Asymmetric nitrogen

79.* Transfer of chirality from nitrogen to carbon in transformations of dimethyl 1-methoxyaziridine-2,2-dicarboxylate and synthesis of dimethyl 1-silyloxyaziridine-2,2-dicarboxylate

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The possibility of transferring chirality from nitrogen to carbon by a three-step transformation of racemic dimethyl 1-methoxyaziridine-2,2-dicarboxylate into 3-amino-2-chloromethyl-2-methoxyaminopropan-1-ol was demonstrated. The first representative of 1-silyloxyaziridines, *viz.*, dimethyl 1-(*tert*-butyldimethylsilyloxy)aziridine-2,2-dicarboxylate, was synthesized by acidolysis or thermolysis of triazoline, obtained by the reaction of *tert*-butyldimethylsilyloxime of dimethyl mesoxalate with CH_2N_2.

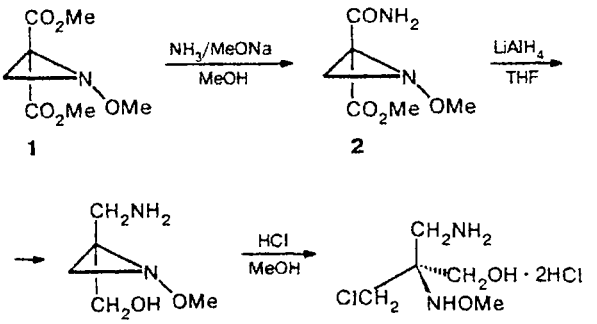
Key words: transfer of chirality from nitrogen to carbon; dimethyl 1-methoxyaziridine-2,2-dicarboxylate; methyl 2-carbamoyl-*c*-1-methoxyaziridine-*r*-2-carboxylate; 2-aminomethyl-*r*-2-hydroxymethyl-*c*-1-methoxyaziridine; 3-amino-2-chloromethyl-2-methoxyaminopropan-1-ol; dimethyl 1-(*tert*-butyldimethylsilyloxy)-4,5-dihydro-1*H*-1,2,3-triazole-5,5-dicarboxylate; dimethyl 1-(*tert*-butyldimethylsilyloxy)aziridine-2,2-dicarboxylate; ^1H and ^{13}C NMR spectra.

Currently chiral aziridines are widely used in stereoselective transformations and in the synthesis of biologically active and natural compounds.[2—4] 1-Alkoxyaziridine-2,2-dicarboxylic esters, which are prepared in enantiomerically pure forms with known absolute configurations, are especially promising in this respect.[5—7] Recently we synthesized 1-aryloxy-2,2-dicarboxylic ester and partly resolved it into enantiomers by crystallization from an optically active solvent.[8] Optical resolution of these compounds can also be accomplished by chromatography on chiral phases or by enantioselective enzymatic hydrolysis, as has been described for 2-alkyloxaziridine-3,3-dicarboxylates[9] and 1-chloroaziridine-2,2-dicarboxylates.[10]

Previously, it has been proved unambiguously that nucleophilic substitution involving the ester moiety in 1-alkoxyaziridine-2,2-dicarboxylates is *trans*-stereoselective.[11—13] This opens up a way to stereoselective syntheses of polyfunctional chiral synthons by transferring the chiral center from the N atom to a C atom. This transfer was accomplished for the first time[14] by Stevens rearrangement of optically active (+)-allylbenzylmethylphenylammonium iodide into (−)-3-(*N*-methyl-*N*-phenylamino)-4-phenylbut-1-ene. Later, asymmetric reactions of chiral aziridines containing nitrogen and carbon asymmetric centers have been developed.[15—17] However, the transfer of chirality from asymmetric trivalent nitrogen to other atoms has not so far been described.

In the present work, we demonstrate the possibility of transferring the chirality from an N atom to a C atom using transformations of racemic dimethyl 1-methoxyaziridine-2,2-dicarboxylate (**1**)[11] as examples (Scheme 1, the absolute configuration is shown arbitrarily).

Scheme 1



1 2 3 4

* For Part 78, see Ref. 1.

