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Stereocontrolled synthesis of α-furyl amines and α-furyl carbinols

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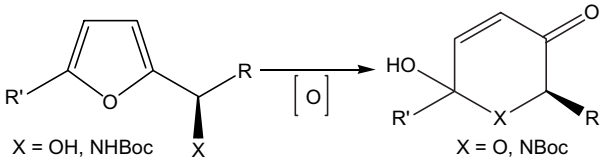
Abstract—A novel stereocontrolled synthesis of optically active α-furyl amines and α-furyl carbinols from α,β-aziridine and α,β-epoxy aldehydes using a *one-pot* aldol reaction–intramolecular enolcyclization is described.

Furans are considered very useful building blocks for a wide variety of natural or biologically active compounds; no doubt among their numerous derivatives α-furyl carbinols and α-furyl amines are the most employed in organic synthesis. The former, for example, are used as precursors in the synthesis of sugar, cyclopentenones, antimicotics and pheromones,[1] while the latter in the synthesis of α-amino acids, β-lactams, indolizidines, quinolizidines and piperidine alkaloids.[2]

To these purposes, an important transformation of both α-furyl carbinols and α-furyl amines is their oxidative rearrangement: oxidants such as *m*-chloroperbenzoic acid,[3] peracetic acid,[4] bromine in methanol,[5] pyridinium chlorochromate,[6] NBS,[7] etc., are able to transform them into the corresponding six-membered heterocycles [2*H*-pyran-3(6*H*)-ones and dihydropyridones, respectively, key intermediates in many synthetic sequences (Scheme 1)].



Scheme 1.

Keywords: α,β-Epoxy aldehydes; α,β-Aziridine aldehydes; Aldol condensation; Enolcyclization; α-Furyl amines; α-Furyl carbinols.
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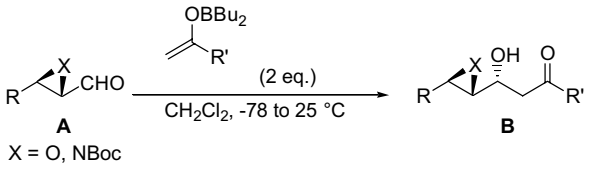
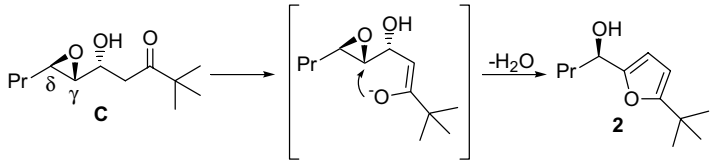
Conventional routes developed for the preparation of chiral furyl alcohols include Sharpless asymmetric dihydroxylation of vinyl furans,[8] asymmetric catalytic hydrogenation of furyl ketones,[9] kinetic and enzymatic resolution of racemic furyl alcohols[10] and asymmetric catalytic alkylation of furaldehydes.[11] Likewise, chiral furyl amines are prepared through kinetic resolution of racemic furyl amines,[12] alkylation of chiral imines[13] or asymmetric aminohydroxylation of vinyl furans.[14] Despite this, to the best of our knowledge, no methods have ever been reported, which make use of open chain as starting material; in this letter we wish to describe a novel synthesis of these compounds from α,β-epoxy and α,β-aziridine aldehydes using a *one-pot* aldol reaction–intramolecular enolcyclization.

Recently, we have reported a stereocontrolled addition of boron enolates to *trans* α,β-epoxy[15] and α,β-aziridine aldehydes[16] of type **A**: the reaction proceeds with excellent *anti* stereoselectivity furnishing the corresponding β-hydroxy ketone **B** independently of the hindrance present at the heterocyclic ring (Scheme 2).

On the basis of the behaviour observed with some similar substrates,[17] we supposed that the particular



Scheme 2.



Scheme 3.

Table 1. Conditions tested to generate the enolate

Base	Solvent	Additive	Yield (%)
LDA	THF	—	15
LDA	THF	LiOH	20
LDA	THF	$LiClO_4$	40
LDA	THF	LiCl	50
LDA	DME	LiCl	30
LDA	Et_2O	LiCl	50
Na_2CO_3	CH_2Cl_2	—	20
Bu_2BOTf/DIPEA	CH_2Cl_2	—	80

structure of **B**, having a heterocyclic ring in γ,δ-position to a ketonic group, was suitable for an intramolecular cyclization through the formation of an enolate intermediate (Scheme 3). The Baldwin rules suggest the regioselective attack of the enolic oxygen in the γ position leading to the furan ring.[18]

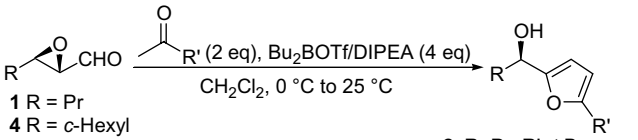
With this in mind, we submitted **C**, chosen as test compound, to various basic conditions in order to generate the enolate; in some cases Lewis acid was employed as additive to activate the heterocycle in the cyclization step. As shown in Table 1, the best result was obtained using the Bu_2BOTf/DIPEA system, which afforded furan **2** in good yield.

Since Bu_2BOTf/DIPEA is also the system used in the aldolic condensation, we thought it was possible to obtain the furan structure directly during the addition reaction by a *one-pot* procedure, increasing both the ratio aldehyde/methyl ketone/base and the reaction time. Indeed, using a ratio α,β-epoxy aldehyde–methyl ketone–Bu_2BOTf/DIPEA = 1:2:4 in CH_2Cl_2 at room temperature, **2** was obtained in ca. 6 h in a satisfactory chemical yield (71%).

