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Nucleophilic Additions of 2-Furyllithium to Carbonyl Derivatives of L-Serine. Formal Synthesis of (2R,3R)-b-Hydroxy Aspartic Acid.

P. Merino*, S. Franco, F.L. Merchan and T. Tejero

Departamento de Quimica Organica, Facultad de Ciencias, ICMA, Universidad de Zaragoza, E-50009 Zaragoza, Aragon, Spain. Fax: +34 (9)76 761194. E-mail: pmerino@posta.unizar.es

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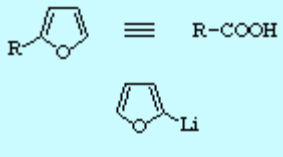
Abstract. The nucleophilic addition of 2-furyllithium to esters derived from L-serine is described. The obtained furyl ketone **5** is stereoselectively reduced (ds>=95%) with sodium borohydride to afford the corresponding syn aminoalcohol **12** in enantiomerically pure form. Compound **12** was further converted into valuable a-hydroxy-[beta]-amino acids by means of the furan-to-acid equivalence.

Keywords: L-Serine, Furan, Furylketones, Hydroxyaminoacids, Aspartic Acid.

Due to the synthetic equivalence of a variety of heterocyclic systems with several functional groups of interest [1] the introduction of heterocyclic nuclei into carbon frameworks is the key stage in the synthesis of many biologically active compounds [2]. Among the most extensively studied heterocyclic systems are furan [3], benzotriazole [4] and thiazole [5]. In particular the furan ring is very attractive because it is resistant to acids and bases and nevertheless it is readily cleaved to carboxyl by means of either ruthenium-mediated oxidation or ozonolysis [6].



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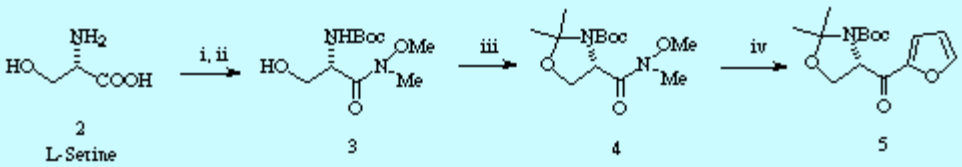
Reactions of 2-furyllithium **1** with sufficiently active electrophiles, e.g. organic halides, are convenient methods for the formation of a C-C bond [7]. Also, the reaction of metalated furans with carbonyl compounds constitutes a useful way of introducing the furan ring; in this context, a vast number of examples concerning the addition of metalated furans to aldehydes and ketones can be found in the literature [8]. By contrast, only a few reports on the addition of organometallic derivatives of furan to acid derivatives, such as acid halides, esters or amides have been described [9]. In this communication we wish to report our latest efforts at expanding the scope of the synthetic utility of the furan ring. The nucleophilic addition of 2-furyllithium **1** to acid derivatives of L-serine and progress towards a-hydroxy-b-amino acids are discussed.

The starting material of our studies was the O,N-dimethylhydroxamate **4** (Scheme 1) easily available from L-Serine **2** in three steps as described [10]. We chose compound **4** since we sought that O,N-dimethylhydroxylamates had been described as suitable electrophiles in nucleophilic additions of organometallic compounds towards the synthesis of ketones [11].

Scheme 1[a]



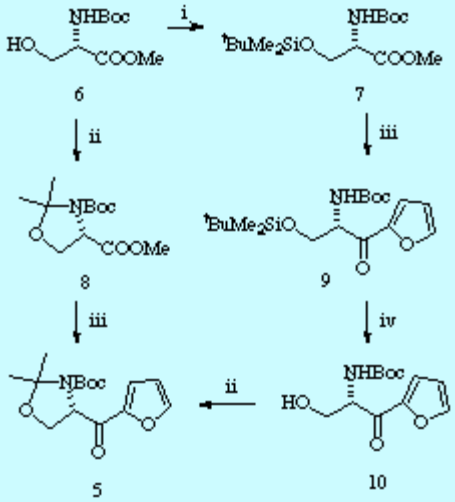
2 L-Serine 3 4 5

[a]Reagents and Conditions: i, Boc_2O, NaOH, r.t. ii, MeNH(OMe)•HCl, WSC, H_2O-THF. iii, DMP, acetone, BF_3OEt_2, r.t. iv, 2-furyllithium, THF, -40 °C.

