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Oxazaborolidine catalysed enantioselective reduction of 2-acyl thiophenes and 2-acyl furans

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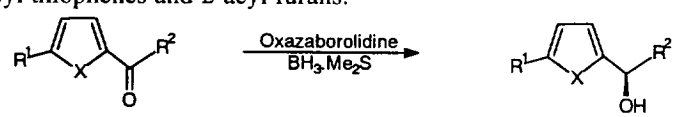
Abstract: 2-Thienyl and 2-furyl carbinols are prepared in good enantiomeric excess (up to 93% *ee*) through oxazaborolidine catalysed reduction of the corresponding ketones.

Optically active thienyl and furyl carbinols form an important class of compounds, because the heterocyclic group can be used for a variety of manipulations. For example, one can synthesize a series of dihydropyranes which would serve subsequently as suitable substrates for the facile introduction of various other functionalities, and for the synthesis of certain biologically active compounds.[1] 2-Furyl ethanol is a key intermediate in the synthesis of L-daunosamine.[2] The synthetic utility of these compounds for the synthesis of useful α-alkoxy carboxylic acids and γ-lactones and carbohydrates has been demonstrated.[3]

Hitherto the preparation of these compounds involved Sharpless kinetic resolution[4] or enzymatic resolution[5] or the enantioselective alkylation of furfuryl aldehyde and thiophene aldehyde with dialkylzinc compounds.[6] The kinetic resolution which is widely applied for the preparation of these compounds suffers with the inherent disadvantage that the maximum yield can be 50%. The enantioselective alkylation can be limited to only a few dialkylzinc derivatives. The enantioselective reduction of thienyl and furyl ketones is addressed scantily in the literature.[7] As a part of our programme dealing with the asymmetric reductions of prochiral ketones,[8] we examined some heterocyclic ketones as the substrates. The present report describes the oxazaborolidine catalysed reduction of some representative 2-acyl thiophenes and 2-acyl furans.



X= O, S (up to 93% *ee*)

We initially studied the reduction conditions for the two typical derivatives such as 2-acetyl furan and 2-acetyl thiophene which have been studied earlier.[7] The reduction of these compounds proceeded smoothly with 1 equivalent of borane dimethylsulphide complex (BMS) and 10 mol% of oxazaborolidine catalyst (CBS)[9] to give alcohols in good yields and *ee*'s. (Table 1). As mentioned by us elsewhere,[8b] the optimum temperature for the reduction was found to be 45°C. Significantly the reaction proceeded with 1 equivalent of BMS inspite of the fact that hetero atom chelates to borane. The variation of the amount of BMS to 2 equivalents does not alter the yield or stereoselection significantly. Increasing the amount of catalyst from 10 mol% to 20 mol% did enhance the enantiomeric excess in the case of 2-thienyl compounds but has very little or no effect in the case of 2-furyl derivatives. In all the cases examined, oxazaborolidine derived from (*S*)-(−)-diphenyl prolinol provided carbinols of *R* configuration. It is noteworthy to mention that 1,2-dithienyl ethanedione and 1,2-difuryl ethanedione were also reduced with high enantiomeric excesses (>99%) and good diastereoselection.[8a]

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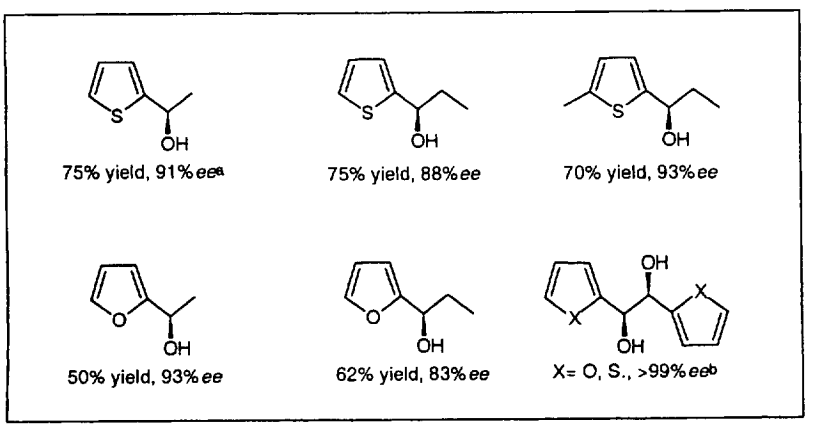
Table 1. Enantioselective reduction of representative ketones

entry	compound	catalyst (mol%)	BMS (eq)	% yield[a]	% *ee*[b]
1	2-acetyl thiophene	5	0.6	*c*	*c*
2	2-acetyl thiophene	5	1	60	53
3	2-acetyl thiophene	10	1	70	60
4	2-acetyl thiophene	10	2	75	82
5	2-acetyl thiophene	20	2	75	91
6	2-acetyl furan	20	1	50	90
7	2-acetyl furan	20	2	50	93

[a] Isolated yields. [b] Estimated by comparison with the reported maximum specific rotations. [c] Incomplete reduction.

Table 2. Optically active 2-thienyl and 2-furyl carbinols



[a] Estimated by capillary GC of MTPA-ester. [b] Diastereomeric ratio (75:25 for X=O, 92:8 for X=S) and *%ee* estimated by NMR using shift reagent, see ref. 8a.

