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Stereocontrol by Diethylaluminum Chloride in the Addition of 2-Lithiofuran and *N*-Methyl-2-Lithioimidazole to α-Alkoxy Nitrones. Total Synthesis of 5-*O*-Carbamoylpolyoxamic Acid.

Alessandro Dondoni*[a], Santiago Franco[b], Francisco Luis Merchán[b], Pedro Merino*[b], and Tomás Tejero[b]

a) Dipartimento di Chimica, Laboratorio di Chimica Organica , Università, Ferrara, Italy.

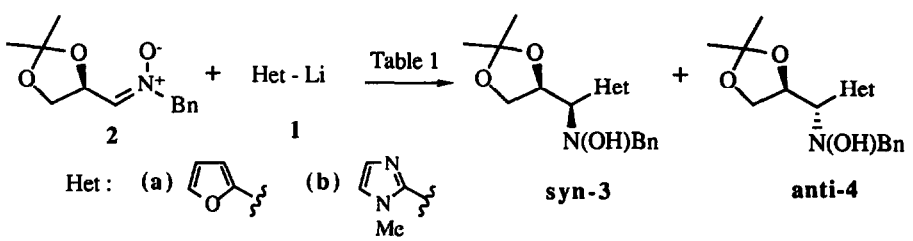
b) Departamento de Química Orgánica, ICMA, Universidad de Zaragoza, CSIC, Zaragoza, Spain.

Key Words: furan, imidazole, nitrones, α-amino-β-hydroxy acids, polyoxamic acid

Abstract: *The addition of the title metalated heterocycles **1** to the nitrone **2** derived from D-glyceraldehyde acetonide leads to the corresponding syn-adducts as major products (ds 88-96 %) while the reaction in the presence of Et_2AlCl leads to anti isomers (ds 79-95 %); the synthesis of 5-O-carbamoylpolyoxamic acid from 4-O-benzyl-2,3-O-isopropylidene-L-threose via the nitrone-furan adduct is described*

In the preceeding paper[1c] we have described the diastereofacial selectivity control exerted by Lewis acids on the addition of 2-lithiothiazole to the nitrone **2** derived from D-glyceraldehyde acetonide.The application of the thiazole-aldehyde synthesis[2] to the resultant syn- and anti-hydroxylamine adducts showed a new route to optically active polyalkoxy α-amino aldehydes from deaminated one-carbon lower homologues (aminohomologation). By this strategy, totally chemical syntheses of D-mannosamine from D-arabinose[1a] and lincosamine and destomic acid from α-D-galactodialdopyranose[1b] were described We now wish to report a significant extension of the scope of the above methodology using the synthetically interesting heterocycles[3] furan and *N*-methylimidazole as carbon nucleophiles (Scheme 1).

Scheme 1



The reaction of the 2-lithio derivatives **1a** and **1b** of furan and *N*-methylimidazole respectively[4] with the nitrone **2** in THF-Et_2O as a solvent at -80 °C afforded the corresponding syn-adducts **3a** and **3b** in good yields and high degrees of diastereoselectivity (Table 1, entries 1 and 3). On the other hand, the addition of **1a** and

1b to the precomplexed[1c] nitrone **2** with 1.0 equiv. of Et_2AlCl in Et_2O as a solvent, showed a reversed diastereoselectivity leading to the anti-isomers **4a** and **4b** as major products (entries 2 and 4). On the basis of transition state models holding for the addition of 2-lithiothiazole[1c] to **2**, the stereochemistry of syn-**3** and anti-**4** was tentatively assigned as indicated, which was confirmed later (vide infra).

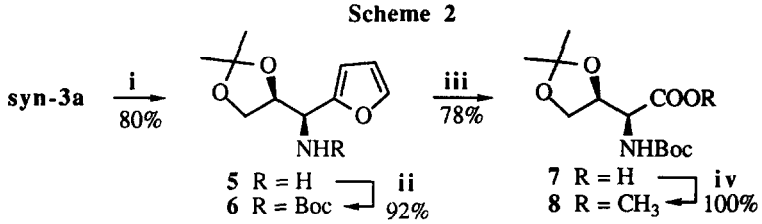
Table 1. Addition[a] of Het-Li **1** to **2**

entry	Het-Li	T (°C)	Lewis Acid[b]	syn-**3** : anti-**4** [c]	yield (%)[d]
1	**1a**	- 80	none	96 : 4	92
2	**1a**	- 80	Et_2AlCl	5 : 95	89
3	**1b**	- 80	none	88 : 12	81
4	**1b**	- 80	Et_2AlCl	21 : 79	76

a: All reactions were carried out with 3:1 ratio **1**/**2** in THF-Et_2O as a solvent. b: 1.0 equiv. c: Measured from the intentisities of ^1H NMR signals. d: Determined on isolated mixtures of syn-**3** and anti-**4**.

