Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Asymmetric Synthesis. XVIII. Stereocontrolled Synthesis of α-Substituted-2-furfurylamines via Chiral Intermediates

Liu Shikui , Mi Aiqiao , Wu Lanjun & Jiang Yaozhong

To cite this article: Liu Shikui , Mi Aiqiao , Wu Lanjun & Jiang Yaozhong (1993) Asymmetric Synthesis. XVIII. Stereocontrolled Synthesis of α-Substituted-2-furfurylamines via Chiral Intermediates, Synthetic Communications, 23:17, 2485-2488, DOI: 10.1080/00397919308011135

To link to this article: http://dx.doi.org/10.1080/00397919308011135

SYNTHETIC COMMUNICATIONS, 23(17), 2485-2488 (1993)

ASYMMETRIC SYNTHESIS XVIII. STEREOCONTROLLED SYNTHESIS OF α-SUBSTITUTED-2-FURFURYLAMINES VIA CHIRAL INTERMEDIATES*

Liu Shikui, Mi Aiqiao, Wu Lanjun, Jiang Yaozhong**

Chengdu Institute of Organic Chemistry, Academia Sinica, Chengdu 610015, P. R. China

Abstract: The stereocontrolled synthesis of (R)-α-alkyl-2-furfurylamines (5), using (-)-2-hydroxypinan-3-one (1) as a chiral auxiliary, had been studied. The e. e values of (5) were 91.4—>98%, which determined by capillary GC (stationary phase: Chirasil-Val).

Optically active α-substituted-2-furfurylamines (5) are important alkaloidal analogues, and their conversion alkaloids[1] and amino acids[2] has been developed. Especially this class of compounds has been employed in the intermolecular Diels-Alder reactions of furans[3]. Further application in the synthesis of natural products and bioactive compounds would be considerably stimulated if homochiral 2-furfurylamines were accessible. The significant activities associated with furans have stimulated much interest in the search for new methodologies for the synthesis of this class of compounds[3a].

* The project supported by National Nature Science Foundation of China and Humboldt Foundation of F. R. Germany

** To whom correspondence should be addressed

Scheme 1

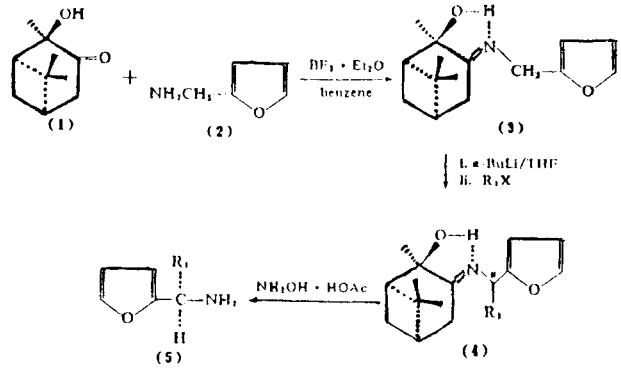
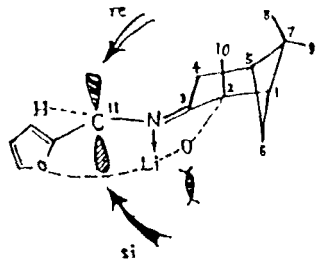


Table 1. α-alkyl-2-furfurylamines 5a-e

No.	R	%C.Y[a]	%e.e[b]	$[\alpha]_D^{25}$ (in EtOH)	^{1}HNMR(δ_{ppm})
5a	Me	59	91.4	22.71(1.02)[c]	1.32(d,J = 9Hz,3H),1.77(S,2H),3.88(m,1H)
				(99% O.P)[d]	6.09(d,J = 3Hz,1H),6.28(dd,J = 1.8Hz,1.8Hz,1H),7.25(S,1H)
5b.	Me_2CH	52	92.5	−7.84(0.88)	1.00(dd,J = 4Hz,4Hz,6H),1.71(S,2H),2.10(m,1H)
					3.75(d,J = 5Hz,1H),6.00(m,1H),6.28(m,1H),7.35(m,1H)
5c.	$CH_2=CHCH_2$	48	96	26.21(1.30)	1.80(S,2H),2.50(m,2H),3.96(t,J = 4.8Hz,1H),4.98(m,1H)
					5.18(m,1H),5.75z(m,1H),6.10(m,1H),6.25(m,1H),7.30(m,1H)
5d.	$PhCH_2$	60	> 98	18.3(1.00)	1.35(m,1H),1.75(m,1H),2.90(dd,J = 8.3Hz,8.3Hz,1H),
					3.18(dd,J = 5Hz,5Hz,1H),4.20(dd,J = 5Hz,1H),
					6.09(d,J = 4Hz,1H),6.29(q,J = 5Hz,1H),7.19(m,2H)
					7.28(m,2H),7.30(d,J = 2Hz,1H),7.36(q,J = 3Hz,1H)
5e	p-MeOPhCH_2	67	> 98	15.02(1.075)	2.82(d,J = 8.2Hz,1H),2.87(d,J = 8.2Hz,1H),3.08(d,J = 5.4Hz,1H)
					3.13(d,J = 5.4Hz,1H),3.77(S,3H),4.14(dd,J = 5.4Hz,5.4Hz,1H)
					6.08(q,J = 4.5Hz,1H),6.28(dd,J = 1.8Hz,1.8Hz,1H),6.78(d,J = 7.5Hz,2H),
					7.01(d,J = 8Hz,2H),7.36(dd,J = 0.8Hz,0.8Hz,1H)

a. Total yield based on (3). All the compounds were purified by bulb-to-bulb and gave satisfactory analytical analyses and were characterized by spectroscopic means (i.r.,mass and NMR). b. By chiral capillary GC, stationary phase: Chirasil-Val. c. The density of concentration, g / 100ml. d. Based on the reported rotations (R form: $[\alpha]_D$ −22.9 ° (EtOH)) [2b].