Finally we have generalised the reaction with 20 mol% of catalyst and 2 equivalent of BMS for a number of ketones which are available through a simple sequence of reactions starting from thiophene and furan (Table 2).

In conclusion we have shown that oxazaborolidine catalysed reduction of 2-acyl thiophenes and 2-acyl furans furnishes the corresponding carbinols in high enantiomeric excesses and good yields. Reductive desulphurisation of thienyl carbinols can further provide optically active aliphatic alcohols which are not easily accessible through any known procedure.

Experimental

BMS was purchased from Aldrich Chemical Company and diluted to 2M in toluene. 2-Acyl thiophenes and 2-acyl furans were purchased or prepared according to the standard literature procedures.[10] NMR spectra were recorded on a Bruker 200 MHz with TMS as an internal standard in $CDCl_3$. Optical rotations were recorded on JASCO-DIP-181 digital polarimeter. GC analysis was performed on a Shimadzu GC-17A fitted with a 5% Ph Me Silicone column (25 m × 0.2 mm).

Reduction of 2-acyl thiophenes

To diphenyl prolinol[11] (0.508 g, 2 mM) in 2 ml THF was added BMS (5 ml of 2M solution in toluene, 10 mM) and stirred at 45°C for 16 h. To the resulting catalyst solution at 45°C was added 2-acyl thiophene (10 mM dissolved in 5 ml THF) through a syringe pump over 30–35 min. The progress

of the reaction was monitored by TLC. After 10 min of the addition, the reaction mixture was cooled to room temperature and cautiously quenched with MeOH. The solvents were removed under reduced pressure. The resultant residue was dissolved in ether and washed with 3N HCl followed by brine. The organic phase was dried over anhydrous Na_2SO_2 and evaporated. The residue was purified by "flash chromatography" followed by Kugelrohr distillation to give pure thienyl carbinols.

(R)-(+)-1-(2-Thienyl) ethanol

Yield 75%; bp 130°C (bath)/10 mm; ^{1}HNMR (δ) 1.6 (d, J 6.4 Hz, 3H), 2.7 (bs, 1H), 5.1 (q, J 6.4 Hz, 1H), 6.95–7.05 (m, 2H), 7.2–7.3 (m, 1H); $[\alpha]_D$+21.9 (neat), +30.68 (c=4.34 benzene) for 91%*ee* as estimated by GC analysis of the corresponding MTPA ester.

(R)-(+)-1-(2-Thienyl) propanol

Yield 75%; bp 150°C (bath)/10 mm; ^{1}HNMR (δ) 0.95 (t, J 6.4 Hz, 3H), 1.9 (m, 2H), 2.5 (bs, 1H), 4.85 (t, J 6.4, 1H), 6.95–7.05 (m, 2H), 7.2–7.3 (m, 1H); $[\alpha]_D$+25.45 (c=2.01 $CHCl_3$) [lit.[6a] +25.9 (c=2.02 $CHCl_3$) for 95% *ee*].

(R)-(+)-1-(5-Methyl-2-thienyl) propanol

Yield 70%; bp 150°C (bath)/10 mm; ^{1}HNMR (δ) 0.95 (t, J 6.5 Hz, 3H), 1.9 (m, 2H), 2.4 (s, 3H), 2.6 (bs, 1H), 4.7 (t, J 6.5, 1H), 6.5–6.6 (m, 1H), 6.7–6.8 (m, 1H); $[\alpha]_D$+25.68 (c=1.24 $CHCl_3$); [lit.[5b] −29.1 (c=1.2 $CHCl_3$) for 99% *ee* of (*s*)-(−) enantiomer].

Reduction of 2-acyl furans

The reduction of 2-acyl furans was carried out as described above for the thiophene analogues. After the reduction was over, the reaction mixture was cooled to room temperature and quenched cautiously with MeOH. The residue obtained after the evaporation of solvents under reduced pressure was directly purified by "flash chromatography" followed by Kugelrohr distillation. Such a non aqueous work-up procedure is necessary since 2-furyl carbinols have significant solubility in water and these deteriorate on treatment with acid.

(R)-(+)-1-(2-Furyl) ethanol

Yield 50%; bp 130°C (bath)/10 mmHg; ^{1}HNMR (δ) 1.45 (d, J 6.5 Hz, 3H), 3.5 (bs, 1H), 4.55 (m, 1H), 6.15–6.35 (m, 2H), 7.3 (m, 1H); $[\alpha]_D$ +22.82 (neat) [lit.[5b] −24.4 (neat) for 99% *ee* of (*S*)-(−)enantiomer].

(R)-(+)-1-(2-Furyl) propanol

Yield 62%; bp 150°C (bath)/10 mm; ^{1}HNMR (δ) 0.95 (t, J 6.4 Hz, 3H), 1.85 (m, 2H), 2.3 (bs, 1H), 4.6 (t, J 6.4, 1H), 6.15–6.25 (m, 1H), 6.3–6.4 (m, 1H), 7.35–7.45 (m, 1H); $[\alpha]_D$ +16.04 (c=2.04 $CHCl_3$) [lit.[6c] +17.9 (c 1.75 $CHCl_3$) for 93% *ee*].

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