

Full Paper

Reactions of (Benzamidomethyl)triethylammonium Chloride with Some Inorganic Nucleophiles in Aqueous Media

Emil Popovski ^{1,*}, Jane Bogdanov ¹, Metodija Najdoski ¹ and Evamarie Hey-Hawkins ²

¹ Institute of Chemistry, Faculty of Natural Sciences & Mathematics, Sts. Cyril and Methodius University, PO Box 162, 1000 Skopje, Macedonia; E-mails: jbb15@psu.edu, metonajd@iunona.pmf.ukim.edu.mk

² Faculty of Chemistry and Mineralogy, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany; E-mail: hey@rz.uni-leipzig.de

* Author to whom correspondence should be addressed; E-Mail: emilp@iunona.pmf.ukim.edu.mk

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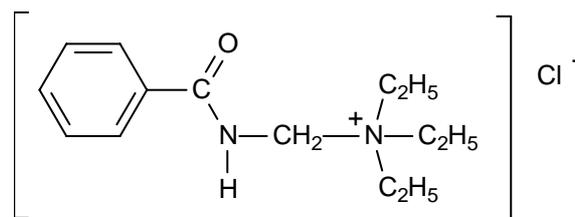
Abstract: A variety of benzamidomethyl derivatives were prepared in water under alkaline conditions (pH>9) via reaction of (benzamidomethyl)triethylammonium chloride (**1**) with different inorganic nucleophiles. Reaction of **1** with hydroxylamine did not give the expected mono(benzamidomethyl)-hydroxylamine (**3**) but rather gave *N,N*-di(benzamidomethyl)hydroxylamine (**2**). Reactions of **1** with sodium azide and potassium cyanide gave benzamidomethyl azide (**4a**) and benzamidomethyl cyanide (**4b**) respectively. Potassium thiocyanate and sodium iodide reacted with **1**, and the anion-exchanged products (benzamidomethyl)triethylammonium isothiocyanate (**5a**) and (benzamidomethyl)triethylammonium iodide (**5b**) were thus obtained. Cyanamide and potassium cyanate reacted readily with **1** and both gave the same mixture of di(benzamidomethyl)amine (**7**) and tri(benzamidomethyl)amine (**8**). All the reactions occurred smoothly, under mild conditions, to give the products in moderate to high yields.

Keywords: Benzamidomethylation, inorganic nucleophiles, aqueous medium

Introduction

Quaternary ammonium salts have been used extensively in preparative organic chemistry. Their properties have been thoroughly studied and they have been found to be superb phase-transfer catalysts in terms of stability, toxicity and cost [1]. Our previous research has shown that

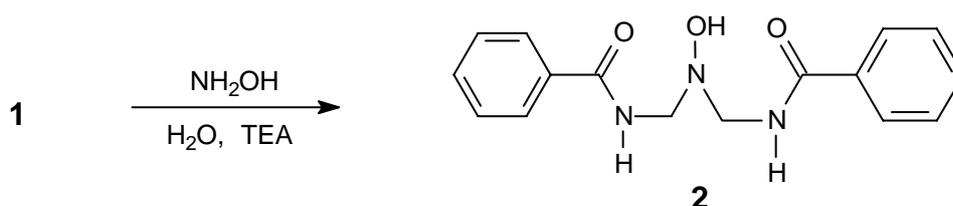
(benzamidomethyl)-triethylammonium chloride (**1**) is an excellent benzamidomethylating agent, both in non-aqueous and in aqueous media (pH > 9) [2,3]. We were especially interested in benzamidomethylation of phenols, thiols, amines and dithiocarbamates in aqueous media using **1**, because of the mild reaction conditions, high yields and simple isolation of products [3]. In the course of this work, we have also carried out reactions of **1** with ammonia obtaining a mixture of di(benzamidomethyl)amine and tri(benzamido-methyl)amine [3]. Our intention was to further explore the reactions of **1** in aqueous media with other inorganic nucleophilic compounds.

**1**

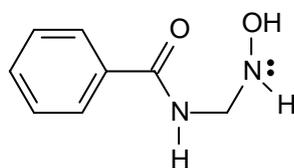
Results and Discussion

The reactions of **1** with aqueous solutions of hydroxylamine always gave *N,N*-di(benzamidomethyl)-hydroxylamine (**2**) as a colorless precipitate, regardless of the mole ratio of reactants and the rate and mode of addition (normal vs. inverse, Scheme 1). Mono(benzamidomethyl)hydroxylamine (**3**) was not obtained even when a two or three-fold excess of hydroxylamine was used. This phenomenon is comparable to our previous finding that primary amines give dibenzamidomethyl derivatives with **1** [3].