The addition of 1.05 equivalents of 2-furyllithium **1** to hydroxamate **4** in THF as a solvent afforded the expected furyl ketone **5** in only 20% yield after 12 h at -40 deg.C, a substantial amount of starting material (c.a. 50%) being recovered. Longer times of reaction did not improve the conversion and when the reaction was carried out at higher temperatures the yield dropped considerably. It is worth of mention that Guanti and co-workers reported that compound **4** showed a poor reactivity upon the addition of several organometallic reagents such as ethyl- and vinyllithium [12].

In order to obtain the furyl ketone **5** with an acceptable chemical yield and purity we decided to explore an alternative approach using the well-known methyl ester [13] **6**. Two different protecting groups arrangements were checked, the best results being obtained with the oxazolidine **8** (Scheme 2). Whereas the addition of 2-furyllithium **1** (2.1 equiv., THF, -40 deg.C) to ester **7** afforded the corresponding ketone **9** in 45% yield, the addition of **1** (1.05 equiv., THF, -40 deg.C) to ester **8** provided the furyl ketone **5** in 74% yield after 4 h of reaction [14]. In both cases a small amount of starting material (c.a. 10%) was recovered.

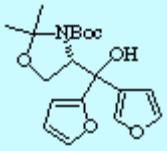
Scheme 2[a]



6 7 8 9 5 10

[a]Reagents and Conditions: i, $^tBuMe_2SiCl$, DMF, imidazole, r.t. ii, DMP, acetone, BF_3OEt_2, r.t. iii, 2-furyllithium, THF, -40 °C. iv, Bu_4NF, THF, r.t.

If the reaction is extended in order to achieve a higher degree of conversion, the frequent drawback associated with the nucleophilic addition of organometallic reagents to esters (the addition of two molecules of reagent) became apparent with the formation of substantial amounts of the tertiary alcohol **11**.



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The furyl ketone **9** can be converted into furyl ketone **5** by replacing the protecting groups, i.e. fluoride-mediated desilylation to afford ketone **10** and subsequent formation of the oxazolidine ring (Scheme 2)

Mindful of the highly syn-selective reduction of both a-amino and a-alkoxy ketones with sodium borohydride [15] we decide to exploit that reagent for preparing the required syn aminoalcohol **12**. The reduction of **4** was carried out with an excess of $NaBH_4$ in methanol as a solvent at -60 deg.C and it occurred with an excellent level of diastereoselectivity (ds>=95%), only one isomer being detectable by ^1H NMR spectroscopy (300 MHz) [16]. The almost complete syn selectivity found in the reduction reaction may be ascribed to the Felkin-Anh-Houk open-chain model for asymmetric induction [17] and is also consistent with the earlier observations made regarding the stereoselectivity of the reduction of a-amino ketones [15]. Thus the transition state model associated with the reduction of **5** is presented in Figure 1.

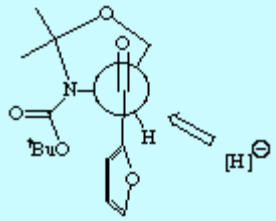
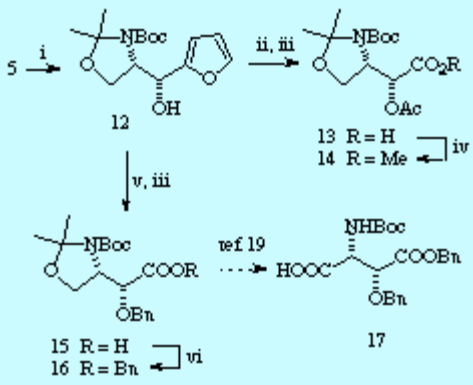


Figure 1. Proposed model for the reduction of **5**

The application of the furan-to-acid conversion to **12**, after protection of the hydroxyl group as an acetate, afforded the carboxylic acid **13** which was converted *in situ* into the a-hydroxy-b-amino ester **14** [18]. The same protocol was applied to **12** after benzylation of the secondary alcohol thus providing (after *in situ* benzylation of the resulting carboxylic acid **15**) the known [19] benzyl ester **16**. The physical and spectroscopic properties of **16** were in good agreement with those reported for its enantiomer [19]. Since the antipode of compound **16** has been previously converted [19] to the enantiomer of the 2-amino-3-hydroxy diamino acid **17**, the reaction sequence described above constitutes a formal synthesis of **17**, a protected form of the (2R,3R)-b-hydroxy aspartic acid [20].