The proclivity of the furan ring to undergo various synthetic elaborations is well documented.[3] A very attractive one was the oxidation to carboxylic acid[5] since the application to adducts **3a** or **4a** would provide a straightforward entry to α-amino acids. Thus, the catalytic hydrogen transfer reduction of **3a** afforded the amine **5** (Scheme 2) which was characterized as the *N*-tert-butoxycarbonyl derivative **6**, oil, $[\alpha]_D$ = -27.8 ° (c 0.4, $CHCl_3$). The furan ring of **6** was then oxidized[5b] to give the carboxylic acid **7** using RuO_2 in the presence of $NaIO_4$ as a reoxidant. Transformation of **7** into the corresponding methyl ester[6] **8** served for a complete.characterization of the acid as well as a confirmation[7] of the assigned stereochemistry of **3a**. It is worth to point out that the above methodology as an overall indicates a nitrone-based stereoselective route to α-amino-β-hydroxyacids[8] from α-hydroxyaldehydes employing the furan ring as a masked carboxylate moiety. Exploitation of the *N*-methylimidazole derivatives syn-**3b** and anti-**4b** in synthesis is still underway.

Scheme 2

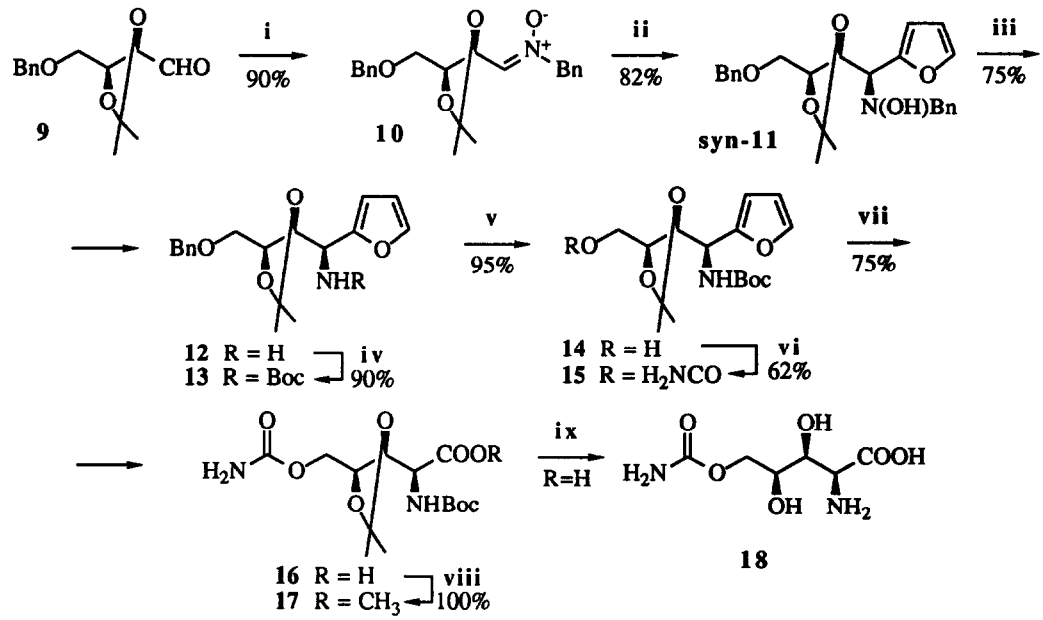


Reagents and conditions: *i*, $HCOONH_4$, MeOH, Pd-C 10%, reflux, 3 h. *ii*, Boc_2O, dioxane, r.t., 12 h. *iii*, RuO_2, $NaIO_4$, CH_3CN-H_2O-CCl_4, r.t., 5 min. *iv*, CH_2N_2, Et_2O, r.t., 5 min.

We envisaged application of the above nitrone-based amino acid synthesis for the preparation 5-*O*-carbamoylpolyoxamic acid[9] **18**, a building block of the nucleoside antibiotic polyoxin J. To this aim (Scheme 3) the protected L-threose **9** (Mukaiyama's aldehyde)[9c] was converted to the nitrone **10** (mp 67-68 °C, $[\alpha]_D$ = -20.3 ° (c 0.18, $CHCl_3$)) which reacted with 2-lithiofuran **1a** (THF, -80 °C) to give[10] the *N*-benzylhydroxylamine syn-**11** (ds 92% by ^1H NMR) in 82% isolated yield after column chromatography (silica, 4:1 hexane / diethyl ether) as an oil, $[\alpha]_D$ = -42.7 ° (c 1.0, $CHCl_3$). This compound treated with $TiCl_3$ in

aqueous methanol and then with wet SiO_2 furnished the amine **12** which was characterized as the *N*-tert-butoxycarbonyl derivative **13**, oil, $[\alpha]_D$ = -41.88 ° (c 0.47, $CHCl_3$). Debenzylation of **13** followed by carbamoylation afforded the compound **15**, oil, $[\alpha]_D$ = -24.0 ° (c 1.50, $CHCl_3$), from which the carboxylic acid **16** was revealed by Ru-based oxidation of the furan ring.[5] This compound was characterized through its methyl ester[11] **17** showing physical properties in good agreement with literature values which confirmed the assigned stereochemistry to the adduct syn-**11**. The ready transformation of **16** to the polyoxamic acid derivative **18** by acidic treatment has been previously described.[9a] The overall yield of **16** (21.7 % from the aldehyde **9**) is comparable to that obtained by another synthetic route[9e] starting from the same aldehyde **9**.

