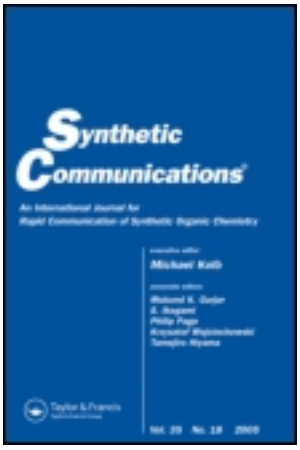

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Satya Venkata [a], Eric Shamo [a] & Vladimir Benin [a]
[a] Department of Chemistry, University of Dayton, Dayton, Ohio, USA
Published online: 19 Mar 2009.

To cite this article: Satya Venkata , Eric Shamo & Vladimir Benin (2009) Preparation and Characterization of Some Substituted Benzyl N-Nitrosocarbamates Containing an N-2-(Methylthio)ethyl or a Bis(2-aminoethyl)sulfide Functionality, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:8, 1406-1414, DOI: 10.1080/00397910802527755

To link to this article: http://dx.doi.org/10.1080/00397910802527755

Synthetic Communications®, 39: 1406–1414, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802527755

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Preparation and Characterization of Some Substituted Benzyl N-Nitrosocarbamates Containing an N-2-(Methylthio)ethyl or a Bis(2-aminoethyl)sulfide Functionality

Satya Venkata, Eric Shamo, and Vladimir Benin
Department of Chemistry, University of Dayton, Dayton, Ohio, USA

Abstract: The synthesis and characterization of some substituted benzyl N-nitrosocarbamates with an N-2-(methylthio)ethyl or a bis(2-aminoethyl)sulfide functionality is reported, as a part of a long-term goal to design and prepare novel photolabile structures that could be used as substances for controlled release of alkylating and/or crosslinking agents. The synthesis was accomplished by reaction of benzyl chloroformates with the corresponding amines, resulting in the preparation of carbamates. The latter were subsequently nitrosated, utilizing two different N-nitrosation methods, to yield the target structures.

Keywords: Carbamates, 2-(methylthio)ethyl group, N-nitrosation, N-nitrosocarbamates

INTRODUCTION

In recent years, a considerable amount of effort in drug design has been focused on the development of drugs that are supposed to release their active species in the desired locality and/or conditions and also on identifying structures with photosensitive groups that would cleave upon irradiation with near ultraviolet (UV) or visible light, yielding active intermediates for biological applications.[1] First reported by Barltrop and Schofield in

Received August 21, 2008.
Address correspondence to Vladimir Benin, Department of Chemistry, University of Dayton, 300 College Park, Dayton, OH 45469-2357, USA. E-mail: vladimir.benin@notes.udayton.edu

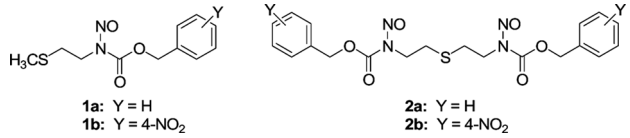


Figure 1. Target structures containing the N-2-(methylthio)ethyl (**1**) or the bis(2-aminoethyl)sulfide (**2**) functionality.

1962.[2] photolabile protecting groups have found numerous applications in biology in the past decade.[3,4] The protecting groups (also known as "caging" groups) can render a bioactive compound inert until they are removed by photolysis, thus releasing the compound rapidly. Some examples of commonly used photolabile caging groups include the o-nitrobenzyl,[5] desyl,[6] and 2-methoxy-5-nitrophenyl (MNP).[7] However, the commonly employed 2-nitrobenzyl photosensitive protecting group has found limited use in compounds destined for biochemical systems, because of the release of a toxic by-product: 2-nitrobenzaldehyde.[8,9]