Scheme 3[a]



[a]Reagents and Conditions: i, $NaBH_4$, MeOH, -60°C. ii, Ac_2O, Py, r.t iii, $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, r.t iv, CH_2N_2, Et_2O, 0 °C. v, NaH, BnBr, DMF, 0°C. vi, BnBr, DMF, K_2CO_3, r.t

In conclusion, a new approach to syn a-hydroxy-b-amino acids via furan chemistry has been achieved. The scope of this methodology and its application to the synthesis of various compounds of interest will be reported in due course.

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[14] *Typical experimental procedure:* To a cold (-80 deg.C) stirred solution of butyllithium (2.63 mL, 4.2 mmol of 1.6M solution in hexanes) in THF (10 mL), was added, dropwise, a solution of furan (0.272 g, 0.29 mL, 4 mmol) in the same solvent (10 mL). After the solution had been stirred at -80 deg.C for 5 min and at 0 deg.C for 2 h, the resulting mixture was cooled to -80 deg.C and a solution of the corresponding ester (3.86 mmol of **8** or 1.93 mmol of **9**) in THF (15 mL) was added slowly. The mixture was allowed to warm to -40 deg.C, stirred at this temperature for 4 h, and saturated aqueous $NaHCO_3$ (10 mL) was then added. The mixture was allowed to warm to room temperature over 15 min, diethyl ether was added (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to give the pure products. Data for **5**: white solid; mp 122-123 deg.C; $[a]_D$ -32.9 (c 0.52, $CHCl_3$); IR ($n_{C=O}$) 1695, 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 55 deg.C) d 1.28 (s, 3H), 1.57 (s, 3H), 1.71 (s, 9H), 3.95 (dd, 1H, J = 8.8, 3.4 Hz), 4.26 (dd, 1H, J = 8.8, 7.3 Hz), 5.15 (m, 1H), 6.5 (bs, 1H), 7.23 (m, 1H), 7.57 (m, 1H). Data for **9**: oil; $[a]_D$ -4.9 (c 0.67, $CHCl_3$); IR ($n_{C=O}$) 1690, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) d-0.10 (s, 3H), -0.08 (s, 3H), 0.75 (s, 9H), 1.42 (s, 9H), 3.90 (dd, 1H, J = 10.1, 4.7 Hz), 4.05 (dd, 1H, J = 10.1, 3.6 Hz), 5.05 (ddd, 1H, J = 10.1, 8.2, 3.6 Hz), 5.55 (bd, 1H, J = 8.2 Hz), 6.52 (dd, 1H, J = 3.5, 1.5 Hz), 7.28 (dd, 1H, J = 3.5, 1.0 Hz), 7.05 (dd, 1H, J = 1.5, 1.0 Hz).

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[16] Data for **12:** sticky oil; $[a]_D$ -5.7 (c 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O, 55 deg.C) d 1.48 (s, 3H), 1.51 (s, 9H), 1.53 (s, 3H), 3.75 (bt, 1H, J = 5.4 Hz), 3.85 (dd, 1H, J = 9.5, 6.1 Hz), 4.35 (bt, 1H, J = 6.8 Hz), 4.78 (d, 1H, J = 8.8 Hz), 6.29 (d, 1H, J = 3.0 Hz), 6.31 (dd, 1H, J = 3.0, 1.6 Hz), 7.38 (d, 1H, J = 1.6 Hz)

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[18] Data for **14**: oil; $[a]_D$ -65.3 (c 0.81, $CHCl_3$), Lit.[15]: $[a]_D$ -64.2 (c 0.60, $CHCl_3$) ; ^1H NMR (DMSO-d_6, 115 deg.C) d 1.62 (s, 3H), 1.65 (s, 9H), 1.69 (s, 3H), 2.10 (s, 3H), 3.66 (s, 3H), 3.95 (m, 2H), 4.20 (m, 1H), 5.21 (bd, 1H, J = 5.2 Hz).

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