Reductive Opening of the Thiazolidine Ring. Selective *N*-Methylation of Cysteamines

Carlo Melchiorre*, Dario Giardinà and Piero Angeli

Institute of Organic and Pharmaceutical Chemistry, University of Camerino, 62032 Camerino (MC), Italy

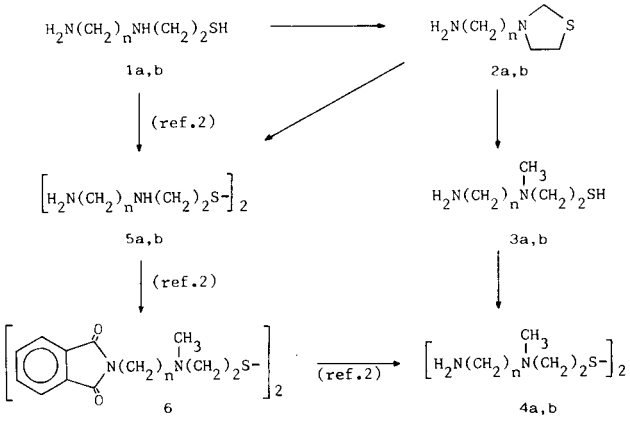
Received March 24, 1980

The reaction of thiazolidines **2** and **7** with borane was investigated. It gave *N*-methylcysteamines **3** and **8** through thiazolidine ring opening. Sodium borohydride and lithium aluminum hydride were ineffective.

J. Heterocyclic Chem., **17**, 1215 (1980).

In the course of the research on structure-activity relationships of tetramine disulfides, a new class of irreversible and selective blocking agents for the adrenergic α-receptor (1), it became of interest to us to synthesize few *N*-substituted derivatives of this class of compounds in order to provide some information on the topography of the receptor through the substituents effects. In a previous paper (2) we reported the synthesis of the *N,N'*-dimethyl derivatives **4** through the protection of primary amine functions followed by the methylation with formaldehyde-formic acid (**6**). This synthetic scheme was time consuming (column chromatography) and afforded the desired compounds in poor yields. We wish to report here a new method for the selective *N*-methylation of the inner nitrogens of some *N*-(ω-alkylamine)cysteamines through opening of the thiazolidine ring by borane.

Scheme 1



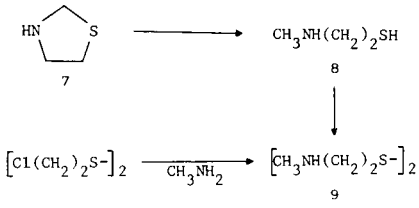
a, n = 6

b, n = 8

It is known that thiazolidine ring may act as an effective protecting group for both amine and thiol functionalities of cysteamine or cysteine (3). Opening of the thiazolidine ring may be easily accomplished in different ways with agents such as acids or oxidizing agents (3-5). We have found that the thiazolidine ring may be opened by borane giving *N*-methylation as shown in Schemes 1 and 2.

N-(ω-alkylamine)thiazolidines **2** were easily synthesized starting from the diaminothiols **1** (2). Oxidation with iodine-iodide of **2** gave the disulfides **5** which were identical to those obtained from **1** (2). On the contrary, the reaction of thiazolidines **2** with borane resulted in the selective *N*-methylation affording the diaminothiols **3**, which in turn were oxidized to the corresponding disulfides **4**. The structure of the cleavage product was proved to be identical with the product **4** obtained with a different synthetic route (Scheme 1).

Scheme 2



In order to study the effect of the *N*-alkyl substituent on the reactivity, the thiazolidine itself **7** (5) was allowed to react with borane. Again a complete cleavage of the ring occurred affording *N*-methylcysteamine (**8**) which was oxidized to *N,N'*-dimethylcystamine (**9**), identical to that obtained by another way (Scheme 2) and to that reported in the literature (6). Lithium aluminum hydride was reported to produce the cleavage of 2-phenyl-3-*n*-butyl-4-thiazolidinone affording *N*-benzyl-*N*-*n*-butylcysteamine with a complete opening of the thiazolidine ring (7). Following the procedure reported, we tested the efficacy of lithium aluminum hydride on substituted and unsubstituted thiazolidines, **2** and **7**, respectively. We found that lithium aluminum hydride was ineffective on **7** while in the reaction with **2** it afforded, after oxidation of the intermediate thiols **3**, *N*-methyl disulfides **4** in very poor yields (< 10%). In order to generalize the reductive opening of thiazolidine ring we allowed to react thiazolidines **2** and **7** with sodium borohydride, which turned out to be completely ineffective in alcoholic solution. In the light of these results it can be concluded that the reduction of thiazolidines can be accomplished with satisfactory yields with borane but not with lithium aluminum hydride in ether solution or sodium borohydride. Thus, reduction of thiazolidines with borane may provide a useful method for the selective *N*-methylation of cysteamines and hence a synthetic route to afford *N,N'*-dimethylcystamines.