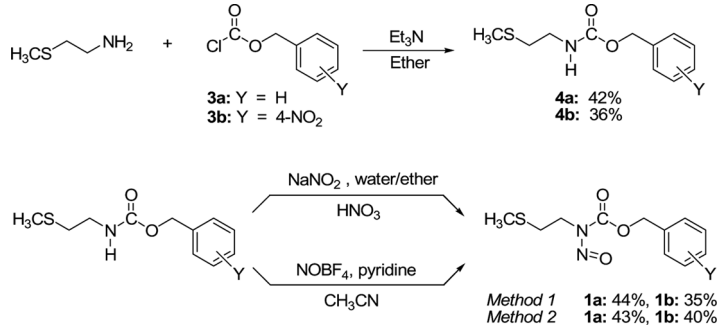
Zimmerman first demonstrated the efficient photosolvolysis of benzyl acetate in 50% aqueous dioxane.[10] His studies showed that the process occurred in a homolytic fashion and led to radical-derived products: 4,4′-dimethoxybibenzyl and 4-methoxybenzyldioxane. However, a more recent study of Ruane et al. on the photocleavage of substituted benzyl diazeniumdiolates demonstrated that the nature of the cleavage process depended on the pattern of substitution in the benzylic group.[11] It was found that compounds with π-donor substituent groups at the 3- and 5-positions of the benzene ring tended to decompose via heterolytic, rather than homolytic bond cleavage, and generate resonance-stabilized (in the excited state) benzylic carbocations.

Based on the demonstrated potential of substituted benzylic moieties as photolabile protecting groups, we endeavored to design and prepare several substituted benzyl N-nitrosocarbamates, with the longer-term goal of developing a new class of anticancer agents, capable of releasing the active substance photolytically, in controlled conditions. In the current report, we describe the synthesis and characterization of two sets of structures containing the N-2-(methylthio)ethyl (**1**) or the bis(2-aminoethyl)sulfide (**2**) functionality (Fig. 1).

RESULTS AND DISCUSSION

Preparation of Benzyl N-2-(Methylthio)ethyl-N-nitrosocarbamates (1)

The preparation of these structures was carried out via the corresponding carbamates, as reflected in Scheme 1. 2-(Methylthio)ethylamine,



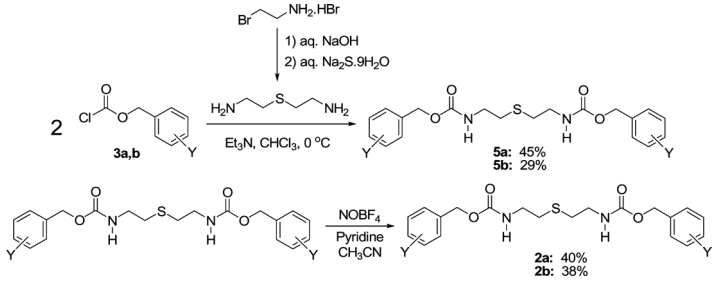
Scheme 1. Preparation of benzyl N-2-(methylthio)ethyl-N-nitrosocarbamates.

prepared according to the protocol of Clarck and McAlees,[12] was reacted with the corresponding benzyl chloroformate in the presence of an equivalent amount of triethylamine in ether, following the procedure of Sato et al.[13] The reaction led to the generation of the carbamate, **4a** or **4b**, in moderate yield. The resultant carbamate structures were further nitrosated to yield the N-nitrosocarbamates **1a,b**. We did not expect the presence of a sulfide group to pose problems in the nitrosation step, as there are no known examples of S-nitrosation of sulfides that yield stable S-nitroso products.[14] Our density functional theory (DFT) calculations ($B3LYP/6\text{–}31 + G(d)$) could not locate an energy minimum for an S-nitrosocarbamate derivative, but a structure was identified that corresponds to the intermediate for an S- to N-nitroso rearrangement. Such S- to N-nitroso rearrangements have also been suggested to occur both inter- and intramolecularly in other reactions, such as the N-nitrosation of dimethylsulfide[15] or the de-amination of methionine and S-methyl cysteine.[16]

The N-nitrosation was achieved by following one of two different methods: Method 1 (aqueous method)[17] involved a two-phase (water–ether) system, with the nitrosating agent, ^{+}NO, generated in the aqueous layer, upon reaction of $NaNO_2$ with HNO_3. Method 2 (anhydrous method)[18] involved the use of nitrosonium tetrafluoroborate ($NOBF_4$) as a nitrosating agent in the presence of a pyridine base, in anhydrous acetonitrile.

