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A novel synthesis of optically active α-amino acids

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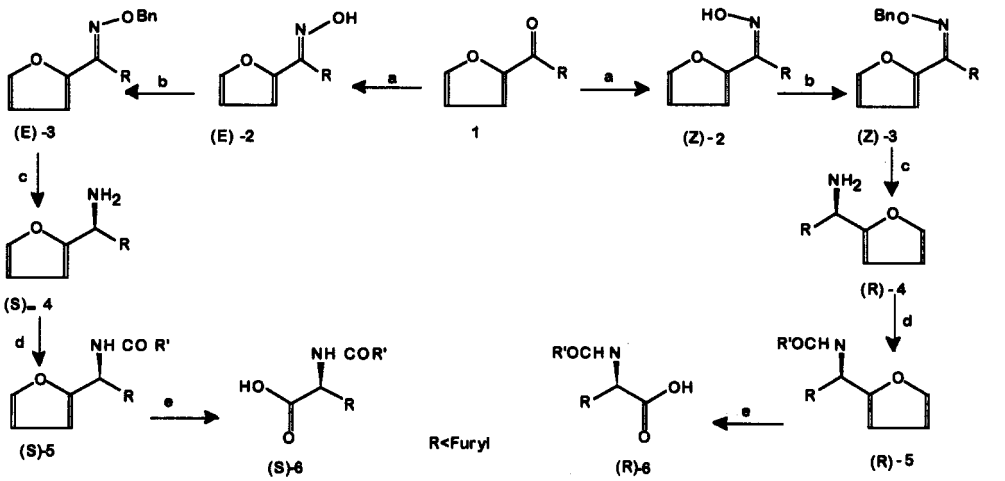
Abstract: A new enantioselective synthesis of α- amino acids are described in which the key step is the enantioselective reduction of E, and Z furyl ketone oxime ethers with chiral boron complexes. The chirality of amino acid is fully controlled by appropriate choice of geometrical isomer of the oxime ether.

Optically active α-amino acids constitue important materials in all disciplines of biology, medicine, biochemistry, and chemistry. Many attempts have been made to develop asymmetric syntheses of α-amino acids: asymmetric derivatization of glycine, homologation of the β-carbon, electrophilic amination of enolates, nucleophilic amination of α-substituted acids, asymmetric Strecker synthesis, asymmetric hydrogenation of dehydroamino acids, and enzymatic syntheses of α-amino acids[1].

In this paper, we report a highly enantioselective , simple method for the synthesis of α-amino acids starting from furyl ketones via enantioselective reduction of furyl ketone oxime ethers.



Scheme 1

a) $NH_2OH.HCl,EtOH$[2] b) NaH,DMF,BnBr, d) BH_3THF, (-)-Norephedrine, d) R'COCl, Pyr. e) O_3

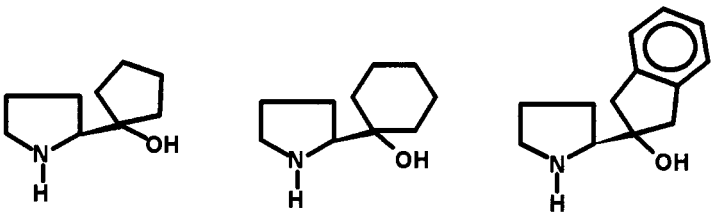
As illustrated in Scheme 1, the furyl ketone **1** was selectively converted to the E or Z oxime **E-2** and **Z-2** using Wargha procedure and other described methods in the literature[2] in good yield. The reaction of oximes with NaH, and benzyl bromide gave the corresponding O-benzy oxime ethers **3** in good yield without isomerization. The direct synthesis of oxime ethers using furyl ketones and O-benzyl hydroxylammonium hydrochloride gave a mixture E/Z isomers, that were separated by column chromatography. (E) and (Z) isomers are identified by the ^{1}H NMR (200 MHz): the (E) isomer displays three multiplets of furane ring at δ 6.35, 6.61 and 7.41 ppm(C-4, C-3, C-5 H) and the (Z) isomer displays the signal of C-3 H down field shift by 7.4 ppm. Purity of the (E) and (Z) isomers was apparent by glc analysis of the corresponding O-benzy derivatives of oximes. The enantioselective reduction of oxime ethers was carried out with chiral boron reagents prepared from (-)- norephedrine and BH_3.THF complex[3]. The reduction of oxime ethers with this reagent gave the furyl amines **4** in 88-96 % ee and in good chemical yield (Table 1).