Scheme 1.



The probable explanation of this phenomenon is that **3** is indeed formed but is rapidly benzamidomethylated by **1**. Another plausible explanation is that **3**, under the reaction conditions, undergoes self-alkylation to give the observed product, *N,N*-di(benzamidomethyl)hydroxylamine (**2**) (along with hydroxylamine).

**3**

ammonium cations [13]. The physicochemical data and yields for the derivatives **2-5b** are given in Table 1 and the NMR data is given in Table 2.

Table 1. Physicochemical data of compounds **2-5b**.

Compound	Yield %	M.p. °C	Calc./found			FTIR (KBr) / cm ⁻¹			
			C	H	N	νNH ^a	Amide I	Amide II	Other
2	63	140-143	64.2	5.7	14.0	3315	1639	1549	
			64.0	5.9	13.8	3262	1628	1540	
4a	48	62	54.5	4.6	31.8	3299	1645	1528	2125 and 2085 ν(N ₃)
			54.3	4.2	31.6				
4b	73	143-144 ^b	67.5	5.0	17.5	3244	1640	1538	absence of ν(C≡N) bond
			67.7	5.3	17.3				
5a	96	127-128	61.4	7.9	14.3	3229	1671	1545	2039 ν(SCN ⁻)
			61.3	8.2	14.0	3180			
5b	65	165	46.4	6.4	7.7	3207	1678	1523	
			46.1	6.6	7.5	3178			

^aFor compound **2** νNH = (νNH and νOH)

^bRef. [5] = 144 °C; Ref. [6] = 141-143 °C; Ref. [7] = 146-148 °C

As an aside, the water solubility of the (benzamidomethyl)triethylammonium salts is dependant on the counter-ion. For instance, the chloride **1** is the most soluble, the iodide **5b** is partially soluble, and the isothiocyanate **5a** is insoluble in water at room temperature.

The reaction of cyanamide with **1** and the reaction of potassium cyanate with **1** in aqueous solution (pH > 9) gave the same mixture of two products: di(benzamidomethyl)amine (**7**) and tri(benzamidomethyl)amine (**8**) (Scheme 3). These products were previously prepared by a different route and fully characterized in our laboratories [3]. Based on the known chemistry of cyanamide [14], we postulate that di(benzamidomethyl)cyanamide (**6**) is formed first, and is rapidly hydrolyzed under the reaction conditions to give **7**. A portion of **7** reacts with the remaining of **1** to give **8**.

It is known that reactions of electrophiles, such as alkyl halides, with cyanate anion give alkyl isocyanates (R-NCO) almost exclusively [15]. In the case of the reaction between **1** and potassium cyanate the benzamidomethyl isocyanate (**9**) is the most likely intermediate and is hydrolyzed under the reaction conditions to the amine **10** (via the intermediacy of the N-substituted carbamic acid which decomposes to give an amine and carbon dioxide) [15]. The primary amine **10** reacts with the rest of the unreacted **1** to give a mixture of **7** and **8**.

Conclusions

In summary, (benzamidomethyl)triethylammonium chloride (**1**) displays an interesting reactivity in aqueous media (pH>9), depending on the nature of the nucleophiles. With hard nucleophiles it gives

substitution products, some of which, depending on their nature, subsequently hydrolyze. With soft nucleophiles anion exchange takes place.

Scheme 3.