Preparation of Bis[(N-benzyloxycarbonyl-N-nitroso)aminoethyl]-sulfides (2)

The preparation of these structures was conducted in accordance with the synthetic sequence reflected in Scheme 2. Bis(2-aminoethyl)sulfide, prepared from the hydrobromide salt of 2-bromoethylamine,[19] was reacted with a benzyl chloroformate (**3a,b**) to generate the



Scheme 2. Preparation of bis[(N-benzyloxycarbonyl-N-nitroso)aminoethyl]-sulfides.

corresponding carbamate (**5a,b**). The carbamates were subsequently nitrosated, using the anhydrous method (method 2), to yield the target structures **2a,b**.

CONCLUSIONS

In the current report, we have described in detail the preparation and characterization of two sets of structures, which could be classified as N-nitrosocarbamates or bis(N-nitrosocarbamates). All compounds have been designed to contain either an N-2-(methylthio)ethyl or a bis(2-aminoethyl)sulfide functionality. The target structures were prepared via the corresponding carbamates or bis(carbamates) as precursors and subsequent N-nitrosation, following an aqueous or anhydrous method.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra of all compounds have been recorded at 300 MHz and 75 MHz respectively and referenced to the solvent ($CDCl_3$: 7.27 ppm and 77.0 ppm; acetonitrile-d_3: 1.93 ppm and 118.6 ppm). Elemental analysis was provided by Atlantic Microlab, Norcross, GA. High-resolution mass spectrometry (HRMS) data was provided by the Mass Spectrometry and Proteomics facility at the Ohio State University. Carbamates **4a** and **4b** are known compounds.[13,20,21] Nevertheless, their syntheses, based on the slightly modified protocol of Sato et al.,[13] are reported here to make available additional NMR data. 2-(Methylthio)-ethylamine and bis(2-aminoethyl)sulfide were prepared following published literature procedures. Benzyl chloroformate and 4-nitrobenzyl chloroformate were purchased from Acros Organics. Nitrosonium tetrafluoroborate was purchased from Fluka.

General Procedure for the Preparation of Benzyl N-2-(Methylthio)ethylcarbamates (4a,b)[13]

A solution of 2-(methylthio)ethylamine (2.90 g, 31.83 mmol) in ether (20 mL) was stirred for 5 min followed by addition of methylene chloride (5 mL). Triethylamine (3.22 g, 31.83 mmol, 4.43 mL) was added, and the solution was stirred for 10 min at 0 °C under nitrogen. Benzyl chloroformate (**3a**, 0.54 g, 3.18 mmol, 0.45 mL) or 4-nitrobenzyl chloroformate (**3b**, 0.68 g, 3.18 mmol) in ether (10 mL) was added dropwise to the mixture for about 30 min. The mixture was stirred 24 h at ambient temperature and vacuum filtered, and the solvent evaporated under reduced pressure. The residue was further separated, and the product was purified by column chromatography on silica gel.

Benzyl N-2-(Methylthio)ethylcarbamates (**4a**)

Isolated by separation of the crude reaction mixture on a silica-gel column (hexane–methylene chloride = 1:1, followed by pure methylene chloride). Yield: 0.28 g (42%) of colorless oily liquid. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.62 (t, $J = 6.3$ Hz, 2H), 3.38 (m, 2H), 5.15(s, 2H), 5.28 (broad s, 1H) 7.30–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 15.3, 30.4, 39.4, 69.8, 128.5, 128.7, 128.9, 134.4, 153.7. HRMS (FAB$^+$) m/z calcd. for $C_{11}H_{15}NO_2S$ $[M + Na]^+$ 248.0721; found 248.0721.

4-Nitrobenzyl N-2-(Methylthio)ethylcarbamate (**4b**)

Isolated by separation of the crude reaction mixture on a silica-gel column (hexane–ethyl acetate = 2:1). Yield: 0.30 g (36%) of bright yellow solid: Mp 61–63 °C (lit.[13] 63–64 °C). ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.68 (t, $J = 6.3$ Hz, 2H), 3.42–3.44 (t, $J = 6.3$ Hz, 2H), 5.18 (s, 2H), 5.21 (broad s, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 8.24 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (CD_3CN) δ 15.5, 34.7, 41.0, 65.9, 124.9, 129.2, 146.4, 148.8, 157.3. Anal. calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 49.07; H, 5.31; N, 10.19.