0022-152X/80/061215-02$02.25

EXPERIMENTAL

Melting points were taken in sealed capillaries on a Büchi SMP-20 apparatus and are uncorrected. The ir spectra were recorded with a Perkin Elmer 127 spectrophotometer and nmr spectra were measured on a Varian EM-390 90 MHz spectrometer using TMS or DSS as internal standards. Although the ir and nmr spectral data are not included (because of the lack of unusual features), they were obtained for all the compounds described and were consistent with the assigned structures.

N-(ω-Aminoalkyl)thiazolidine Dihydrochlorides (**2a** and **2b**).

A mixture of *N*-(ω-aminoalkyl)cysteamine dihydrochloride (**1a** or **1b**) (5.0 mmoles) (2) and 40% formaldehyde (6.0 mmoles) in water (4 ml.) was left at room temperature overnight. The solvent was removed *in vacuo* to dryness and to the residual syrup was added isopropyl alcohol-ether. Trituration and standing gave **2a** or **2b** in 75-85% yield, as a white solid, which was recrystallized from isopropyl alcohol. Compound **2a** had m.p. 136-138°.

Anal. Calcd. for $C_9H_{22}Cl_2N_2S$: C, 41.38; H, 8.49; N, 10.72. Found: C, 41.60; H, 8.52; N, 10.51.

Compound **2b** had m.p. 137-139°.

Anal. Calcd. for $C_{11}H_{26}Cl_2N_2S$: C, 45.67; H, 9.06; N, 9.68. Found: C, 46.01; H, 9.25; N, 9.39.

N,N'-Bis(ω-aminoalkyl)cystamine Tetrahydrochlorides (**5a** and **5b**).

A solution of 0.1*N* iodine in 0.25% potassium iodide (10 ml.) was added dropwise to a solution of **2a** or **2b** (1.0 mmole) in water (10 ml.). After the addition was over, the mixture was stirred for 1 hour and then it was washed with chloroform (2 × 20 ml.). The aqueous layer was made basic with sodium hydroxide pellets (4.0 g.), saturated with sodium chloride and extracted with chloroform (3 × 30 ml.). Removal of the washed (saturated sodium chloride) and dried (sodium sulfate) solvent gave an oil which was dissolved in absolute ethanol (5 ml.) and treated with gaseous hydrochloric acid. The white solid was filtered and recrystallized from methanol-isopropyl alcohol to give **5a** or **5b** in 70% yield identical to that obtained by another way (2).

N,N'-Bis(ω-aminoalkyl)-*N,N'*-dimethylcystamine Tetraoxalates (**4a** and **4b**).

A.

Compound **2a** or **2b** (3.0 mmoles) (as free base) was dissolved in dry tetrahydrofuran (20 ml.) in a round-bottom flask equipped with a condenser, inlet and outlet for nitrogen, and an addition funnel with side arm and a rubber cup. The apparatus was flushed with nitrogen then 2 ml. of borane-methyl sulfide complex (Aldrich) were transferred with a syringe into the addition funnel and slowly added to the solution. After standing at room temperature under stirring and nitrogen for 30 minutes the cloudy mixture was heated to reflux for 5 hours. It was then cooled and 5 ml. of methanol were added dropwise. The solution was left to stand overnight with stirring under nitrogen, then it was cooled (ice) and gaseous hydrochloric acid was bubbled through the solution for 15 minutes. The resulting mixture was refluxed for 2 hours, cooled and added to 20 ml. of ether. *N*-(ω-aminoalkyl)-*N*-methylcysteamine dihydrochloride (**3a** or **3b**) separated as an oily compound which was dissolved in 5 ml. of methanol and evaporated to dryness. This operation was repeated five times. Crude **3a** or **3b** was dissolved in water (10 ml.), washed with chloroform (2 × 20 ml.) and then treated with potassium ferricyanide (5.1 g.) in 15 ml. of water. The mixture was left under stirring for 1 hour then it was made basic with sodium hydroxide pellets (4.0 g.) and extracted with chloroform (3 × 30 ml.). Removal of the washed (saturated sodium chloride) and dried (sodium sulfate) extract gave an oil which was converted into the oxalate salt by treating an ether solution with 4 equivalents of oxalic acid dihydrate (1.51 g.). The resulting solid was filtered, washed with ether and recrsytallized from water-methanol affording in 45-50% yield **4a** or **4b** which was identical with that obtained by another way (Scheme 1) (2).