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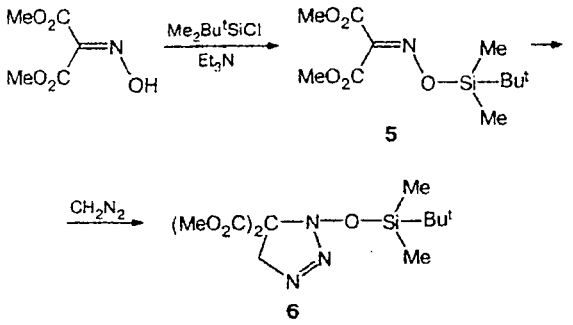
trans-Amide **2** was identical to that described previously.[11] This compound is known to possess high configurational stability ($\Delta G^{\#}_{inv}$ = 30.6 kcal mol^{-1}).[11] Thus, the configuration of the resulting chiral carbon center is controlled by the configuration of the asymmetric N atom in the molecule of aziridine **1**. It is also known that the diethyl analog of this compound is smoothly reduced by $LiAlH_4$ to 2,2-bis(hydroxymethyl)-substituted derivative without substantial racemization.[6] Under the same conditions, amide **2** is reduced to amino alcohol **3**. If the ring is cleaved under the action of an acid, the nitrogen chiral center disappears, and the chirality is thus transferred to the central C atom of the polyfunctional *tert*-alkylmethoxyamine **4**. It is clear that this compound can be used in a wide variety of syntheses.

It should be expected that products of similar transformations of previously unknown 1-silyloxyaziridine-2,2-dicarboxylates would possess even a greater synthetic potential. In this work, we synthesized dimethyl 1-(*tert*-butyldimethylsilyloxy)-4,5-dihydro-1*H*-1,2,3-triazole-5,5-dicarboxylate (**6**). Acidolysis (or thermolysis) of the latter gave dimethyl 1-(*tert*-butyldimethylsilyloxy)aziridine-2,2-dicarboxylate (**7**), which is the first representative of 1-silyloxyaziridines (Scheme 2).

Scheme 2

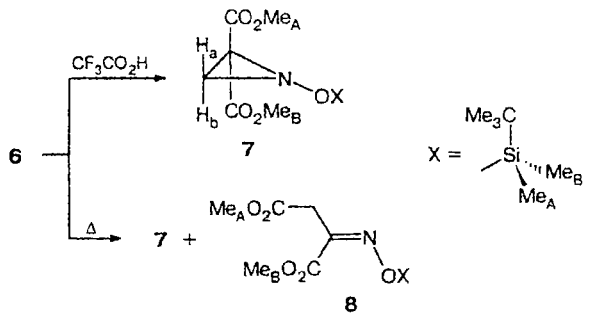


Silyloxytriazoline **6** is thermally more stable than the corresponding alkoxy analogs, which entirely decompose over a period of 10—30 h at 15—20 °C in benzene solutions to give aziridines and products of insertion at the C—C bond in a ratio of 4 : 1. Acidolysis of alkoxytriazolines yields only aziridines.[11,18,19]

We studied thermolysis and acidolysis of silyloxytriazoline **6**. On treatment with traces of CF_3COOH, compound **6** is converted only in aziridine **7**, whereas thermolysis of **6** (1 week at 15—20 °C) gives rise to a mixture of aziridine **7** and *Z*-*O*-*tert*-butyldimethylsilyloxime of dimethyl oxaloacetate (**8**) (Scheme 3). The strong positive ASIS effect,* 0.35 and 0.31 ppm for the CH_2 and Me_AO groups of silyloxime **8**, respectively, implies that the solvation with an aromatic solvent occurs from the sterically less hindered side. This corresponds to the *Z*-configuration of oxime **8**.

* The shift induced by an aromatic solvent.

Scheme 3



Silyloxyaziridine **7** is quite stable; it is not hydrolyzed in air and is resistant to treatment with acids (5 days in the presence of CF_3COOH). It is a promising synthon for the preparation of 1-hydroxyaziridine-2,2-dicarboxylates. Unfortunately, we were not able to remove the *O*-silyl protection. The reaction of compound **7** with Bu_4NF [20] or KHF_2 in THF results in its decomposition. Silyloxyaziridine **7** is also unstable with respect to bases. An attempt to carry out its amidation (a fivefold excess of NH_3 in anhydrous MeOH) led to a mixture of nonidentified products, similarly to its reaction with fluorides.

The ^1H NMR spectrum of silyloxyaziridine **7** does not change at 120 °C, which points to a high configurational stability of this compound ($\Delta G^{\#}_{inv}$ > 20 kcal mol^{-1}).