General Procedure for the Preparation of Benzyl N-2-(Methylthio)-ethyl-N-nitrosocarbamates (1a,b)

Method 1 (Aqueous Method)

A mixture of sodium nitrite (1.37 g, 19.92 mmol) in water (4 mL) was added to a solution of benzyl N-2-(methylthio)ethylcarbamate (**4a**,

0.50 g, 2.22 mmol) or 4-nitrobenzyl N-2-(methylthio)ethylcarbamate (**4b**, 0.60 g, 2.22 mmol) in ether (4 mL). Without stirring or cooling, nitric acid (2.66 mL, 35% aq. sol.) was added directly to the lower layer over 1 h via syringe. Then 8 mL of water and 8 mL of ether were added, the organic layer was separated and dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield the corresponding benzyl N-2-(methylthio)ethyl N-nitrosocarbamate (**1a,b**). Further purification was achieved by column chromatography on silica gel.

Method 2 (Anhydrous Method)

Solid nitrosonium tetrafluoroborate ($NOBF_4$) (0.82 g, 7.09 mmol) was added in one portion to a stirred solution of anhydrous pyridine (0.56 g, 7.09 mmol, 0.57 mL) and benzyl N-2-(methylthio)ethylcarbamate (**4a**, 1.00 g, 4.73 mmol) or 4-nitrobenzyl N-2-(methylthio)ethylcarbamate (**4b**, 1.28 g, 4.73 mmol), in anhydrous acetonitrile (10 mL) at $-20\,^{\circ}C$. The mixture was stirred at $0\,^{\circ}C$ under nitrogen for 2 h, and the progress of the reaction was monitored by thin-layer chromatography (TLC, hexane–methylene chloride = 1:1). The product exhibited a rapidly moving yellow spot. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel of the crude reaction mixture.

Benzyl N-2-(Methylthio)ethyl-N-nitrosocarbamate (**1a**)

Purified by separation of the crude reaction mixture on a silica-gel column (hexane–methylene chloride = 1:1). Yields: 44% (method 1) and 43% (method 2) of light yellow liquid. ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.46 (t, $J = 6.3$ Hz, 2H), 3.95 (m, 2H), 5.52 (s, 2H), 7.35–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 15.3, 30.4, 39.4, 69.8, 128.5, 128.7, 128.9, 134.4, 153.7. HRMS (FAB^+) m/z calcd. for $C_{11}H_{14}N_2O_3S$ $[M + Na]^+$ 277.0623; found 277.0628.

4-Nitrobenzyl N-2-(Methylthio)ethyl-N-nitrosocarbamate (**1b**)

Purified by separation of the crude reaction mixture on a silica-gel column (hexane–ethyl acetate = 1:2). Yields: 35% (method 1) and 38% (method 2) of light yellow liquid. ^1H NMR (CD_3CN) δ 2.11 (s, 3H), 2.51 (t, $J = 6.3$ Hz, Hz, 2H), 3.95 (t, $J = 6.3$ Hz, 2H), 5.61 (s, 2H), 7.67 (d, $J = 8.7$ Hz, 2H), 8.29 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (CD_3CN) δ 15.6, 31.3, 40.9, 69.3, 125.0, 130.1, 143.8, 149.3, 154.8. Anal. calcd. for $C_{11}H_{13}N_3O_5S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 49.07; H, 5.31; N, 10.19.

General Procedure for the Preparation of Bis[2-(benzyloxy-carbonylamino) Ethyl]sulfides (5a,b)

A solution of bis(2-aminoethyl)sulfide (0.50 g, 4.16 mmol) in chloroform (20 mL) was stirred for 5 min, followed by addition of triethylamine (0.84 g, 8.33 mmol, 1.16 mL). The resultant mixture was stirred for 10 min at 0 °C, and then a solution of benzyl chloroformate (**3a**, 1.42 g, 8.33 mmol, 1.18 mL) or 4-nitrobenzyl chloroformate (**3b**, 1.79 g, 8.33 mmol) in chloroform (10 mL for **3a** or 20 mL for **3b**) was added dropwise under nitrogen for about 30 min. The mixture was stirred for 24 h at ambient temperature and vacuum filtered, and the solvent was removed under reduced pressure. The crude product was further purified via recrystallization from toluene.

