Tunable Stereoselectivity in the Addition of 2-Lithiothiazole to L-Serinal Derived *N*-Benzyl Nitrone. Synthesis of C-2 Epimer 2,3-Diamino-4-Hydroxybutanals

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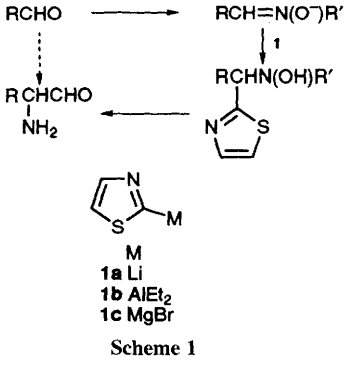
A complete reversal of diastereoselectivity (ds ≥ 95%) in the addition of 2-lithiothiazole to L-serinal derived *N*-benzyl nitrone has been achieved by the change of the hydroxy and amino protective groups in the aldehyde moiety; the resultant epimeric 2-thiazolyl *N*-benzyl hydroxylamines were converted to C-2 epimer 2,3-diamino-4-hydroxybutanals *via* reductive dehydroxylation and thiazolyl-to-formyl conversion.

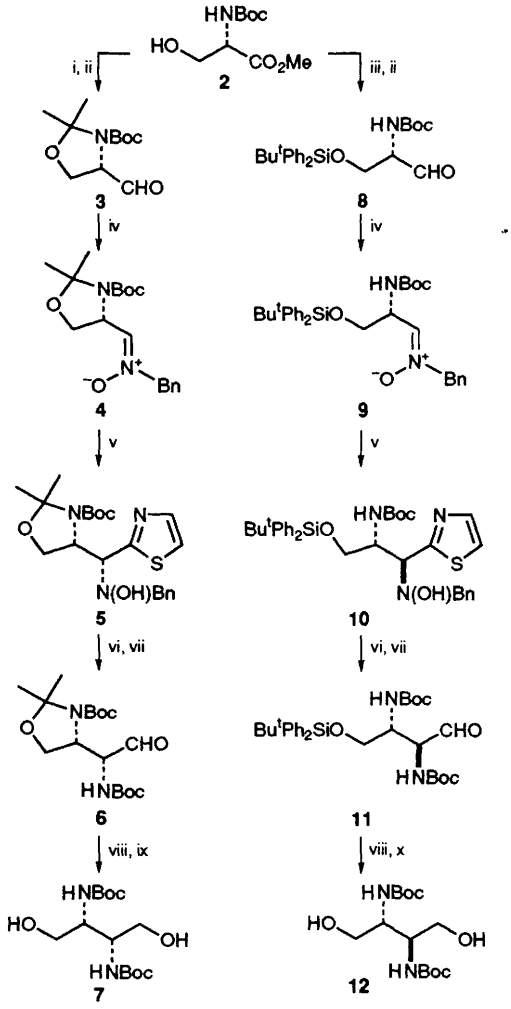
A remarkable extension of the thiazole–aldehyde synthesis[1] exploits nitrones as convenient aldehyde derivatives incorporating a modified iminium moiety.[2] Thus, the addition of a 2-metallated thiazole **1** to the nitrone, followed by the reductive dehydroxylation of the resultant hydroxylamine and the thiazolyl-to-formyl conversion, afford the homologous α-amino aldehyde (homologative amination) (Scheme 1). The stereochemistry of the addition of **1** to nitrones derived from chiral α-alkoxy and glycidic aldehydes was controlled by either the change of the metal and/or the precomplexation of the nitrone with suitable Lewis acids.[2b,3]

Aiming at using chiral α-amino aldehydes[4] as substrates in the above strategy, we would like to describe herein the addition of 2-lithiothiazole **1a** to L-serinal derived nitrone and show a complete reversal of diastereoselectivity induced by different protection of the hydroxy and amino groups in the aldehyde moiety. Tunable stereoselectivity by this approach has been observed in other examples of thiazole–aldehyde synthesis employing amino aldehydes[5] and amino ketones[6] as substrates. The preliminary work presented here is aimed at developing a synthetic route to aldehydes bearing an adjacent chiral 1,2-diamino unit. The synthesis of vicinal diamines[7] is attracting considerable increasing interest since they are the essential structural units of metal ligands,[8] chiral synthetic auxiliaries,[9] natural and unnatural biologically active compounds,[10] and medicinal products.[11]