Experimental

NMR spectra were recorded on a Bruker WM-400 spectrometer (using Me_4Si as the internal standard). Column chromatography was carried out on silica gel L 40/100. Chloro(*tert*-butyl)dimethylsilane was synthesized by a procedure described previously.[21]

Methyl 2-carbamoyl-*c*-1-methoxyaziridine-*r*-2-carboxylate (2). Aziridine **1** (3 g, 16 mmol) was dissolved in 50 mL of MeOH containing traces of MeONa, and 27 mL of a 1% solution of ammonia in anhydrous MeOH was added to this solution. The mixture was kept for 2 weeks at 20 °C, the solvent was evaporated *in vacuo*, and the residue was crystallized from Pr^iOH to give 2.3 g (82%) of monoamide **2** as white crystals. ^1H NMR ($CDCl_3$), δ: 2.52 (d, 1 H, ring CH_2, ^2J = −2.8 Hz); 2.94 (d, 1 H, ring CH_2, ^2J = −2.8 Hz); 3.60 (s, 3 H, MeON); 3.82 (s, 3 H, MeO); 6.28 (br.s, 1 H, NH_2); 6.56 (br.s, 1 H, NH_2).

2-Aminomethyl-*r*-2-hydroxymethyl-*c*-1-methoxyaziridine (3). Monoamide **2** (1 g, 5 mmol) was added in portions to a suspension of $LiAlH_4$ (1.5 g, 39.5 mmol) in 80 mL of anhydrous THF. The mixture was refluxed for 3 h. At 0 °C, H_2O (1.5 mL), a 15% solution of KOH (1.9 mL), and again H_2O

(4.6 mL) were successively added to it. The resulting precipitate was filtered off, the filtrate was dried with K_2CO_3, the solvent was evaporated *in vacuo*, and the residue was purified by chromatography (AcOEt and a 8 : 1 AcOEt—MeOH mixture were successively used as eluents) to give 0.6 g (90%) of aziridine **3** as a thick oil. Found (%): C, 45.42; H, 11.31; N, 21.30. $C_5H_{12}N_2O_2$. Calculated (%): C, 45.45; H, 9.09; N, 21.21. ^{1}H NMR ($CDCl_3$), δ: 1.84 (2 H, ring CH_2, AB-spectrum, $\Delta\nu$ = 17 Hz, $^2J_{AB}$ = −3.1 Hz); 2.80 (2 H, CH_2NH_2, AB-spectrum, $\Delta\nu$ = 183 Hz, $^2J_{AB}$ = −13.1 Hz, $^4J_{HACCCH_2OH}$ = 1.5 Hz); 3.59 (s, 3 H, MeO); 4.05 (2 H, CH_2OH, AB-spectrum, $\Delta\nu$ = 126 Hz, $^2J_{AB}$ = −12.1 Hz, $^4J_{HACCCH_2NH_2}$ = 1.5 Hz).

3-Amino-2-chloromethyl-2-methoxyaminopropan-1-ol dihydrochloride (4). Aziridine 3 (0.6 g, 4.5 mmol) was dissolved in 30 mL of anhydrous MeOH, and a 5% solution of HCl (11 g, 15 mmol of HCl) in anhydrous MeOH was added. The mixture was refluxed for 3 h, the solvent was evaporated *in vacuo*, and the residue was purified by chromatography (AcOEt and a 1 : 1 AcOEt—MeOH mixture were successively used as eluents) to give 0.3 g (31.2%) of dihydrochloride **4** as a thick oil. Found (%): C, 22.48; H, 7.03; N, 13.11. $C_5H_{14}ClN_2O_2 \cdot 2HCl$. Calculated (%): C, 22.46; H, 9.12; N, 13.32. ^{1}H NMR (CD_3OD), δ: 3.14 (2 H, CH_2Cl, AB-spectrum, $\Delta\nu$ = 21 Hz, $^2J_{AB}$ = −13.4 Hz); 3.56 (s, 3 H, MeO); 3.65 (2 H, CH_2NH_2, AB-spectrum, $\Delta\nu$ = 32 Hz, $^2J_{AB}$ = −11.4 Hz); 3.71 (s, 2 H, CH_2OH).

Dimethyl 2-(*tert*-butyldimethylsilyloxyimino)propane-1,3-dioate (5). Anhydrous Et_3N (0.65 g, 6.4 mmol) was added to a solution of isonitrosomalonate (1 g, 6.2 mmol) in 30 mL of anhydrous MeCN. The reaction mixture was stirred for 10 min, and Bu^tMe_2SiCl (0.85 g, 6.2 mmol) in 30 mL of anhydrous MeCN was slowly added to it. The mixture was stirred for an additional 3 h at 20 °C, the solvent was evaporated *in vacuo*, the residue was extracted with anhydrous *n*-pentane, and the extract was filtered and concentrated *in vacuo* to give 1.54 g (98%) of *O*-silyloxime **5** as a colorless oil readily hydrolyzable in air, n_D^{20} 1.4480. Found (%): C, 42.89; H, 8.34; N, 5.53; Si, 11.48. $C_9H_{21}NO_5Si$. Calculated (%): C, 42.86; H, 8.33; N, 5.56; Si, 11.51. ^{1}H NMR ($CDCl_3$), δ: 0.25 (s, 6 H, 2 Me); 0.92 (s, 9 H, Bu^t); 3.86 (s, 3 H, MeO); 3.87 (s, 3 H, MeO).

