Pergamon

Tetrahedron Letters 40 (1999) 5811–5812

TETRAHEDRON LETTERS

A Chiral C_3 Triisopropylamine and its Silatrane Derivatives

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Received 6 May 1999; revised 26 May 1999; accepted 27 May 1999

Abstract: The first chiral C_3 triisopropylamine has been prepared with the stereogenic centers adjacent to the central nitrogen atom. This triol was converted to two new C_3 4,6,11-trimethylsilatranes. An X-ray structure revealed that the methyl substituents adopt sterically congested pseudoaxial orientations.

Homochiral C_3 triethanolamines have taken on increasing importance as precursors to chiral silatranes[1] and chiral boratranes[2] and as ligands for early transition metal catalysts.[3,4] The many C_3 triethanolamine derivatives that have been prepared invariably lack substituents α to the central nitrogen atom (Fig. 1). The absence of these isomeric C_3 triethanolamines is partially attributable to the regiochemistry of epoxide aminolysis - the preferred route for synthesis of triethanolamines. In a broader sense, triisopropylamine derivatives are difficult to make by any route, due to steric congestion around the central nitrogen atom. The nitrogen atom of triisopropylamine is so hindered that it adopts a nearly planar ground state geometry.[5,6] To date, the only type of C_3 amine with stereogenic centers adjacent to nitrogen that has been reported is Steglich's *N, N, N*-tris-aminal derivative **2**.[7]

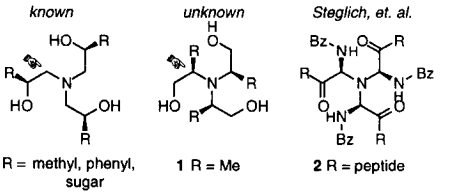

Figure 1. Homochiral C_3 trialkylamine derivatives

We set out to prepare the first homochiral C_3 triethanolamine derivative **1** and its corresponding homochiral C_3 silatrane. The preferred approach to the synthesis of triisopropylamines involves addition to iminium intermediates, with yields generally around 40%.[5,8] This method avoids elimination reactions but makes it difficult to control the stereochemistry of the new stereogenic center. Alkylation of α-halo esters is generally an efficient process because the π system facilitates S_N2 attack. Effenberger has shown α-haloesters to be inferior to the corresponding triflates in additions to amines[9] so we chose to extend his synthesis of dialkylamines[10] to trialkylamines. *L*-Alanine ethyl ester reacted readily with the triflate ester of *S*-ethyl lactate to afford **3**, but the second alkylation reaction occurred slowly. Best results were obtained using 3 equiv. of the triflate **4** in refluxing nitromethane. Under these conditions the C_3 triamine **5** was formed in 32% yield (benzene/H_2O gave 30% yield, while CH_2Cl_2 gave 26% yield); diamine **3** was recovered in 41% yield. The triester **5** was reduced to the C_3 triethanolamine **1** using lithium borohydride with 10 mol% trimethylborate.[11,12] The corresponding triphenyl and tribenzyl analogs of **1** were inaccessible by this route due to competing elimination in the alkylation step.

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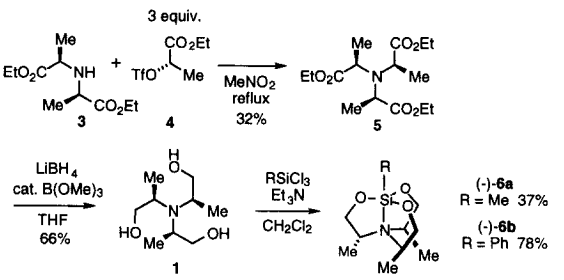
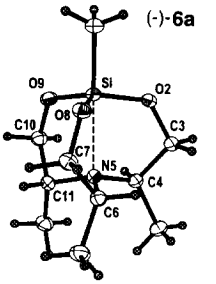
PII: S0040-4039(99)01135-1

Scheme 1





Two silatrane derivatives (-)-**6a** and (-)-**6b** were readily prepared from triol **1** using phenyl and methyl trichlorosilane, respectively.[13] The methyl derivative **6a** was readily crystallized from dichloromethane.[14] The methyl groups of **6a** avoid gauche interactions by adopting pseudo-axial orientations. Steric congestion among these methyl groups reduces the transannular Si-N interaction leading to a 2.32 Å Si-N bond, slightly longer than the typical 2.17 Å Si-N bond of the unsubstituted 1-methylsilatrane.[15]

Acknowledgement: This work is supported by the National Science Foundation (CHE-9623903) with additional support from Eli Lilly, Glaxo-Wellcome, the Camille and Henry Dreyfus Foundaton, and the Alfred P. Sloan Foundation. Coordinates for **6a** have been submitted to the CCDC.

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12. Tris-(1*R*-(ethoxycarbonyl)ethyl)amine, **5:** ^{1}H NMR ($CDCl_3$) δ 4.14 (dq, *J* = 27.4, 7.2, 3H), 4.12 (dq, *J* = 27.4, 7.2 Hz, 3H), 3.98 (q, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.2 Hz, 9H), 1.24 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 174.8, 59.9, 53.7, 18.9, 14.1. Tris-(2-hydroxy-1*R*-methylethyl)amine, **1:** ^{1}H NMR ($CDCl_3$) δ 4.54 (s, br, 3H), 3.35 (s, 3H), 3.33 (d, *J* = 1.6 Hz, 3H), 3.07 (m, 3H), 0.98 (d, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 63.6, 49.9, 16.5.
13. (-)-(4*R*, 6*R*, 11*R*)-1, 4, 6, 11-tetramethylsilatrane, **6a:** $[\alpha]_D$ = -91 (c 1.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.60 (dd, *J* = 10.9, 5.4 Hz, 3H), 3.43 (t, *J* = 11.1 Hz, 3H), 3.06 (sept, *J* = 5.6 Hz, 3H), 1.11 (d, *J* = 7.6 Hz, 9H), -0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 64.4, 49.4, 14.5, -2.6. (-)-(4*R*, 6*R*, 11*R*)-1-phenyl-4,6,11-trimethylsilatrane, **6b:** mp 182-184°C ($CHCl_2$); $[\alpha]_D$ = -50 (c, 1.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.67 (dd, *J* = 11.1, 5.6 Hz, 3H), 3.48 (t, *J* = 11.1 Hz, 3H), 3.12 (m, 3H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.1, 134.0, 138.1, 127.3, 64.2, 49.8, 14.5.
14. Crystal Data for **6a**: Orthorhombic; space group, $P2_12_12_1$; unit cell dimensions: a=9.4677(5) Å, b=10.4975(6) Å, c=12.1865(6) Å; V 1211.18(11) Å^3; Z=4; Density (calc.), 1.269 Mg/m^3; Final R [I>2σ^2]: R1=0.0269; R (all data), wR2 = 0.0690; T 158K.
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