Tetrahedron Letters, Vol. 34, No. 34, pp. 5475-5478, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Stereocontrolled Addition of 2-Lithiothiazole to the Nitrone Derived from D-Glyceraldehyde Acetonide. A Revision and Extension

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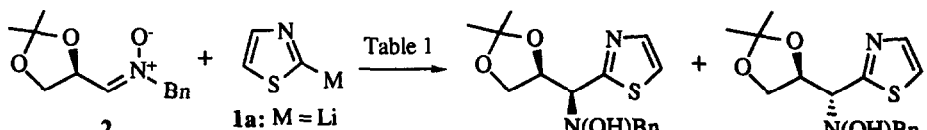
Key Words: thiazole, nitrones, hydroxylamines, aminohomologation, stereocontrolled addition

Abstract: *The sense of diastereoselective addition of 2-lithiothiazole* ***1a*** *to the nitrone* ***2*** *derived from D-glyceraldehyde is reversed by the use of Lewis acids (Et_2AlCl, $TiCl_4$) as complexing agents; the configuration of the hydroxylamine adduct obtained from* ***1a*** *and* ***2*** *in the absence of the above chelating agents, previously reported from these laboratories was revised.*

We have recently reported the addition of 2-lithiothiazole (**1a**) to nitrones followed by the thiazole to formyl deblocking as a new strategy for the one-carbon chain elongation of aldehydes with concomitant formation of a new stereocenter bearing an amino group (aminohomologation).[1] Having applied this methodology to the nitrone derived from α-D-galactohexodialdo 1,5-pyranose in a stereodivergent way[2] to give destomic acid and lincosamine precursors, we decided to explore in more detail the addition of C-2 metalated thiazoles **1** to the chiral model α-alkoxy substituted nitrone **2**, derived from D-glyceraldehyde. The results are summarized in Table 1.

The reactions[3] of 2-lithiothiazole (**1a**), 2-thiazolyl magnesium bromide (**1b**), and 2-(diethylaluminum)-thiazole (**1c**) with **2** (entries 1-3), occurred with good selectivities to give in all cases the same *N*-benzylhydroxylamine adduct as major diastereoisomer. A very modest selectivity in favor of the epimeric *N*-benzylhydroxylamine adduct was observed by addition of **1a** to **2** in the presence of 1 equiv. of $MgBr_2$ or $ZnBr_2$ (entries 4 and 5). The extent of the reversed diastereoselectivity became quite high using the Lewis acids Et_2AlCl or $TiCl_4$ as complexing agents[4] of **2** (entries 6 and 7). All reactions, with the exception of that employing the Grignard reagent **1b**, afforded the hydroxylamine adducts syn-**3a** and anti-**3b** in good overall yields.[5] These compounds were readily separated by column chromatography (silica, 3:1, hexane/diethyl ether).



2 **1a:** M = Li; **1b:** M = MgBr; **1c:** M = $AlEt_2$ **syn-3a** **anti-3b**

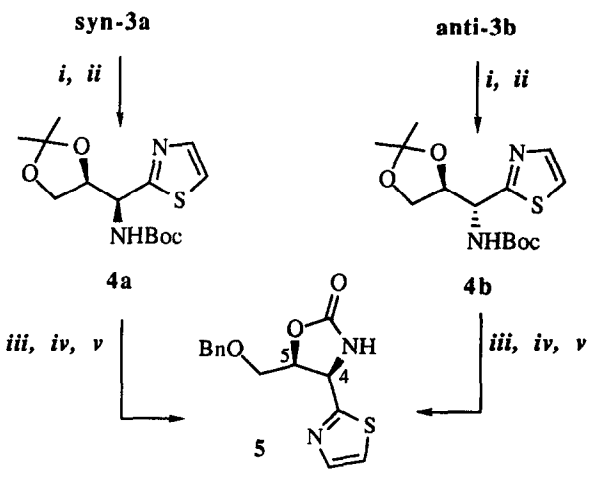
Table 1. Addition[a] of metalated thiazoles **1** to **2**

entry	M	T (°C)	Lewis Acid[b]	syn-**3a** : anti-**3b**[c]	yield (%)[d]
1	Li	- 80	none	92 : 8	82
2	MgBr	- 50	none	89 : 11	40
3	$AlEt_2$	- 20	none	83 : 17	73
4	Li	- 80	$MgBr_2$	46 : 54	81
5	Li	- 80	$ZnBr_2$	44 : 56	78
6	Li	- 80	Et_2AlCl	3 : 97	84
7	Li	- 80	$TiCl_4$	5 : 95	69

a: All reactions were carried out with 3:1 ratio **1**/**2** in Et_2O as a solvent. b: 1.0 equiv. c: Measured from the intensities of ^1H NMR signals at δ 7.822 (syn-**3a**) and δ 7.854 (anti-**3b**). d: Determined on isolated mixtures of syn-**3a** and anti-**3b**.