Readily available *N*-*tert*-butoxycarbonyl L-serinal acetonide[12] **3** was converted into the *N*-benzyl nitrone **4** (72%) by reaction with benzylhydroxylamine in the presence of anhydrous $MgSO_4$ as a dehydrating agent (Scheme 2).† Nuclear Overhauser effect difference spectroscopy (NOEDS) between CH=N$^+$ and CH_2Ph signals (8–10% enhancement) supported the *Z* configuration of **4**. The addition of 2-lithiothiazole **1a** (generated *in situ* from 2-bromothiazole and *n*-butyllithium)[6] to the nitrone **4** in diethyl ether–tetrahydrofuran (1 : 1) at −78 °C, occurred with a high level of diastereoselectivity (ds ≥ 95% by NMR) to give the *N*-benzyl hydroxylamine **5** in 89% isolated yield. The *syn* arrangement of substituents in **5** was established by X-ray crystallography (Fig. 1).‡ Quite surprisingly, the sense and level of the diastereofacial selectivity did not change by either the use of the other metallated thiazoles **1b** and **1c** or the addition of **1a** to precomplexed **4** with the Lewis acids Et_2AlCl, $MgBr_2$ or $ZnBr_2$. Reductive dehydroxylation and concomitant debenzylation of **5** by $TiCl_3$ in aqueous methanol,[2,3] followed by the protection of the primary amine product as the *N*-Boc derivative and the release of the formyl group from the thiazole ring,[13] afforded the protected *syn* diamino aldehyde **6** in 52% overall yield. The one-pot reduction of this aldehyde to alcohol and deacetonization led



Scheme 1



Scheme 2 *Reagents and conditiions*: i, DMP, C_6H_6, TsOH, reflux; ii, DIBAH, toluene, −78 °C, 3 h; iii, ButPh_2SiCl, DMAP, NEt_3, DMF, room temp. 12 h; iv, $PhCH_2NHOH$, CH_2Cl_2, $MgSO_4$, room temp., 2 h; v, 2-lithiothiazole **1a** (from 2-bromothiazole, BuLi, Et_2O, −78 °C) Et_2O–THF (1 : 1) −78 °C, 10 min; vi, $TiCl_3$, MeOH–H_2O, room temp. 15 min, then Boc_2O, dioxane, room temp. 16 h; vii, $CF_3SO_3CH_3$, MeCN, room temp. 10 min, then $NaBH_4$, MeOH, 0 °C, 30 min, then CuO–$CuCl_2$, MeCN–H_2O, room temp. 15 min.; viii, $NaBH_4$, MeOH, 0 °C, 30 min; ix, TsOH, MeOH, 50 °C, 2 h; x, NBu_4F, THF, room temp. 2 h. DMP = 2,2-dimethoxypropane, DIBAH = diisobutylaluminium hydride.

to the optically active {$[\alpha]_D$ −65.6 (*c* 0.12, $CHCl_3$)} *N,N'*-diBoc *threo*-2,3-diaminobutane-1,4-diol **7** (mp 118–122 °C).

Targeted at a reversal of diastereoselectivity, the *N*-benzyl nitrone **9** was prepared (82%) as a single *Z* isomer (NOEDS as for **4**) from *O*-*tert*-butyldiphenylsilyl-*N*-*tert*-butoxycarbonyl L-serinal **8** by the same procedure employed to convert **3** to **4**. The addition of 2-lithiothiazole **1a** to **9** as above, afforded the hydroxylamine **10** with high *anti* selectivity (ds ≥ 95% by NMR) and good isolated chemical yield (86%). This compound was transformed into the corresponding *anti* diamino aldehyde **11** (50% overall yield) by the standard hydroxylamine reduction[2,3] and thiazolyl-to-formyl deblocking[13] protocols. The reduction of **11** to alcohol and desilylation led to the optically inactive {$[\alpha]_D$ 0 (*c* 0.25, $CHCl_3$)} *erythro* 2,3-diaminobutane-1,4-diol derivative **12** as a sticky oil.

The control of the face selectivity of nitrones **4** and **9** with 2-lithiothiazole **1a** is shown to be opposite to that observed for reactions of their aldehyde precursors **3** and **8** with neutral and anionic nucleophiles. Additions on the Garner's L-serinal **3** proceed preferentially with *anti* selectivity[5,14] according to a nonchelation-controlled Felkin–Anh model,[15] whereas the same reactions[16] on **7** (as well as on the *O*-benzyl substituted analogue)[5] occur with chelation-controlled *syn* selectivity owing to an intramolecular hydrogen bond (Cram chelate model).[15] The same stereochemical outcomes have been observed in addition[4] reactions to other *N*-mono- and *N,N*-diprotected aldehydes. Hence, transition-state models other than those applied to carbonyl additions are required for nitrone reactions. The modified Felkin–Anh transition-state model **A** (Fig. 2) wherein the medium sized substituent lies in the outside position because of the steric interaction with the nitrone group,[2b] accounts for the formation of the major *syn* adduct **5** from **4**. Models with the outside conformational position have been formulated for alkene addition.[15,17]

Furthermore, model **B** having a different reactive conformation of the nitrone,[18] explains the formation of the major *anti* adduct **10** from **9**. In this case the antiperiplanar position is occupied by the bulky siloxy group and the attack of **1a** occurs from the opposite side. Reaction *via* a Cram-chelate type arrangement,[5,16] would lead to the *syn* instead of the observed *anti* adduct.

In conclusion, a stereoselective route to C-2 diastereomeric 2,3-diamino-4-hydroxybutanals **6** and **11** from L-serine has been described. The scope and limitation of this approach to α,β-diamino aldehydes starting from other α-amino acids now become of interest.