Scheme 2. Schematic structure of lithium organic compound obtained from (+)-(3)



(4) from (+)-(3)

For these observations and our continued work on the asymmetric synthesis of α-substituted benzylamines[4] and α-substituted-(2-pyridyl)-methylamines[5] via pinanone ketimines, we became interested in the development of new methodology to the asymmetric synthesis of homochiral 2-furfurylamines. Now we wish to report the asymmetric synthesis of α-alkyl-2-furfuryamines (5) by reaction of alkyl halides with the pinanone ketimine (3) derived from 2-furfurylamine (2).

The asymmetric synthesis of (5) was attempted in three steps starting from easily accessible (-)-2-hydroxypinan-3-one (1) as a precursor. Accordingly, ketol (1) was treated with 2-furfurylamine (2): in the presence of $BF_3 \cdot Et_2O$ in benzene to give the chiral pinanone ketimine (3). Ketimine (3)was deprotonated using n-BuLi in THF at -78℃ . The resulting anion was subsequently treated with variety of alkyl halides to give the alkylated products (4), which were directly treated with hydroxylamine acetate, to obtain the α-alkyl-2-furfurylamines (5) in high enantiomeric excess 91.4-98% (Scheme 1, Table 1).

From a mechanistic viewpoint, we may consider that the electrophilic reagent (alkyl halides) should attack from *re* face of the anion from the (+)-ketimine which derived from ketol (1), because of the strong cyclic chelation and π-lithium association, give product in *R* configuration (Scheme 2).

Experimental:

Pinanone ketimine (3): A solution of (2) (52.6mmol) and ketol(1)[6] ($[\alpha]_D^{25}$ -39.49 ° ,O.P.99%, 35.1mmol) containing boron trifluoride etherate (0.4mL)in benzene was refluxed for 2.5h. under N_2.The reaction mixture was con-

centrated and the residue was purified by bulb-to-bulb distillation to give ketimine (+)-3,yield 80%, b.p 130℃ / 0.2Torr, $[\alpha]_D^{18}$ 3.77(c,1.54, $CHCl_3$).

General procedure of alkylation, followed by transamination: A solution of n-BuLi in hexane (8mmol) was added to a stirred solution of (3) (3.36mmol) in THF (10mL) at -78℃ by syringe under N_2.After stirring for 2-3h, the halides (6-8mmol) were added and stirred at -78℃ . Until the reaction was completed (monitored by TLC), 10% NH_4Cl was added. The resulting mixture was stirred for 2h.) and the solution was extracted with Et_2O. The ether layer was washed with brine,dried over anhydrous $MgSO_4$, and evaporated in vacuo to give the alkylated products (4). To the residue 20mL of 0.5M hydroxylamine acetate in anhydrous ethanol was added and stirred for 24h at room temperature (monitored by TLC). The solvent was removed,10 mL of CH_2Cl_2 was added and the mixture was stirred for 0.5h,then filtrated.To the filtrate 10mL of 5% HCl was added, and stirred for 2h, then extracted with $CHCl_3$. To the aqueous layer added K_2CO_3(S) to reach pH 9 and extracted with CH_2Cl_2(5× 10mL).The organic layer was dried and evaporated. The residue was distilled by bulb-to-bulb to give pure (R)-α-alkyl-2-furfurylamine (5).

References and Notes

1.a. Drueckhammer, D., Barbas, C. and Nozaki, K., J. Org. Chem., 1988, 53, 1607. b. Ciufolini, M. and Wood, C. Tetrahedron Lett., 1986, 27(24), 5085. c. Paul, R. and Tchelicheff, S., Bull. Soc. Chim. France, 1953, 1014.

2.a. Jiang, Y. Z., Deng, J. G., Hu, W. H., Liu, G. L., and Mi, A. Q., Synthetic Commun. 1990, 20, 3077. b. Terent'ev, A. P., Gracheva, R. A. and Titova, L. F., Zh. Obshch. Khim., 1964, 34(2), 513.

3.a. Mukaiyama, T. and Iwasawa, N., Chem. Lett., 1981,29. b. Hernandez, J. E., Ferandez, S. and Arias, G., Synthetic Commun., 1988, 18, 2055. c. Sternbach, D. D. and Oossana, D. M., J. Am. Chem. Soc., 1982, 104, 5853. d. Takano, S., Oshima, Y., Ito, F. and Ogasawara, K., Yakugaku Zasshi, 1980, 100(12), 1194.

4.Chen, Y. W., Mi, A. Q., Xiao, X. and Jiang, Y. Z., Synthetic Commun. 1989, 19, 1423.

5.Mi.A. Q., Xiao, X., Wu, L. J. and, Jiang, Y. Z., Synthetic Commun. 1991, 21, 2207.

6.Carlson, R. G. and Pierce, J. K., J. Org. Chem. 1971, 31, 2319.

(Received in the USA 30 March)