As the configuration of the major adduct obtained from the addition of 2-lithiothiazole (**1a**) to the nitrone **2** in the absence of Lewis acids as chelating agents was previously assigned through the oxazolidinone derived from it,[1] we decided to confirm in a similar way the configuration of the epimeric adduct formed from precomplexed **2** with Et_2AlCl or $TiCl_4$. Quite surprisingly, transformation of the hydroxylamine adducts syn-**3a** and anti-**3b** into the corresponding *N*-Boc protected amines[6] **4a** and **4b** (Scheme 1) and cyclization of these compounds to oxazolidinone, afforded the same stereoisomer[7] **5**.

Scheme 1

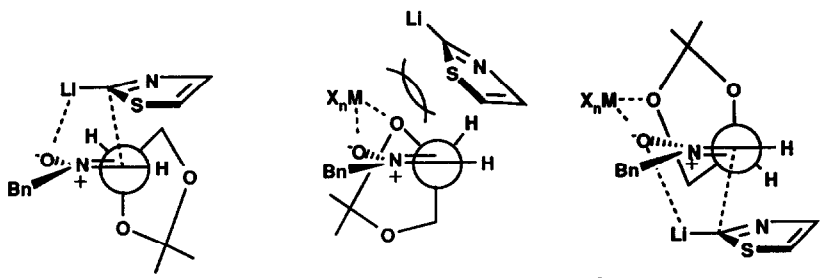


Reagents and conditions: *i*, $TiCl_3$, MeOH-H_2O, r.t., 10 min. *ii*, Boc_2O, dioxane, r.t., 12 h. *iii*, MeOH, TosOH, (cat.), 80°C, 3h. *iv*, $BrCH_2Ph$, NaH, DMF, -10°C, 2h. *v*, NaH, DMF, r.t., 4 h.

Evidently, the elaboration of syn-**3a** to the oxazolidinone occurs with epimerization at the carbon atom adjacent to the thiazole ring, very likely due to the basic conditions required for the benzylation and cyclization of the intermediate **4a**. This observation implies that the above procedure employed for the characterization of syn-**3a** and anti-**3b** is unreliable.

At this point, we were in the uneasy position to wonder whether our previous stereochemical assignement was correct.[1] Fortunately, the adduct obtained from **1a** and precomplexed **2** with Et_2AlCl or $TiCl_4$ was a crystallizable solid whose structure was determined by X-ray crystallography.[8] This compound turned out to be the isomer anti-**3b**. As a consequence, in contrast to our previous assignement,[1] the hydroxylamine adduct that was formed from **1a** and **2** in the absence of complexing agents is syn-**3a**.[9] Tentatively, we suggest that this stereochemical outcome is in agreement with a transition state model **A** similar to that involved in nucleophilic addition to C=C (Houk model).[10] This model wherein the medium size substituent occupies the outside position, appeared to be operative in addition[11] and cycloaddition[12] reactions to various α-alkoxy substituted nitrones including compound **2**. On the other hand, the reversed stereoselectivity observed upon precomplexation of **2** with Et_2AlCl or $TiCl_4$ is consistent with a β-chelation model **C** rather than the α-chelation one shown in **B**.

Figure 1



It is worth pointing out that the anti-selectivity of the addition of **1a** to the nitrone derived from D-arabinose in the absence of Lewis acids was demonstrated[1] by the conversion of the corresponding hydroxylamine adduct to N-acetyl-D-mannosamine and D-mannosamine hydrochloride. We now report that the same sense of selectivity was maintained by addition of **1a** to the nitrone precomplexed with 1.0 equiv. of Et_2AlCl. The lack of stereochemical control observed in this case suggests that the mechanism of addition is more complex that either a chelation or non-chelation rationale can explain. More details are required to understand the nature of the aluminum (or titanium) complex with this nitrone and thus the possible mechanism of the addition.

Acknowledgment. We thank the Ministerio de Educacion y Ciencia (Spain) and Consiglio Nazionale delle Ricerche (Italy) for finantial support. Thanks are also due to DGA (Spain) for a fellowship to S.F.