Moreover, it is possible to obtain the α-furyl carbinol **2** in optically active form; its enantiomeric excess, as determined by ^1H NMR analysis of the corresponding MTPA ester, results the same as that of the starting chiral 2,3-epoxy alcohol, thus demonstrating that the reaction occurs with complete stereoselectivity.

The effectiveness of this methodology was tested also on the α,β-epoxy aldehydes **4** and **7**, where a sterically demanding substituent is present at position C-3 and using, besides pinacolone, also 3-methyl-2-butanone, a ketone which may enolize in two different directions. In Table 2 the satisfactory results obtained are reported, which demonstrate that this stereocontrolled reaction does not depend on the hindrance present at the oxirane ring and, consequently, the methodology can be considered of general applicability.

Table 2. α-Furyl carbinols from α,β-epoxy aldehyde[19]



1 R = Pr
4 R = *c*-Hexyl
7 R = *t*-Bu

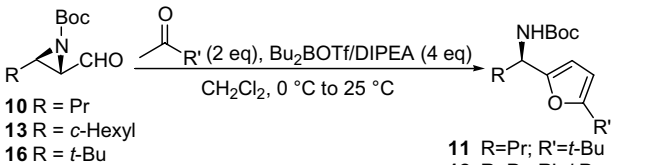
2 R=Pr; R'=*t*-Bu
3 R=Pr; R'=*i*-Pr
5 R=*c*-Hexyl; R'=*t*-Bu
6 R=*c*-Hexyl; R'=*i*-Pr
8 R=*t*-Bu; R'=*t*-Bu
9 R=*t*-Bu; R'=*i*-Pr

α,β-Epoxy aldehyde	Ketone	α-Furyl alcohol	Yield (%)
1		**2**	71
		**3**	75
4		**5**	75
		**6**	81
7		**8**	65
		**9**	67

The same reaction conditions, when employed on α,β-aziridine aldehyde **10**, **13** and **16**, afforded the expected α-furyl amines with good chemical yields (Table 3).

In conclusion, we have developed a new and general *one-pot* stereocontrolled aldol reaction–intramolecular enolcyclization, which allowed us to prepare α-furyl amines and α-furyl carbinols with various substitution patterns starting from α,β-aziridine aldehydes and α,β-epoxy aldehydes. Moreover, the possibility to obtain these compounds in optically active form makes this methodology very attractive; studies directed to the application in the synthesis of spiroketal pheromones[20] are currently underway.

Table 3. α-Furyl amines from α,β-aziridine aldehyde



10 R = Pr
13 R = *c*-Hexyl
16 R = *t*-Bu

11 R=Pr; R'=*t*-Bu
12 R=Pr; R'=*i*-Pr
14 R=*c*-Hexyl; R'=*t*-Bu
15 R=*c*-Hexyl; R'=*i*-Pr
17 R=*t*-Bu; R'=*t*-Bu
18 R=*t*-Bu; R'=*i*-Pr

α,β-Aziridine aldehyde	Ketone	α-Furyl amine	Yield (%)
10		**11**	72
		**12**	72
13		**14**	70
		**15**	71
16		**17**	78
		**18**	80

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19. Representative procedure for *one-pot* aldol reaction-intramolecular enolcyclization: di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 4 mmol) was added dropwise to a stirred solution of ketone (2 mmol) in 4 mL of CH_2Cl_2 at 0 °C. After 10 min, ethyldiisopropylamine (4 mmol in 3 mL of CH_2Cl_2) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. To the above enolate, a solution of α,β-aziridine aldehyde or α,β-epoxy aldehyde (1 mmol) in 2 mL of CH_2Cl_2 was added. The reaction was allowed to warm to room temperature and after ca. 6 h (TLC monitoring) was quenched with a mixture of MeOH (6 mL), aqueous phosphate buffer (4 mL, pH = 7) and H_2O_2 (4 mL of a 30% solution). The aqueous layer was extracted with two portions of AcOEt and the combined organic extracts dried (Na_2SO_4) and concentrated. The residue was purified on silica gel.
1-(5-*tert*-Butyl-furan-2-yl)butan-1-ol, **2**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.08 (d, *J* 2.9, 1H); 5.87 (d, *J* 2.9, 1H); 4.63 (t, *J* 6.6, 1H); 1.91–1.74 (m, 3H); 1.53–1.31 (m, 2H); 1.25 (s, 9H); 0.92 (t, *J* 7.3, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 163.6; 154.8; 105.9; 102.2; 67.5; 37.4; 32.6; 28.9; 18.8; 13.8.
[1-(5-*tert*-Butyl-furan-2-yl)butyl]-carbamic acid *tert*-butyl ester, **11**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.01 (d, *J* 2.9, 1H); 5.84 (d, *J* 2.9, 1H); 4.85–4.55 (m, 2H); 1.87–1.52 (m, 2H); 1.43 (s, 9H); 1.42–1.25 (m, 2H); 1.24 (s, 9H); 0.91 (t, *J* 7.3, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 160.9; 155.2; 153.0; 105.7; 102.8; 79.3; 50.7; 36.5; 32.5; 28.3; 27.7; 19.0; 13.9.
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