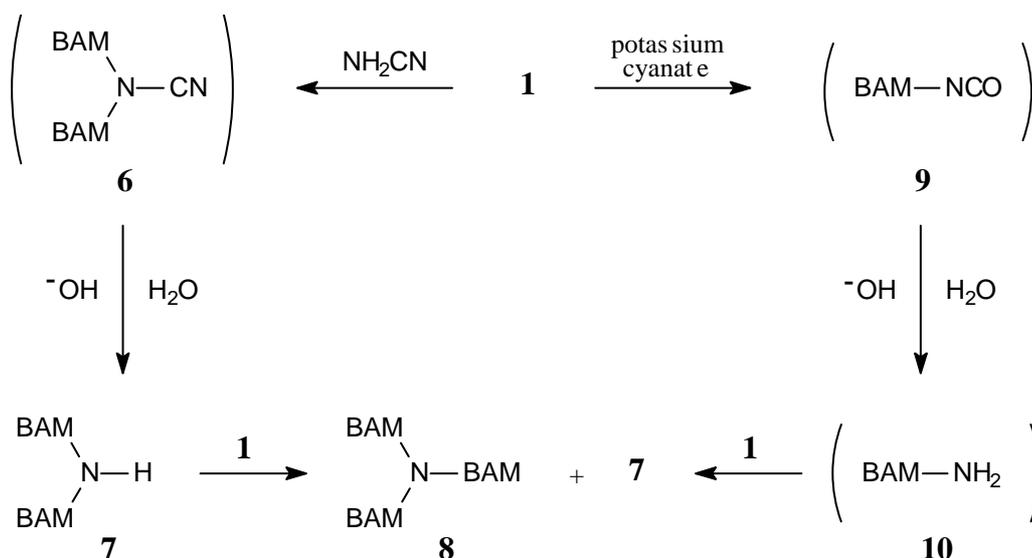


Table 2. NMR data for compounds 2-5b.

Comp.	¹ H-NMR (DMSO- <i>d</i> ₆ ; δ in ppm)				¹³ C-NMR (DMSO- <i>d</i> ₆ ; δ in ppm)
	CONH	Aromatic	NHCH ₂	Other	
2	s(t), 8.87 2H	m, 7.94-7.46 10H	d, 4.32 4H, <i>J</i> 4.2	s, 8.28, 1H <i>OH</i>	166.81 C=O; 60.00 CH ₂ ; Ar: 134.25; 131.34; 128.27; 127.38
4a	t, 9.55 1H, <i>J</i> 6.0	m, 7.91-7.49 5H	d, 4.74 2H, <i>J</i> 6.3	-	167.35 C=O; 55.53 CH ₂ ; Ar: 133.06; 132.14; 128.65; 127.49
4b	t, 8.87 1H, <i>J</i> 4.9	m, 7.90-7.46 5H	d, 4.34 2H, <i>J</i> 5.6	-	166.79 C=O; 117.75 C≡N; 27.85 CH ₂ ; Ar: 132.94; 132.02; 128.59; 127.45
5a	t, 9.40 1H, <i>J</i> 7.0	m, 7.96-7.53 5H	d, 4.74 2H, <i>J</i> 7.2	q, 3.23, 6H, 3 × CH ₂ , <i>J</i> 7.2 t, 1.27, 9H 3 × CH ₃ , <i>J</i> 7.1	168.64 C=O; 129.73 SCN; 59.68 N- CH ₂ -N; 50.10 N-CH ₂ -C; 7.36 CH ₃ Ar: 132.61; 132.52; 128.45; 128.32
5b	t, 9.38 1H, <i>J</i> 7.0	m, 7.96-7.52 5H	d, 4.74 2H, <i>J</i> 7.0	q, 3.23, 6H, 3 × CH ₂ , <i>J</i> 7.0 t, 1.26, 9H 3 × CH ₃ , <i>J</i> 7.0	168.61 C=O; 59.69 N-CH ₂ -N; 50.08 N-CH ₂ -C; 7.39 CH ₃ Ar: 132.62; 132.52; 128.42; 128.14

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Experimental Section

General

Melting points were determined on a Reichert heating plate and were uncorrected. C,H elemental analysis was carried out with Coleman Model 33. N elemental analysis was carried out by the Dumas method. NMR spectra were recorded on a Bruker 400 MHz instrument using DMSO- d_6 as solvent and tetramethylsilane as internal standard. Infrared spectra (KBr pellets) were measured on a Perkin-Elmer System 2000 FT IR. All the reagents and solvents were obtained from commercial sources and were used without further purification. (Benzamidomethyl)triethylammonium chloride (**1**) was obtained as described in our previous work [2].

N,N-Di(benzamidomethyl)hydroxylamine (**2**).

A solution of hydroxylamine hydrochloride (0.289 g; 4.16 mmol) in water (10 mL) was added to a solution of **1** (2.690 g; 9.93 mmol) in water (30 mL). Triethylamine (0.7 mL) was added in one portion and colourless crystals started to form after several seconds. The mixture was stirred for 1 h at room temperature and filtered. Purification was performed by recrystallization from ethanol.

Benzamidomethyl azide (**4a**).

A solution of sodium azide (0.337 g; 5.20 mmol) in water (10 mL) was added to a solution of **1** (1.867 g; 6.70 mmol) in water (10 mL). Several drops of triethylamine were added (pH > 9). The mixture was stirred at room temperature and crystals were obtained after 3 h by cooling in ice bath. The product was filtered off and air-dried to give colorless crystals (from water).