Dimethyl 1-(*tert*-butyldimethylsilyloxy)-4,5-dihydro-1*H*-1,2,3-triazole-5,5-dicarboxylate (6). Silyloxime **5** (1.5 g, 5.9 mmol) was kept with excess CH_2N_2 in anhydrous ether for 1 month at −10 °C. Then the mixture was filtered, and the solvent was evaporated *in vacuo* to give 1.7 g (97%) of triazoline **2** as a thick oil, which completely crystallized over a period of 3 h at −10 °C, m.p. 80—82 °C (decomp.). ^{1}H NMR ($CDCl_3$), δ: 0.31 (s, 6 H, 2 Me); 0.95 (s, 9 H, Bu^t); 3.79 (s, 6 H, 2 MeO); 4.76 (s, 2 H, ring CH_2).

Dimethyl 1-(*tert*-butyldimethylsilyloxy)aziridine-2,2-dicarboxylate (7). Silyloxytriazoline **6** (0.5 g, 1.7 mmol) was dissolved in 10 mL of ether, the solution was cooled to −10 °C, and traces of CF_3COOH were added. The mixture was kept at this temperature until the evolution of nitrogen was completed, the solvent was evaporated *in vacuo*, and the residue was chromatographed to give 0.35 g (77%) of aziridine **7** as a colorless oil, n_D^{20} 1.4402. Found (%): C, 45.15; H, 8.64; N, 5.23; Si, 10.88. $C_{10}H_{23}NO_5Si$. Calculated (%): C, 45.11; H, 8.65; N, 5.26; Si, 10.90. ^{1}H NMR ($CDCl_3$), δ (the magnitudes of the ASIS-effect are given in brackets [$\delta_{CDCl_3} - \delta_{C_6D_6}$]): 0.15 [−0.06] (s, 3 H, Me_A); 0.19 [−0.04] (s, 3 H, Me_B); 0.87 [−0.04] (s, 9 H, Bu^t); 2.05 [0.31] (d, 1 H, H_a, ^2J = −2.1 Hz); 2.84 [0.09] (d, 1 H, H_b, ^2J = −2.1 Hz); 3.77 [0.51] (s, 3 H, Me_AO); 3.80 [0.35] (s, 3 H, Me_BO). ^{13}C NMR (C_6D_6), δ: −5.27 (qq, Me_A, ^1J = 119.2 Hz, ^3J = 2.2 Hz); −5.22 (qq, Me_B, ^1J = 119.2 Hz, ^3J = 2.2 Hz); 18.02 (s, $\underline{C}Me_3$); 26.13 (q.sept., $\underline{Me_3}C$, ^1J = 125.7 Hz, ^3J = 5.8 Hz); 43.51 (dd, C(3), ^1J = 173.7 Hz, ^1J = 177.7 Hz); 51.20 (dd, C(2), ^2J = 2.9 Hz); 52.20 (q, Me_AO, ^1J = 146.8 Hz); 52.35 (q, Me_BO, ^1J = 146.8 Hz); 163.47 (q, C_AO, ^3J = 3.6 Hz); 166.37 (q, C_BO, ^3J = 3.6 Hz).

Thermolysis of triazoline 6. (*Z*)-Dimethyl 2-(*tert*-butyldimethylsilyloxyimino)butan-1,4-oate (8). Silyloxytriazoline **6** (0.2 g, 0.6 mmol) was kept for 1 week at 15—20 °C, and then the thick oil was chromatographed (with heptane as the eluent) to give 0.15 g of a mixture of silyloxyaziridine **7** and oxime **8** in a ratio of 5 : 1 (found from the integral intensities of the ^{1}H NMR signals for the *tert*-butyl groups). ^{1}H NMR spectrum of silyloxime **8** ($CDCl_3$), δ (the ASIS-effects are given in brackets [$\delta_{CDCl_3} - \delta_{C_6D_6}$]): 0.23 [0.04] (s, 6 H, 2 Me); 0.95 [0.02] (s, 9 H, Bu^t); 3.63 [0.31] (s, 2 H, CH_2); 3.68 [0.31] (s, 3 H, Me_AO); 3.87 [0.27] (s, 3 H, Me_BO). ^{13}C NMR (C_6D_6), δ: −5.25 (q, Me_A, Me_B, ^1J = 119.2 Hz); 18.00 (s, C(1′)); 26.01 (q.sept., C(2′), C(3′), C(4′), ^1J = 125.7 Hz, ^3J = 5.8 Hz); 31.52 (t, CH_2, ^1J = 132.2 Hz); 50.20 (q, Me_AO, ^1J = 146.8 Hz); 51.18 (q, Me_BO, ^1J = 146.8 Hz); 163.92 (q, C_AO, ^3J = 3.6 Hz); 166.40 (q, C_BO, ^3J = 3.6 Hz).