B.

Compound **2a** or **2b** (2.0 mmoles) in dry ether (50 ml.) was added dropwise to a stirred mixture of lithium aluminum hydride (0.6 g.) in dry ether (50 ml.) under dry nitrogen. After the addition was over, the mixture was heated to reflux for 18 hours and cooled, and the excess of lithium aluminum hydride was destroyed with water (3 ml.). The solvent was decanted, washing the solid with ether (200 ml.). Removal of the dried (sodium sulfate) solvent gave crude **3a** or **3b** as a yellowish oil which was oxidized with potassium ferricyanide to afford **4a** or **4b** (less than 10% yield as a free base) as described in method A. The compounds were identified by comparison on tlc [solvent: concentrated ammonia-methanol (20:80)] with samples obtained *via* method A.

N,N'-Dimethylcystamine Dihydrochloride (**9**).

A.

Thiazolidine (**7**) (5) was allowed to react with borane-dimethyl sulfide complex to afford crude *N*-methylcysteamine hydrochloride (**8**) as an oily compound which was oxidized with potassium ferricyanide to **9** (free base) following the procedure described for **4**. Crude **9** was dissolved in isopropyl alcohol (10 ml.) and treated with gaseous hydrochloric acid. The white solid was filtered, washed with ether and recrystallized from methanol-isopropyl alcohol, 0.7 g. (45% global yield), m.p. 203-204° (lit. (6) m.p. 210-211°).

B.

2,2'-Dichloroethyl disulfide (4.68 g., 23.9 mmoles) (8) and 40% methylamine (12 ml.) were dissolved in absolute ethanol (50 ml.) and left overnight under stirring at room temperature. The solvent and amine excess were removed under vacuum and the residue treated with concentrated hydrochloric acid (5 ml.). The solution was evaporated to dryness *in vacuo*. The residue was then dissolved in water (20 ml.), washed with chloroform (3 × 30 ml.), made basic with sodium hydroxide pellets (8.0 g.) and extracted with chloroform (3 × 50 ml.). Removal of the washed (saturated sodium chloride) and dried (sodium sulfate) extract gave a pale yellow oil which was distilled, 95-96° (1.0 mm). The oil was dissolved in isopropyl alcohol (20 ml.) and treated with gaseous hydrochloric acid, affording **9** in 35% yield, identical to that obtained *via* method A.

REFERENCES AND NOTES

(1) C. Melchiorre, M. S. Yong, B. Benfey, L. Brasili, G. Bolger and B. Belleau, in "Recent Advances in Receptor Chemistry", F. Gualtieri, M. Giannella and C. Melchiorre, Eds., Elsevier/North-Holland Biomedical Press, 1979, p. 207.

(2) C. Melchiorre, M. S. Yong, B. G. Benfey and B. Belleau, *J. Med. Chem.*, **21**, 1126 (1978).

(3) R. G. Hiskey, V. R. Rao and W. G. Rhodes, in "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., Plenum Press, London and New York, 1973, Chapter 7.

(4) J. C. Sheehan and D.-D. H. Yang, *J. Am. Chem. Soc.*, **80**, 1158 (1958).

(5) S. Ratner and H. T. Clarke, *ibid.*, **59**, 200 (1937).

(6) T. C. Owen, *J. Chem. Soc. C*, 1373 (1967).

(7) I. R. Schmolka and P. E. Spoerri, *J. Am. Chem. Soc.*, **79**, 4716 (1957).

(8) G. M. Bennett, *J. Chem. Soc.*, 418 (1921).