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Chiral Furan-2-yl-Substituted Reagents Based on (+)-α-Methylbenzylamine

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Abstract—The Schiff base obtained by condensation of furfural with (+)-α-methylbenzylamine was reduced with sodium tetrahydridoborate, and the resulting amine was alkylated with methyl iodide to obtain the corresponding chiral tertiary amine. Oxidation of the reduction product with *m*-chloroperoxybenzoic acid gave (1*R*)-*N*-(furan-2-ylmethylidene)-1-phenylethanamine *N*-oxide.

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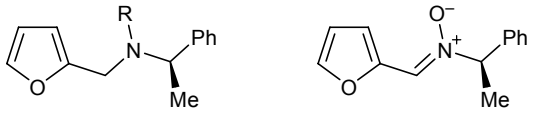
Continuously increasing needs of medicinal chemistry in enantiomerically pure compounds stimulate development of new chiral reagents for asymmetric synthesis. For this purpose, relatively inexpensive and accessible (+)- and (–)-α-methylbenzylamines are widely used as source of chirality [1, 2]. In the present communication we report on the synthesis of homochiral tertiary amine **I** and nitrone **II** from (+)-α-methylbenzylamine through secondary amine **III** [3].



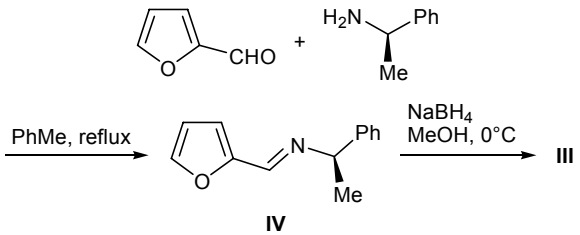
I, **III** **II**

I, R = Me; **III**, R = H.

Chiral secondary amines have found diverse applications in asymmetric synthesis. In particular, they were used to develop methods for desymmetrization of cyclic *meso*-anhydrides [4], imides [5], and epoxides [6], asymmetric deprotonation of prochiral cyclic ketones [7], catalytic conjugate addition [8], stereoselective aldol reactions [9], etc. [10]. Chiral tertiary amines were also used: P,N-containing rhodium catalysts for asymmetric hydrogenation of olefins were described [11, 12]; condensations of organometallic compounds with aldehydes, catalyzed by chiral tertiary amines were reported [13]; Sharpless osmium complexes based on quinine and cinchonidine catalyzed asymmetric dihydroxylation of olefins [14]; Baylis–Hillman reaction was performed in the presence of chiral tertiary amines NR_3 [15], etc. The use of nitrones may be illustrated by two most important reactions, 1,3-dipolar cycloaddition to unsaturated compounds and addition of nucleophiles [16, 17]. Examples of using sterically hindered nitrones as spin trap for hydroxy radicals were given in [18].

By condensation of furfural with (+)-α-methylbenzylamine with simultaneous removal of liberated water we obtained Schiff base **IV** which was reduced (without additional purification) with sodium tetrahydridoborate (Scheme 1). After chromatographic purification on silica gel, the yield of amine **III** was more than 90%. An analytical sample of Schiff base **IV** can be obtained by purification of the crude product by column chromatography on silica gel.

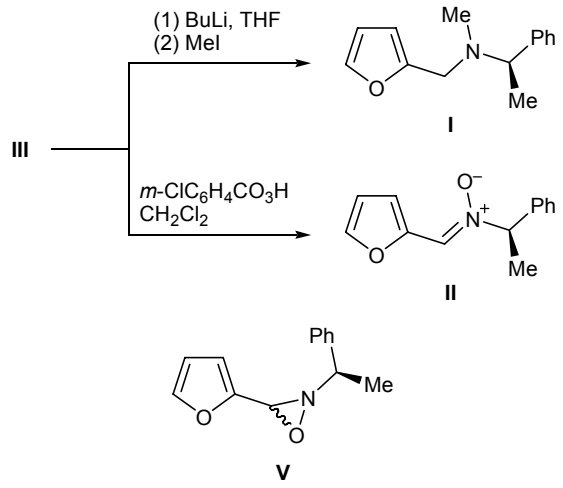
Scheme 1.



IV

Tertiary amine **I** was synthesized by metalation of compound **III** with butyllithium and subsequent alkylation with methyl iodide. The oxidation of **III** with *m*-chloroperoxybenzoic acid smoothly afforded nitrone **II**. The latter can also be prepared directly from Schiff base **IV** by oxidation with the same reagent, but

Scheme 2.



in this case the reaction was accompanied by formation of a considerable amount of nonpolar oxaziridine **V** as a mixture of diastereoisomer at a ratio of 4:1.

The furyl substituent in compounds **I**–**III** is expected to act as an additional coordinating fragment in metal-catalyzed reactions and as a latent functional group.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer from films or dispersions in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument at 300.13 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and reference ($CHCl_3$, δ 7.27 ppm; $CDCl_3$, δ_C 77.00 ppm). The mass spectra (electron impact, 70 eV) were obtained on a Thermo Finnigan MAT 95XP mass spectrometer. The progress of reactions was monitored by TLC on Sorbfil plates; spots were detected by treatment with a 10% solution of 4-methoxybenzaldehyde in ethanol containing sulfuric acid or with an alkaline solution of potassium permanganate. The optical rotations were determined on a Perkin Elmer 241 MC polarimeter. (+)-α-Methylbenzylamine was commercial product (Fluka), $[\alpha]_D^{25}$ = +38.5°.

(1*R*)-*N*-(Furan-2-ylmethylidene)-1-phenylethanamine (IV). A solution of 3.94 g (0.041 mmol) of furfural and 5.00 g (0.041 mmol) of (+)-α-methylbenzylamine in 10 ml of anhydrous toluene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. The mixture was concentrated under reduced pressure and was subjected to subsequent reduction. An analytical sample of Schiff base **IV** was obtained by purification of the product by column chromatography on silica gel deactivated with triethylamine; petroleum ether–ethyl acetate (100:3) was used as eluent. Oily substance, R_f 0.40 (petroleum ether–ethyl acetate, 8:1, double elution), $[\alpha]_D^{20}$ = –73° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1691, 1678 (C=C); 1645 (C=N), 1016 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.63 d (3H, Me, *J* = 6.5 Hz), 4.50 q (1H, C**H**Me, *J* = 6.5 Hz), 6.45 m (1H, 4-H), 6.74 m (1H, 3-H), 7.20–7.46 m (5H, Ph), 7.52 d (1H, 5-H, *J* = 1.7 Hz), 8.14 s (1H, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 24.57 (Me), 69.95 (**C**HMe), 111.62 (C^3), 114.42 (C^4), 126.78 (C^o), 127.02 (C^p), 128.52 (C^m), 144.63 (C^i), 144.78 (CH=N), 148.39 (C^5), 151.59 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 199 (46) $[M]^+$, 184 (19) $[M - Me]^+$, 105 (100) $[M - N{=}CHC_4H_3O]^+$. Found, %: C 78.20; H 6.71; N 7.11. $C_{13}H_{13}NO$. Calculated, %: C 78.36; H 6.58; N 7.03.

(1*R*)-*N*-(Furan-2-ylmethyl)-1-phenylethanamine (III). The crude product containing Schiff base **IV** (see above) was dissolved in 35 ml of anhydrous methanol, 2.15 g (0.048 mol) of 85% sodium tetrahydridoborate was added at 0°C under stirring in an argon atmosphere, the mixture was stirred for 2 h (TLC), 8 ml of acetone was added dropwise at 0°C, and 5 ml of a saturated aqueous solution of ammonium chloride was then added. Methanol was distilled off, the residue was extracted with ethyl acetate, the extract was washed with saturated solutions of ammonium chloride and sodium chloride, dried over $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 7.68 g (93% calculated on the initial furfural), oily substance, R_f 0.33 (petroleum ether–ethyl acetate, 9:1, double elution), $[\alpha]_D^{20}$ = +78.4° (*c* = 1.0, $CHCl_3$); (neither $[\alpha]_D^{20}$ nor spectral parameters of compound **III** were given in [3]). IR spectrum, ν, cm^{-1}: 3320 (N–H); 1369, 1211 (C–N). ^{1}H NMR spectrum, δ, ppm: 1.38 d (3H, Me, *J* = 6.6 Hz), 1.70 br.s (1H, NH), 3.55 d and 3.65 d (1H each, NCH_2, *J* = 14.4 Hz), 3.80 q (1H, C**H**Me, *J* = 6.6 Hz), 6.11 d.d (1H, 3-H, *J* = 0.5, 3.0 Hz), 6.30 d.d (1H, 4-H, *J* = 1.6, 3.0 Hz), 7.25–7.40 m (6H, 5-H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 24.39 (Me), 44.06 (CH_2), 57.13 (**C**HMe), 106.87 (C^3), 110.16 (C^4), 126.85 (C^o), 127.12 (C^p), 128.59 (C^m), 141.80 (C^5), 145.19 (C^i), 154.15 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 186 (100) $[M - Me]^+$, 105 (14) $[M - NHCH_2C_4H_3O]^+$, 81 (58) $[M - NHCH(Me)Ph]^+$. Found, %: C 77.50; H 7.54; N 7.01. $C_{13}H_{13}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

(1*R*)-*N*-Methyl-*N*-(furan-2-ylmethyl)-1-phenylethanamine (I). A solution of 1.4 g (6.97 mmol) of amine **III** in 20 ml of anhydrous THF was cooled to –78°C, 7.0 ml (10.45 mmol) of a 1.5 N solution of butyllithium in hexane was added dropwise under stirring, the mixture was allowed to warm up to –20°C, stirred for 30 min, and cooled again to –78°C, and a solution of 0.87 ml (13.93 mmol) of methyl iodide in 5 ml of anhydrous THF was added dropwise. The mixture was allowed to slowly warm up to room temperature, stirred for 1 h until the initial compound disappeared, and treated with a saturated solution of ammonium chloride, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 ml). The extracts were combined with the organic phase, dried over $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (10:1) as eluent. Yield 1.2 g (80%), light yellow liquid, $[\alpha]_D^{20}$ = +69.6° (*c* = 4.57, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1310 (C–N), 1013 (C–O–C). ^1H NMR spectrum, δ, ppm: 1.43 d (3H, Me, *J* = 6.3 Hz), 2.23 s (3H, NMe), 3.44 d (1H, NCH_2, *J* = 14.4 Hz), 3.58 q (1H, C**H**Me, *J* = 6.3 Hz), 3.67 d (1H, NCH_2, *J* = 14.4 Hz), 6.16–6.17 m (1H, 3-H), 6.31–6.33 m (1H, 4-H), 7.26–7.39 m (6H, 5-H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 19.63 (Me), 38.81 (NMe), 50.92 (**C**HMe), 62.67 (CH_2), 108.24 (C^3), 109.93 (C^4), 126.86 (C^o), 127.55(C^p), 128.20 (C^m), 141.76 (C^5), 143.81 (C^i), 152.79 (C^2).

(1*R*)-*N*-(Furan-2-ylmethylidene)-1-phenylethanamine *N*-oxide (II). A solution of 0.30 g (1.49 mmol) of amine **III** in 10 ml of anhydrous methylene chloride was cooled to 0°C, 0.92 g (3.73 mmol) of 70% *m*-chloroperoxybenzoic acid was added, and the mixture was stirred for 3 h (TLC). The mixture was then washed with saturated solutions of $Na_2S_2O_3$ and $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.24 g (75%), crystalline substance, mp 80–81°C, R_f 0.16 (petroleum ether–ethyl acetate, 8:2, double elution), $[\alpha]_D^{20}$ = –31.2° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1591 (C=C); 1215, 1296 (N–O); 1010 (C–O–C). ^1H NMR spectrum, δ, ppm: 1.89 d (3H, Me, *J* = 6.8 Hz), 5.15 q (1H, C**H**Me, *J* = 6.8 Hz), 6.54 d.d (1H, 3-H, *J* = 1.65, 3.3 Hz), 7.35–7.50 m (6H, 4-H, Ph), 7.61 s (1H, CH=N), 7.77 d (1H, 5-H, *J* = 3.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.83 (Me), 73.41 (**C**HMe), 112.09 (C^3), 114.96 (C^4), 123.83 (CH=N), 127.12 (C^o, C^p), 128.62 (C^m), 138.06 (C^i), 143.34 (C^5), 146.74 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 215 (9.5) $[M]^+$, 105 (100) $[M - N(O)=CHC_4H_3O]^+$. Found, %: C 72.53; H 6.18; N 6.60. $C_{13}H_{13}NO_2$. Calculated, %: C 72.54; H 6.04; N 6.51.

REFERENCES

1. Juaristi, E., Escalante, J., Leon-Romo, J.L., and Reyes, A., *Tetrahedron: Asymmetry*, 1998, vol. 9, p. 715.
2. Juaristi, E., Escalante, J., Leon-Romo, J.L., and Reyes, A., *Tetrahedron: Asymmetry*, 1999, vol. 10, p. 244.
3. Zylber, J., Tubul, A., and Brun, P., *Tetrahedron: Asymmetry*, 1995, vol. 6, p. 377.
4. Evans, A.C., Longbottom, D.A., Matsuoka, M., and Ley, S.V., *Synlett*, 2005, p. 646.
5. Gill, C., Greenhalgh, D.A., and Simpkins, N.S., *Tetrahedron Lett*., 2003, vol. 44, p. 7803.
6. Hoshino, H., Asami, M., Sakakibara, K., Lii, J.H., and Allinger, N.L., *Tetrahedron*, 2008, vol. 64, p. 575.
7. Aggarwall, V.R. and Olloffson, B., *Angew. Chem., Int. