Reactions of 4-Substituted 1,1-Dimethylsemicarbazides and -thiosemicarbazides with Ethyl Bromoacetate

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Introduction

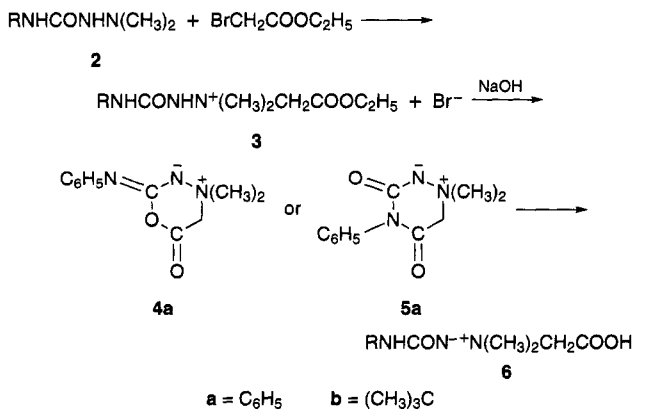
Aminimides **1** are inner salts in which a quaternary, positively charged nitrogen is bonded to a divalent, negatively charged nitrogen. The preparation and reactions of aminimides have been reviewed,[1,2] and an important method of preparation of these compounds is by the reaction of alkylating agents on acyl hydrazides.

$$RCONHNH_2 + RX \rightarrow RCONH^+NR_3\ X^- \xrightarrow{OH^-} \underset{\mathbf{1}}{RCON^{-+}NR_3}$$

In preparing aminimides methyl iodide, allyl bromide, and benzyl bromide have been reported as alkylating agents for formation of the quaternary hydrazonium salts. This work was undertaken to use ethyl bromoacetate as the alkylating agent so as to form glycine derivatives. We speculated that if the aminimide and the ester group were located within the same molecule, a reaction might occur between these two groups. This would demonstrate the reactivity of the aminimide group with the ester. Furthermore, the reactions might occur with formation of novel heterocyclic compounds. The reaction of ethyl bromoacetate with the related thiosemicarbazide was also studied.

Results and Discussion

Treatment of 1,1-dimethyl-4-phenylsemicarbazide and 1,1-dimethyl-4-*tert*-butylsemicarbazide, **2a** and **2b**, with ethyl bromoacetate afforded good yields of the hydrazonium bromides **3a** and **3b**. Aqueous solutions of **3a** and



3b were neutralized with sodium hydroxide which was added until a phenolphthalein end point was reached. This treatment resulted in loss of the ethyl group of the ester. Such rapid saponification of the ester group has been observed[3,4] and suggests an expected neighboring group interaction of the inner salt zwitterion and the ester group.

A moderately stable intermediate anhydro product was isolated from neutralization of **3a**. Structure **4a** or **5a** is suggested for this intermediate based on the following spectroscopic data.[5] The IR spectrum shows the expected coupled C=O and C=N or C=O peaks at 1695 and 1621 cm^{-1}. The ^1H NMR spectrum is as expected with peaks for the *N,N*-dimethyl group at δ 3.28, the methylene group at δ 4.12, and the phenyl at δ 7.17–7.46. Also, the ^{13}C NMR spectrum showed the C=N or C=O peaks at δ 168 and 161. No molecular ion was detected from the mass spectrum. The combustion analysis indicated the expected formula, $C_{11}H_{13}N_3O_2$. Repeated recrystallization of this intermediate resulted in hydrolysis of this intermediate to give **6a**.

Structures **6a** and **6b** were the final products of neutralization of **3a** and **3b**. The IR spectrum of **6a** showed stretching frequencies C=O for COOH at 1709 cm^{-1} and for urea C=O at 1633 cm^{-1}. The ^1H NMR showed peaks at δ 3.07 for the *N,N*-dimethyl group, δ 4.13 for the methylene protons, and δ 6.88–7.22 for the aromatic protons. The ^{13}C NMR showed peaks at δ 160 for C=O and δ 168 for carboxylic C=O carbon. The microanalysis indicated the formula as $C_{11}H_{15}N_3O_3$.