References and Notes

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2. Dondoni, A., Franco, S., Merchan, F., Merino, P., Tejero, T. *Synlett* **1993**, 78.
3. Metalated thiazoles **1** were generated in Et_2O : **1a**, from 2-bromothiazole and n-butyllithium at -80 °C; **1b**, from **1a** and $MgBr_2$ at -80 °C and then -50 °C; **1c**, from **1a** and Et_2AlCl at -80 °C and then at -20 °C.
4. Complexation of **2** is supported by the substantial changes of ^1H and ^{13}C NMR spectra (CD_2Cl_2, from -80 °C to r.t.) in the presence of 1 equiv. of Et_2AlCl.
5. syn-**3a**: oil, $[\alpha]_D$ = - 7.8° (c 0.74, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.28 (s, 3H), 3.70 (dd, 1H, J=7.9, 5.7 Hz), 3.84 (d, 1H, J=12.0 Hz), 3.94 (dd, 1H, J=8.2, 5.7 Hz), 3.98 (d, 1H, J=12.0 Hz), 4.38 (d, 1H, J=6.8 Hz), 4.72 (ddd, 1H, J=8.2, 7.9, 6.8 Hz), 6.45 (s, 1H, ex. D_2O), 7.28 (m, 5H), 7.38 (d, 1H, J=3.2 Hz), 7.82 (d, 1H, J=3.2 Hz).
   anti-**3b**: colourless crystals, mp 157-159 °C (Hexane-Et_2O), $[\alpha]_D$ = - 9.0° (c 0.39, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.32 (s, 3H), 3.71 (d, 1H, J=13.2 Hz), 3.79 (d, 1H, J=13.2 Hz), 4.05 (dd, 1H, J=8.5, 5.3 Hz), 4.15 (dd, 1H, J=8.5, 5.5 Hz), 4.16 (d, 1H, J=7.7 Hz), 4.72 (pseudo dt, 1H, J=7.7, 5.4 Hz), 6.43 (s, 1H, ex. D_2O), 7.26 (m, 5H), 7.39 (d, 1H, J=3.2 Hz), 7.85 (d, 1H, J=3.2 Hz).
6. syn-**4a**: colourless crystals, mp 85-86 °C (Hexane-Et_2O), $[\alpha]_D$ = - 18.6 ° (c 0.88, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, 55 °C) δ 1.32 (s, 3H), 1.43 (s, 3H), 1.45 (s, 9H), 3.87 (dd, 1H, J=8.5, 5.7 Hz), 4.10 (dd, 1H, J=8.5, 6.7 Hz), 4.70 (ddd, 1H, J=7.7, 6.7, 5.7 Hz), 5.08 (dd, 1H, J=7.7, 2.6 Hz), 5.42 (d, 1H, J=2.6 Hz), 7.24 (d, 1H, J=3.2 Hz), 7.73 (d, 1H, J=3.2 Hz).
   anti-**4b**: white solid, mp 93-95 °C (Hexane-Et_2O), $[\alpha]_D$ = + 3.5 ° (c 0.75, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, 55 °C) δ 1.31 (s, 3H), 1.37 (s, 3H), 1.42 (s, 9H), 4.03 (m, 2H), 4.46 (pseudo q, 1H, J=5.7 Hz), 5.13 (dd,1H, J=8.0, 5.6 Hz), 5.52 (d, 1H, J=8.0 Hz), 7.22 (d, 1H, J=3.2 Hz), 7.72 (d, 1H, J=3.2 Hz).
7. In both cases compound **5** was isolated in low yield (10-15%) from a rather complex mixture of products. Although in the absence of the epimer for comparison, the erythro configuration of **5** was assigned on the basis of the rather large H_4-H_5 coupling constant (J = 8.5 Hz). Much lower values (J = 4.9 Hz) have been quoted for threo oxazolidinones. See : Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.*, **1990**, *55*, 1439.
   5: ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (dd, 1H, J=10.9, 6.1 Hz), 3.44 (dd, 1H, J=10.9, 5.2 Hz), 4.26 (d, 1H, J=11.7 Hz), 4.34 (d, 1H, J=11.7 Hz), 5.07 (ddd, 1H, J=8.5, 6.1, 5.2 Hz), 5.37 (d, 1H, J=8.5 Hz), 5.65 (bs, 1H, ex. D_2O), 7.27 (m, 5H), 7.36 (d, 1H, J=3.2 Hz), 7.79 (d, 1H, J=3.2 Hz).
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9. Obviously, the syn-configuration has to be reassigned also to the α-amino aldehyde (compound **7** in our previous report[1]) derived from syn-**3a**.
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(Received in UK 7 May 1993; accepted 1 July 1993)