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References

1. R. G. Kostyanovsky, P. Rademacher, Yu. I. El'natanov, G. K. Kadorkina, G. A. Nikiforov, I. I. Chervin, S. V. Usachev, and V. R. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1346 [*Russ. Chem. Bull.*, 1997, **46**, 1291 (Engl. Transl.)].
2. D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599.
3. W. H. Pearson, B. W. Lian, and S. C. Bergmeier, *Aziridines and Azirines: Monocyclic*, in *Comprehensive Heterocyclic Chemistry II*, Ed. A. Padwa, Pergamon, New York, 1996, **1A**, 1.
4. K. M. Lokantha Rai and A. Hassner, *Aziridines and Azirines: Fused-ring Derivatives*, in *Comprehensive Heterocyclic Chemistry II*, Ed. A. Padwa, Pergamon, New York, 1996, **1A**, 61.
5. R. G. Kostyanovsky and V. F. Rudchenko, *Dokl. Akad. Nauk SSSR*, 1976, **231**, 878 [*Dokl. Chem.*, 1976 (Engl. Transl.)].
6. V. F. Rudchenko, O. A. D'yachenko, A. B. Zolotoi, L. O. Atovmyan, and R. G. Kostyanovsky, *Dokl. Akad. Nauk SSSR*, 1979, **246**, 1150 [*Dokl. Chem.*, 1979 (Engl. Transl.)].
7. V. F. Rudchenko, O. A. D'yachenko, A. B. Zolotoi, L. O. Atovmyan, I. I. Chervin, and R. G. Kostyanovsky, *Tetrahedron*, 1982, **38**, 1961.
8. V. V. Rozhkov, I. I. Chervin, A. V. Prosyanik, and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 3027 [*Russ. Chem. Bull.*, 1996, **45**, 2876 (Engl. Transl.)].
9. M. Bucciarelli, A. Forni, I. Moretti, and F. Prati, *J. Chem. Soc., Chem. Commun.*, 1988, 1614.
10. M. Bucciarelli, A. Forni, I. Moretti, and F. Prati, *Tetrahedron: Asymmetry*, 1990, **1**, 5.
11. R. G. Kostyanovsky, V. F. Rudchenko, A. V. Prosyanik, M. D. Isobaev, I. I. Chervin, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 628 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1977, **26** (Engl. Transl.)].

12. A. B. Zolotoi, O. A. D'yachenko, L. O. Atovmyan, V. F. Rudchenko, I. I. Chervin, and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin.*, 1984, 48 [*Chem. Heterocycl. Compd.*, 1984 (Engl. Transl.)].
13. A. B. Zolotoi, O. A. D'yachenko, L. O. Atovmyan, V. F. Rudchenko, and R. G. Kostyanovsky, *Zh. Strukt. Khim.*, 1984, **25**, 159 [*J. Struct. Chem. (USSR)*, 1984, **25** (Engl. Transl.)].
14. R. K. Hill and T.-H. Chan, *J. Am. Chem. Soc.*, 1966, **88**, 866.
15. F. A. Davis and A. C. Sheppard, *Tetrahedron*, 1989, **45**, 5703.
16. F. A. Davis and B.-C. Chen, *Chem. Rev.*, 1992, **92**, 919.
17. F. A. Davis and R. T. Reddy, *Oxaziridines and Oxazirines*, in *Comprehensive Heterocyclic Chemistry II*, Ed. A. Padwa, Pergamon, New York, 1996, **1A**, 365.
18. R. G. Kostyanovsky, A. V. Prosyanik, A. I. Mishchenko, G. V. Shustov, I. I. Chervin, N. L. Zaichenko, A. P. Pleshkova, P. N. Belov, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 1780 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28**, 1640 (Engl. Transl.)].
19. A. V. Prosyanik, A. I. Mishchenko, N. L. Zaichenko, G. V. Shustov, P. N. Belov, and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 596 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 546 (Engl. Transl.)].
20. E. J. Corey and L. J. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.
21. L. H. Sommer and L. J. Tyler, *J. Am. Chem. Soc.*, 1954, **76**, 1030.

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