Scheme 3



Reagents and conditions: *i*, $PhCH_2NHOH$, CH_2Cl_2, r.t., 12 h. *ii*, 2-lithiofuran, THF,-80 °C, 15 min. *iii*, $TiCl_3$, MeOH-H_2O, r.t., 25 min, then SiO_2, CH_2Cl_2-H_2O. *iv*, Boc_2O,dioxane, r.t., 12 h. *v*, Na, liq. NH_3, -50 °C, 15 min. *vi*, p-nitrophenyl chloroformate, Py, 0 °C, 18 h, then NH_3, MeOH, 0 °C, 1h. *vii*, RuO_2, $NaIO_4$, CH_3CN-H_2O-Cl_4C, r.t., 5 min. *viii*, CH_2N_2, Et_2O, r.t., 5 min. *ix*, H^+ (ref. 9a)

In conclusion, a new stereocontrolled synthesis of α-amino-β-hydroxyacids via the furan addition to nitrones has been explored. The scope of this synthetic methodology and the application to the synthesis of natural products are under investigation in our laboratories.

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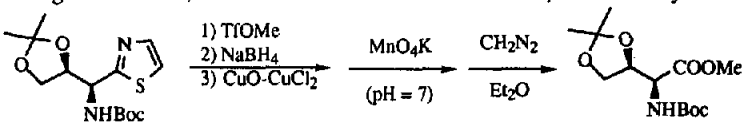
2. For recent reviews on this strategy , see : Dondoni, A. In *Modern Synthetic Methods*, Scheffold, R. (Ed.), Verlag Helvetica Chimica Acta, Basel, 1992, p. 377. Dondoni, A. In *New Aspects of Organic Chemistry II*, Yoshida, Z. and Ohshiro, Y. (Eds), Kodansha, Tokyo, and VCH, Weiheim, 1992, p. 105.
3. For a review on the synthetic utility of five-membered heteroaromatics, see Lipshutz, B.H. *Chem. Rev.* **1986**, *86*, 795.
4. The reagents **1** were generated in situ as follows : **1a**, from furan and n-BuLi in THF at -80 °C , then 0 °C for 2 hr; **1b**, from *N*-methylimidazole and n-BuLi in THF at -80 °C, then at -10 °C for 30 min.
5. For the use of furan as precursor to the carboxyl acid, see: a) Mukaiyama, T., Tsuzuki, R., Kato, J. *Chem. Lett.* **1985**, 837. b) Danishefsky, S.J., DeNinno, M.P., Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929. c) Poss, H.A., Reid, J.A. *Tetrahedron Lett.* **1992**, *33*, 1411.
6. **8**: oil, $[\alpha]_D$ = -66.5 ° (c 0.19, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.31 (s, 3H), 1.43 (s, 9H), 3.76 (s, 3H), 3.78 (dd, 1H, J=8.5, 6.7 Hz), 4.06 (dd, 1H, J=8.5, 6.7 Hz), 4.37 (dd, 1H, J=9.4, 2.3 Hz), 4.56 (pseudo td, 1H, J=6.7, 2.3 Hz), 5.18 (d, 1H, J=9.4 Hz).
7. Compound **8** was identical ($[\alpha]_D$, NMR) to a sample prepared from the thiazole derivative[1c] syn-**19** by formyl deblocking as described,[1a] oxidation under neutral conditions, [12] and methylation.



syn-19 **8**

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10. The same reaction carried out in the presence of 1 equiv. of Et_2AlCl afforded the anti-isomer (ds 93 %).
11. **17**: oil, $[\alpha]_D$ = - 3.7 ° (c 0.49, CH_2Cl_2), [Lit.[9a] $[\alpha]_D$ = - 3.6 ° (c 1.50, CH_2Cl_2)], ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.39 (s, 3H), 1.42 (s, 9H), 3.76 (s, 3H), 3.99 (pseudo dt, 1H, J=8.3, 5.0 Hz), 4.23 (d, 2H, J=5.0 Hz), 4.26 (dd, 1H, J=8.3, 1.8 Hz), 4.48 (dd, 1H, J=9.8, 1.8 Hz), 4.89 (br s, 2H), 5.27 (d, 1H, J=9.8 Hz).
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