TABLE 1. The enantioselective synthesis of N-Benzoyl amino acids

Furyl ketone 1	Oxime 2		Oxime ether 3	Amine 4			N-Benzoyl amine 5	N-benzoyl amino acid 6		
R=	config.	yield(%)	yield(%)	config.	yield(%),	ee(%) [a]	yield(%)	config.	yield(%),	ee(%) [b]
a.Methyl	E	82	83	(S)	77	96	91	(S)	95	96
	Z	77	84	(R)	72	94	72	(R)	86	94
b.Ethyl	E	73	92	(S)	81	96	94	(S)	94	96
	Z	69	84	(R)	78	93	91	(R)	91	93
c.*i*-Propyl	E	71	93	(S)	81	96	93	(S)	94	96
	Z	73	91	(R)	83	95	91	(R)	87	95
d.t-Butyl	Z	76	91	(S)	86	90	94	(S)	89	90
e.Phenyl	E	81	93	(S)	87	95	96	(S)	93	95
	Z	69	91	(R)	91	91	96	(R)	92	91
f.2.3-Dimethoxy-phenyl	E	73	88	(S)	86	93	93	(S)	94	93
	Z	77	94	(R)	88	87	97	(R)	91	87
g.Benzyl	E	77	91	(S)	88	92	94	(S)	88	92

a. Enantiomeric excess determined by analysis of the ^{19}F NMR spectra of the corresponding Mosher amides and (S)- (-)-N-(trifluroacetyl) prolylamides (^{19}F NMR and GLC analysis). b. Enantiomeric excess determined by comparing the optical rotation of **6** with data of known compounds.

We have also used commercially available chiral amino alcohols such as (S)-prolinol, (S)-valinol, (1R,2S)-ephedrine ; and the ones prepared in our laboratory starting from (S)-proline, of which the structure are given below. The optically yield of the amines from the reaction of oxime ethers, which are listed in Table 1, with the above chiral amino alcohols ranged from 47 % to 95 % (Table 2). Among the above chiral alcohols , the highest ee , which is comparable to the values obtained with (-)-norephedrine, was observed wen we used the amino alcohol **C**.



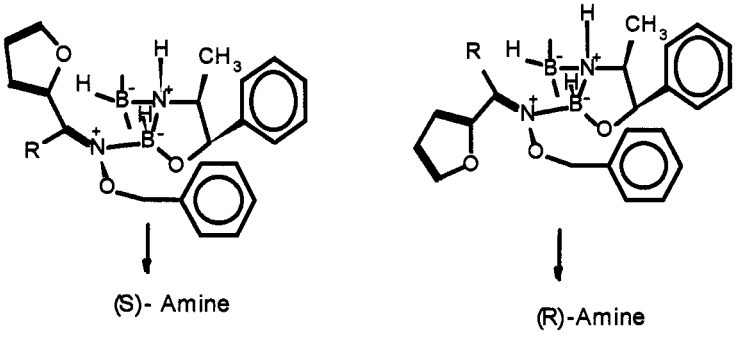
A B C

TABLE 2. The reduction of (E)-oxime ethers (given in Table 1) using different amino alcohols

Amino Alcohol	Amine **4**	
	ee(%)	Cofig.
(S)-Prolinol	61-73	S
(S)-Valinol	47-53	S
(1R,2S)-Ephedrine	48- 76	S
A	51- 72	S
B	53- 68	S
C	78-95	S

The maximum optical yield was obtained when the ratio of borane, amino alcohol and oxime ether ca 2.5:1.25:1.0. An excess of the borane relative to the amino alcohol gave a low optically yield. We found that by changing the (E) , (Z) geometry, we could selectively get each enantiomer of the corresponding furyl amines (Scheme 1, Table 1).In all of the examples, the chiral amino alcohols are easily recovered.

The results indicate that the prochiral nitrogen moiety is responsible for the high selectivity but not the prochiral carbon. The suggested mechanism for the reduction reaction with (-)-norephedrine is shown in Scheme 2[4].



Scheme 2

In all cases the furyl amines **4** was converted into their N- benzoyl or acetyl derivatives in good yield. The ozonolysis of N-acyl furyl amines **5**[5] gave the corresponding N-acyl amino acids **6** in high yields. This oxidation was carried out also with $KMnO_4$[6] and $RuCl_3$ /$NaIO_4$[7].

