reduced pressure and the residue was dissolved in dioxane. After filtration, water was added to the dioxane solution until a white precipitate appeared. Colorless crystals were filtered and purified by repeating the last procedure. Compound **3g** was also synthesized as described for **3i**.

Benzamidomethyl cinnamate (3h)

Colorless crystals were obtained and purified as for **3g**.

Benzamidomethyl hippurate (3i)

To a suspension of **1** (2.122 g, 7.83 mmol) in dioxane (40 mL) was added hippuric acid (**2i**) (1.020 g, 5.69 mmol) and TEA (0.2-0.4 cm³). The mixture was stirred and heated at 50°C for 24 h. After cooling, water was added to the mixture until a white precipitate appeared. Colorless crystals were filtered and purified as for **3g**.

Di(benzamidomethyl)methylamine (5a)

To a solution of **1** (3.256 g, 12.02 mmol) in water (20 cm³) was added an aqueous (10 cm³) solution of **4a** (~ 0.16 g, 5 mmol) and TEA (0.4 cm³). The mixture was stirred for 30 min at room temperature. Colorless crystals were collected by filtration. Purification as for **3a**.

(Benzamidomethyl)phenylamine (5d)

A solution of **1** (1.328 g, 4.9 mmol) in water (50 mL) was slowly dropped into a vigorously stirred aqueous (20 mL) solution of **4c** (1.522 g, 16.3 mmol). The mixture was stirred for 30 min at room temperature and then the colorless crystals were filtered. Recrystallized from toluene.

(Benzamidomethyl)diphenylamine (5f)

An aqueous (10 cm³) solution of **1** (2.03g, 7.5 mmol) was added to a dioxane (30 cm³) solution of **4f** (0.956, 6.4 mmol). Water was added dropwise to the mixture until it became slightly cloudy. The reaction was stirred for 4 h, then water was added until the product appeared as a white precipitate. Recrystallized from hexane : toluene (5 : 1).

Di(benzamidomethyl)amine (5g)

Powdered **1** (2.1769 g, 8.04 mmol) was added with spatula in small portions to the vigorously stirred 37% aqueous solution of NH₃ (60 cm³). After 20 min, the precipitate formed was filtered off and dissolved in a small quantity of acetone. The solution was filtered to remove the admixture of **5h**. Colorless crystals of **5g** were obtained by precipitation with water.

5b, **5c**, **5e** and **5h** were synthesized in a similar manner as **5a**, and only the differences are presented for each product.

Di(benzamidomethyl)propylamine (5b)

Colorless crystals. Purification as for **3c**.

Di(benzamidomethyl)phenylamine (5c)

Colorless crystals. Recrystallization from toluene.

N-(Benzamidomethyl)azacycloheptane (5e)

In this synthesis the mole ratio of **1** and **4e** was 1.2 : 1. Colorless crystals (from hexane).

Tri(benzamidomethyl)amine (5h)

In this synthesis the mole ratio of **1** and NH₃ was 4 : 1. Colorless crystals (from acetone).

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