Bis[2-(benzyloxycarbonylamino)ethyl]sulfide (**5a**)

Recrystallization from toluene yielded 0.73 g (45%) of white solid: mp 93–95 °C. ^{1}H NMR (CD_3CN) δ 2.61 (t, $J = 6.3$ Hz, 4H), 3.25 (q, $J = 6.3$ Hz, 4H), 5.04 (s, 4H), 5.81 (broad s, 2H), 7.28–7.36 (m, 10H). ^{13}C NMR (CD_3CN) δ 32.5, 41.6, 67.2, 129.0, 129.2, 129.8, 138.7, 157.7. Anal. calcd. for $C_{20}H_{24}N_2O_4S$: C, 61.83; H, 6.23; N, 7.21. Found: C, 61.73; H, 6.25; N, 7.33.

Bis[2-(4-nitrobenzyloxycarbonylamino)ethyl]sulfide (**5b**)

The crude reaction product was purified on a short silica-gel column (ethyl acetate–hexane = 2:1), followed by recrystallization from toluene to yield 0.58 g (29%) of light yellow solid: mp 108–111 °C. ^{1}H NMR (CD_3CN) δ 2.63 (t, $J = 6.3$ Hz, 4H), 3.29 (m, 4H), 5.16 (s, 4H), 5.94 (broad s, 2H), 7.54 (d, $J = 8.7$ Hz, 4H), 8.17 (d, $J = 8.7$ Hz, 4H). ^{13}C NMR (CD_3CN) δ 32.6, 41.6, 65.9, 124.9, 129.2, 146.6, 148.8, 157.4. Anal. calcd. for $C_{20}H_{22}N_4O_8S$: C, 50.20; H, 4.63; N, 11.71. Found: C, 49.62; H, 4.73; N, 11.38.

General Procedure for the Preparation of Bis[2-(benzyloxycarbonyl-N-nitrosoamino)ethyl]sulfides (2a,b)

Solid $NOBF_4$ (0.44 g, 3.84 mmol) was added in one portion to a stirred solution of anhydrous pyridine (0.30 g, 3.84 mmol, 0.31 mL) and bis[2-(benzyloxycarbonylamino)ethyl]sulfide (**5a**, 0.50 g, 1.28 mmol) or bis[2-(benzyloxycarbonyl amino)ethyl]sulfide (**5b**, 0.62 g, 1.28 mmol) in

anhydrous acetonitrile (10 mL) at –20 °C. The mixture was stirred at 0 °C under nitrogen for 4 h, and the progress of the reaction was monitored by TLC (hexane–ethyl acetate = 2:1). The product exhibited a rapidly moving yellow spot. The solvent was removed under reduced pressure, and the crude product in either case was further purified by column chromatography on silica gel (hexane–ethyl acetate = 2:1).

Bis[2-(benzyloxycarbonyl-N-nitrosoamino)ethyl]sulfide (**2a**)

Yield: 0.23 g (40%) of light yellow liquid. ^{1}H NMR (CD_3CN) δ 2.48 (t, $J = 6.3$ Hz, 4H), 3.85 (t, $J = 6.3$ Hz, 4H), 5.47 (s, 2H), 7.38–7.47 (m, 10H). ^{13}C NMR (CD_3CN) δ 28.8, 40.9, 70.9, 129.9, 130.0, 130.1, 136.4, 154.8. Anal. calcd. for $C_{20}H_{22}N_4O_6S$: C, 53.80; H, 4.97; N, 12.55. Found: C, 53.94; H, 5.08; N, 12.42.

Bis[2-(4-nitrobenzyloxycarbonyl-N-nitrosoamino)ethyl]sulfide **(2b)**

Yield: 0.27 g (38%) of light yellow liquid. ^{1}H NMR (CD_3CN) δ 2.51 (t, $J = 6.3$ Hz, 4H), 3.88 (t, $J = 6.3$ Hz, 4H), 5.57 (s, 4H), 7.65 (d, $J = 8.7$ Hz, 4H), 8.20 (d, $J = 8.7$ Hz, 4H). ^{13}C NMR (CD_3CN) δ 28.9, 40.9, 69.3, 125.0, 130.0, 143.7, 149.2, 154.7. HRMS (FAB^+) m/z calcd. for $C_{20}H_{20}N_6O_{10}S$ $[M + Na]^+$ 559.0859; found 559.0856.

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