A typical procedure is described for the preparation of N-benzoyl l-alanine: The reaction of 0.1 mol (11.0 g) furyl methyl ketone **1a** and 0.125 mol (8.69 g) hydroxylamine hydrochloride gave according to

Wargha procedure[2] 10.25 (82 %) **(E)-2a**. m.p. 104-105 °C (lit.[2] 104 °C).[1] H NMR ($CDCl_3$) δ 2.20 (s,3H,CH_3) , 6.36-6.44 (m,1H,C-4 H), 6.57-6.65 (m.1H,C-3 H), 7.37-7.50 (m,1H,C-5 H), 9.94 (s,broad,1H, NH). To a suspension of 50 mmol (1.2 g) NaH in 60 ml of dry DMF at 0°C was added 40 mmol (5.0 g) of oxime **(E)-2a** dissolved in 50 ml of DMF. The reaction mixture was stirred (1h 0°C) and 50 mmol (5.97 ml) benzyl bromide was added. The mixture was stirred (2h) at RT. After work up and purification by flash chromatography (EtOAc/pentane 1:10) 6.9 g (83%) oxime ether **(E)-3a** was obtained as colorless oil. [1] H NMR ($CDCl_3$) δ 2.15 (s,3H,CH_3), 5.18 (s,2H,CH_2), 6.33-6.43 (m,1H,C-4 H), 6.55-6.66 (m,1H,C-3 H), 7.23-7.48 (m,6H,Ar-H and C-5 H) ; IR(TF) 3140-2885, 1600, 1490 1450 cm^{-1}. (Found: C,72.77; H,6.21; N,6.71. $C_{13}H_{13}NO_2$ requires C,72.53; H,6.08; N,6.50 %).A solution of borane (20 mmol) in THF (20 ml) was added under argon dropwise to a 10 mmol (1.51 g) (-)-norephedrine solution in 10 ml THF at -20 °C. The resulting mixture was warmed to -5 °C and stirring continued by this temperature for 16 h before 8 mmol (1.72 g) of oxime ether **(E)-3a** in 10 ml of THF was added dropwise. The resulting solution was stirred at RT for 48 h and was decomposed by slowly addition of 2M-HCl.The mixture was then extracted with ether ,treated with ammonium hydroxide , and extracted again with ether . The ether layer was dried and evaporated to give a colorless oil which upon distillation (kugelrohr , b.p. 80- 95 °C /11 mm Hg) furnished 683 mg (77 %) amine **(S)-4a**. $[\alpha]^{20}_D$=-23.1 (neat) , ee: 96% (observed by ^{19}F NMR spectrum of Mosher and (S)-(-)-N-(Trifluroacetyl)prolylchloride derivative compared with racemic compound). ^1H NMR ($CDCl_3$) δ 1.38 (d,J=7.5 Hz,3H,CH_3), 1.63 (s,2H, NH_2), 4.03 (q,1H,CH), 6.01-6.10 (m,1H,C-4 H), 6.26-6.33 (m,1H,C-3 H), 7.28-7.33 (m,1H,C-5 H). IR (TF) 3380-3110, 2980-2875, 1590, 1500 cm^{-1}. The purification of distillation residue by column chromatography gave 90% of (-)-norephedrine in pure form. Conversion of 2.5 mmol (277 mg) amine **(S)-4a** to N-benzoyl derivatives (pyridine, 0°C) gave 489 mg (91%) of **(S)-5a** as colorless solid after chromatographic separation (ethyl acetate: pentane 1:3, silica gel 60) (m.p. 109-111°C).$[\alpha]_D^{20}$ =-100.6 (c=1; benzene). ^1H NMR ($CDCl_3$) δ 1.58 (d,J=7.4 Hz,3H,CH_3), 5.25-5.60 (m,1H,CH), 6.21-6.37 (m,2H,C-3 and C-4 H), 6.10-6.61 (s,broad, 1H, NH), 7.28-7.75 and 7.76-7.93 (m, 6H,Ar-H and C-5 H). IR(KBr) 3450,3090-2910, 1660,1510,1480 cm^{-1}. (found: C,72.71 ;H, 6.24 ; N,6.32. $C_{13}H_{13}NO_2$ requires C,72.53 ; H,6.08 ; N,6.50).The solution of N-benzoylamine **(S)-5a** (2.8 mmol,600 mg) in 25 ml of MeOH was cooled to -78°C and ozone passed for 15 min. then argon was bubbled at -78°C to remove excess ozone. The solution was allowed to warm to RT and concentrated to give crude oil, which was prufied by crystallization (water) to afford 513 mg (95%) N-benzoyl l-alanine. M.p. 159-160 °C, ee= 96%.

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