Benzamidomethyl cyanide (**4b**).

A solution of potassium cyanide (0.874 g; 13.43 mmol) in water (20 mL) was added in small portions to a solution of **1** (3.826 g; 13.43 mmol) in water (30 mL). The mixture was stirred for 2-3 h at room temperature. White lumps formed, which were broken up with a glass rod. Colourless crystals were collected by filtration and purification was performed by dissolving the product in dioxane and precipitating with a few drops of cold water.

(*Benzamidomethyl*)triethylammonium thiocyanate (**5a**, colorless crystals from acetone) and *iodide* (**5b**, colorless crystals obtained by washing the precipitate with dioxane, cold water and acetone) were synthesized as described for **4b** and **4a**, respectively.

References and Notes

1. Jones, R. A., *Quaternary Ammonium Salts: Their Use in Phase-Transfer Catalysed Reactions*; Academic Press: San Diego, **2001**; pp. 1-8.
2. Popovski, E.; Klisarova, L.; Vikić-Topić, D. Simple Method for Benzamidomethylation of Phenols in Water Solution. *Synth. Commun.* **1999**, *29*, 3451-3458.
3. Popovski, E.; Klisarova, L.; Vikić-Topić, D. Benzamidomethylation with (Benzamidomethyl)-triethylammonium Chloride. 2. A Simple Method for Benzamidomethylation of Thiols, Amines and Carboxylic acids. *Molecules* **2000**, *5*, 927-936.
4. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C., *Spectrometric Identification of Organic Compounds*. 5th ed.; Wiley: New York, **1991**; p.126.
5. Klages, A. Ueber Das Methylenamino-acetonitril. *Chem Ber* **1903**, *36*, 1506-1512.
6. Martin, A. R.; Ketcham, R. Heterocyclic Ring-Closure Reactions. I. A Novel Oxazole Synthesis from S,S'-Dialkyl or Diaryl Dithiooxaldiimides and Aromatic Aldehydes. *J. Org. Chem.* **1966**, *31*, 3612-3615.
7. Sun, Y. Z.; Martell, A. E.; Welch, M. J. Synthesis of a New Diaminodithiol Bifunctional Chelator for Radiolabeling Biomolecules with Indium(III). *Tetrahedron* **2000**, *56*, 5093-5103.
8. Popovski, E. unpublished results.
9. Loos, R.; Kobayashi, S.; Mayr, H. Ambident Reactivity of the Thiocyanate Anion Revisited: Can the Product Ratio be Explained by the Hard Soft Acid Base Principle? *J. Am. Chem. Soc.* **2003**, *125*, 14126-14132.
10. The IR band (KBr disk) of the SCN anion of tetrabutylammonium thiocyanate is at 2059 cm⁻¹ which is comparable to 2039 cm⁻¹ of **5b**. The ¹³C-NMR chemical shift (CDCl₃) of the SCN anion of tetrabutylammonium thiocyanate is at 129.73 ppm vs. 130.94 ppm for **5b**. The spectral data for tetrabutylammonium thiocyanate were obtained from: SDBS Integrated Spectral Data Base System for Organic Compounds. <http://www.aist.go.jp/RIODB/SDBS>, National Institute of Advanced Industrial Science and Technology, 2/22/2006.
11. Ritchie, C. D. Cation Anion Combination Reactions .23. Solvent Effects on Rates and Equilibria of Reactions. *J. Am. Chem. Soc.* **1983**, *105*, 3573-3578.
12. Pearson, R. G.; Songstad, J. Application of Principle of Hard and Soft Acids and Bases to Organic Chemistry. *J. Am. Chem. Soc.* **1967**, *89*, 1827-1836.
13. Ohtani, N.; Murakawa, S.; Watanabe, K.; Tsuchimoto, D.; Sato, D. Thiocyanation of Alkyl Halides with Alkyl Thiocyanates in the Presence of Quaternary Phosphonium Halides. *J. Chem. Soc.-Perkin Trans. 2* **2000**, 1851-1856.
14. Noller, C. R., *Chemistry of Organic Compounds*. 2nd ed.; Saunders: Philadelphia, **1957**; pp. 320-321.
15. March, J., *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. 4th ed.; Wiley: New York, **1992**; pp. 429, 886.

Sample Availability: Samples of the compounds are available from authors.