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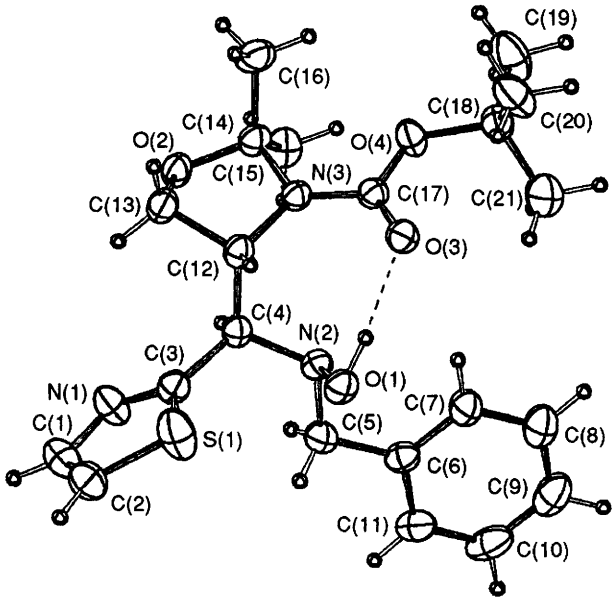

Fig. 1 ORTEP[21] view of compound **5** showing the thermal ellipsoids at 30% probability. The structural parameters for the intramolecular O(1)–H···O(3) hydrogen bond are O(1)–H 0.91(4), O(1)---O(3) = 2.712(3) Å, O(1)–H---O(3) 166(2)°.

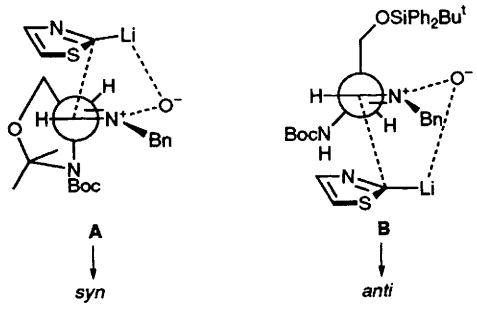

Fig. 2 Proposed transition-state models for the addition of 2-lithiothiazole **1a** to nitrones **4** and **9**

Footnotes

† All new compounds exhibited consistent spectral (^1H and ^{13}C NMR, IR) and analytical data. Optical rotations: 20 ± 2 °C (*c* 1, $CHCl_3$). ^1H NMR spectra (300 MHz, $CDCl_3$, 328 K). *Selected data*: **4**, mp 57 °C, $[\alpha]_D$ −46.6. **5**, mp 128 °C, $[\alpha]_D$ +51.1. **6** oil, $[\alpha]_D$ −33.0, IR ($CHCl_3$) ν/cm^{-1} 1710, ^1H NMR δ 1.38 (s, 3H), 1.42 (s, 9H), 1.47 (s, 9H), 1.52 (s, 3H), 3.93 (dd, 1H, *J* 9.6 and 2.0 Hz), 3.99 (dd, 1H, *J* 9.6 and 6.1 Hz), 4.32 (m, 2H), 5.44 (brs, 1H), 9.60 (brs, 1H). **8** $[\alpha]_D$ +8.6. **9** mp 110 °C, $[\alpha]_D$ +2.50, −4.38 (*c* 1.30, MeOH). **10** mp 115 °C (decomp.), $[\alpha]_D$ +3.5. **11** oil, $[\alpha]_D$ +4.2, IR ($CHCl_3$) ν/cm^{-1} 1725, ^1H NMR δ 1.05 (s, 9H), 1.42 (s, 9H), 1.44 (s, 9H), 3.60 (dd, 1H, *J* 10.2 and 7.0 Hz), 3.76 (dd, 1H, *J* 10.2 and 4.2 Hz), 4.28 (m, 1H), 4.40 (dd, 1H, *J* 7.4 and 3.9 Hz), 5.28 (brs, 1H), 5.56 (brd, 1H, *J* 7.4 Hz), 7.30–7.42 (m, 6H), 7.60–7.70 (m, 4H), 9.65 (brs, 1H).

‡ *Crystal data* for **5**: $C_{21}H_{29}N_3O_4S$, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 12.172(1), *b* = 465(4), *c* = 14.888(4) Å, *V* = 2259(1) Å^3, *Z* = 4, D_c = 1.23 g cm^{-3}, μ = 1.65 cm^{-1}. Of the 3056 unique measured reflections, 1817 with $I \geq 3\sigma(I)$ were used in the refinement. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogen atoms in calculated positions, except the hydrogen bonded to O(1) which was refined isotropically. R(on F) = 0.041, R_w = 0.049. The data were collected on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated Mo-Kα radiation, ω–2θ scan technique ($2 \leq \theta \leq 28°$). All data were corrected for Lorentz and polarization. The structure was solved by direct methods using the SIR88 package.[19] All other calculations were accomplished by MolEN.[20] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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