Compound **6b** was isolated directly from neutralization of **3b**. The IR spectrum of **6b** showed peaks at 1715 and 1655 cm^{-1} attributed to the COOH and urea C=O groups, respectively. The ^1H NMR spectrum had to be run using D_2O as the solvent since **6b** was not soluble in either acetonitrile or dimethyl sulfoxide. The spectrum showed the expected peaks for the *N,N*-dimethyl, the methylene, and the *tert*-butyl groups. In addition, a two-proton signal at δ 4.43 ppm was attributed to HDO and to the exchange of the COOH and NH protons. The ^{13}C NMR spectrum agreed with structure **6b** with the urea and acid C=O groups at δ 158.5 and δ 171, respectively. The expected analysis for $C_9H_{19}N_3O_3$ was obtained.

For comparison, the reaction of 1,1-dimethyl-4-phenylthiosemicarbazide (**7**) with ethyl bromoacetate was carried out. This reaction resulted in the formation of a solid product which contained bromine and the methylene and carbonyl groups of ethyl bromoacetate but which had lost the ethyl group. The structure of the product was determined by X-ray crystallography[6] to be the thiazole derivative **8**.

During our initial effort to purify this compound column chromatography on silica gel was used, and this treatment removes hydrogen bromide from **8**. Changes in the IR and proton NMR are as follows. For **8** the C=O

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(3) Bender, M. L. *J. Am. Chem. Soc.* **1957**, *79*, 1258.
(4) Ingraham, L. L. *Biochemical Mechanisms*; John Wiley and Sons, Inc.: New York, 1962; pp 35–48.
(5) Suitable crystals for X-ray crystallographic analysis could not be obtained for this compound.
(6) Unit cell data for compound **8** are as follows: orthorhombic space group *Pbca*, a = 8.801(2) Å, b = 11.919(2) Å, c = 27.192(10) Å, V = 2852.4(10) Å^3, Z = 8. Final least-squares refinement [on F^2 with $I > 2\sigma(I)$] gave $R1$ and wR values of 0.0432 and 0.1161, respectively, with a goodness of fit of 0.806. The author has deposited atomic coordinates for **8** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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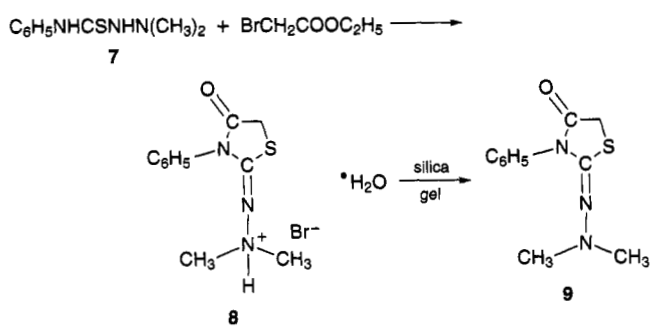

and C=N peaks are at 1730 and 1570 while peaks at 1728 and 1610 are observed in the product. The proton NMR of **8** shows δ 3.06 (6H, s) and 4.20 (2H, s) while the product shows δ 2.45 (6H, s) and 3.80 (2H, s). Because these shifts are as expected 2-(dimethylhydrazono)-3-phenylthiazol-4-one is proposed for the structure of **9**.

Unlike the semicarbazides the reaction of the thiosemicarbazides occurred with alkylation on the more nucleophilic sulfur. A ring closure involving the saponification of the ester resulted in formation of a five-membered ring system.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained in the indicated solvent from either an IBM NR/200 FT NMR or an IBM NR/300 FT NMR spectrometer; reported chemical shifts are in ppm (δ) relative to either $CHCl_3$ (δ 7.24), TMS (δ 0.00), or DSS (δ 0.00). Infrared spectra were recorded on a Digilab Qualimatic FTIR instrument using NaCl plates. MS measurements were made with a VG 7070HS mass spectrometer. Melting points were determined by using a Thomas-Hoover apparatus and were corrected. Elemental analyses were carried out by Desert Analytics, Tucson, AZ.

Materials. Unless indicated otherwise, reagents were purchased from Aldrich Chemical Co., Inc., Milwaukee, WI. Solvents were glass distilled and were obtained from either Burdick and Jackson Laboratories, Inc., Muskegon, MI, or from EM Science, Cherry Hill, NJ.

1-(2-Ethoxy-2-oxoethyl)-1,1-dimethyl-2-[(phenylamino)carbonyl]hydrazinium Bromide (3a). A 250-mL round-bottomed flask was charged with 5 g (27.89 mmol) of 1,1-dimethyl-4-phenylsemicarbazide, **2a**,[7] dissolved in methylene chloride (50 mL). A solution of 3.36 mL (30.26 mmol) of ethyl bromoacetate in 50 mL of methylene chloride was added slowly via addition funnel, and the mixture was refluxed for 72 h. Removal of the solvent using a rotary evaporator left the crude product as an oily liquid. After 5 min the product solidified and was purified by column chromatography on silica gel. Unreacted starting material was eluted with ethyl acetate while the product was eluted with 10:1 acetone–methanol mixture (6.89 g, 85%): mp 141–142 °C; IR (Nujol) 3228, 1729, 1716, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7 Hz), 3.96 (s, 6H), 4.30 (q, 2H, J = 7 Hz), 5.02 (s, 2H), 7.06 (s, 1H), 7.27–7.44 (m, 5H), 8.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.50, 56.50, 63.90, 65.75, 119.82, 125.00, 128.97, 137.25, 153.15, 163.50; MS (EI, 70 eV) *m/z* (relative intensity) (no molecular ion peak detected) 251 (6.47), 178 (24.67), 136 (58.71), 116 (24.29), 93 (28.54), 77 (24.68), 59 (100). Anal. Calcd for $C_{13}H_{20}N_3O_3Br$: C, 45.09; H, 5.82; N, 12.13. Found: C, 45.26; H, 5.74; N, 12.01.

1-(2-Ethoxy-2-oxoethyl)-1,1-dimethyl-2-[(*tert*-butylamino)carbonyl]hydrazinium Bromide (3b). A 250-mL round-bottomed flask was charged with 5 g (31.37 mmol) of 1,1-dimethyl-4-*tert*-butylsemicarbazide[8] dissolved in 50 mL of methylene chloride. Then a solution of 3.48 mL (31.37 mmol) of ethyl bromoacetate in 50 mL of methylene chloride was added slowly using a pressure-equalizing addition funnel. The mixture was refluxed for 72 h. During the stirring a white precipitate formed from the clear reaction mixture. When the solvent was removed using a rotary evaporator, a white solid remained. This product was purified by recrystallization with an acetone–methanol (10:1) mixture: 9.84 g (96%); mp 146–147 °C; IR (Nujol) 3222, 1751, 1707, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 12H), 3.85 (s, 6H), 4.20 (q, 2H, J = 6 Hz), 4.97 (s, 2H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.90, 28.73, 52.50, 56.75, 63.75, 66.00, 154.80, 163.53; MS (CI) *m/z* (relative intensity) 246 (M^+, 2.86), 230 (2.66), 204 (2.54), 173 (53.12), 149 (12.62), 132 (100.00), 115 (100.00), 99 (87.21), 84 (27.12), 72 (100.00), 61 (100.00). Anal. Calcd for $C_{11}H_{24}N_3O_3Br$: C, 40.48; H, 7.42; N, 12.88. Found: C, 40.60; H, 7.56; N, 12.92.

Intermediate from the Neutralization of 3a. In a 50-mL round-bottomed flask was placed a solution of **3a** (1.03 g, 2.97 mmol) in 25 mL of water, and a few drops of phenolphthalein were added as an indicator. Then sodium hydroxide solution was added drop by drop until a light pink-colored end point was observed. The solvent was removed using a rotary evaporator. The product was purified by recrystallization using ethanol as a solvent, and 0.16 g (25%) of white crystals was obtained: mp 213–213.5 °C; IR (Nujol) 1695, 1621 cm^{-1}; ^{1}H NMR (CD_3CN) δ 3.28 (s, 6H), 4.12 (s, 2H), 7.17–7.46 (m, 5H) ppm; ^{13}C NMR (D_2O) δ 57.05, 59.43, 130.99, 132.12, 132.43, 135.50, 161, 168; MS (CI) *m/z* (relative intensity) (no molecular ion detected) 239 (13.26), 233 (0.78), 220 (10.40), 213 (10.96), 205 (5.71), 191 (16.80), 177 (35.11), 165 (10.67), 149 (8.20), 142 (15.36), 137 (11.52). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.25; H, 5.97; N, 19.17. Found: C, 59.44; H, 5.86; N, 18.95.

1-(2-Hydroxy-2-oxoethyl)-1,1-dimethyl-2-[(phenylamino)carbonyl]hydrazinium Inner Salt (6a). Obtained by recrystallization of the intermediate from neutralization of **3a**: IR (Nujol) 3266, 1709, 1632, cm^{-1}; ^{1}H NMR (CD_3CN) δ 3.07 (s, 6H), 4.13 (s, 2H), 6.88–7.22 (m, 5H); ^{13}C NMR (D_2O) δ 30.60, 54.50, 58.19, 69.75, 158.5, 171.25. Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.66; H, 6.37; N, 17.71.

1(2-Hydroxy-2-oxoethyl)-1,1-dimethyl-2-[*tert*-butylamino)carbonyl]hydrazinium Inner Salt (6b). Compound **3b**, 3.70 g (11.33 mmol), dissolved in 50 mL of water was placed in a 100-mL round-bottomed flask with a few drops of phenolphthalein as an indicator. Then sodium hydroxide solution was added drop by drop until a light pink-colored end point was observed. When the water was removed using a rotary evaporator, a gummy cream-colored product remained, which solidified after 1 week. The product was purified by recrystallization with a methylene chloride and methanol mixture (10:1) and obtained as colorless crystals (1.85 g, 82%); mp 194–194.5 °C; IR (Nujol) 3261, 1715, 1655 cm^{-1}; ^{1}H NMR (D_2O) δ 0.91 (s, 9H), 3.25 (s, 6H), 3.96 (s, 2H), 4.43 (s, 2H); ^{13}C NMR (D_2O) δ 30.60, 54.50, 58.19, 69.75, 158.5 (C=N), 171.25 (C=O); MS (CI) *m/z* (relative intensity) (no molecular ion detected) 142 (3.57), 120 (0.68), 100 (1.10), 84 (39.06), 73 (10.33), 58 (100.00). Anal. Calcd for $C_9H_{19}N_3O_3$: C, 49.74; H, 8.81; N, 19.34. Found: C, 49.69; H, 9.01; N, 19.24.

2-(Dimethylhydrazono)-3-phenylthiazol-4-one Hydrobromide (8). A solution of 1,1-dimethyl-4-phenylthiosemicarbazide (**7**),[9] 5.00 g (25.60 mmol), in 100 mL of dichloromethane was placed in a 250-mL flask. Then ethyl bromoacetate (2.839 g, 25.60 mmol) was added drop by drop via syringe. The solution was refluxed for 1 week, and a precipitate formed during the reflux period. Upon removal of the solvent a white solid was obtained. Crystals that were suitable for X-ray crystallographic analysis were obtained by recrystallization from an acetone–methanol (10:1) mixture: IR (KBr) 1730, 1570 cm^{-1}; ^{1}H NMR δ 3.06 (6H, s), 4.20 (2H, s), 7.26–7.50 (5H, m).

2-(Dimethylhydrazono)-3-phenylthiazol-4-one (9). This product was obtained by column chromatography (silica gel, ethyl acetate) of **8** and was recrystallized from an acetone–methanol (10:1) mixture solvent (4.6970 g, 78%): mp 179–180 °C; IR (Nujol) 1728, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 3.80 (s, 2H), 7.26–7.50 (5H, m); ^{13}C NMR ($CDCl_3$) δ 33.15, 47.19, 127.55, 128.75, 129.21, 136.20, 172.95, 209.50; MS (EI, 70 eV) *m/z* (relative intensity) 235 (M^+, 100), 178 (66.31), 135 (8.23), 118 (33.10), 104 (28.93), 91 (15.97), 77 (58,01), 65 (9.74), 58 (27.03). Anal. Calcd for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.57; N, 17.86. Found: C, 56.13; H, 5.59; N, 17.84.

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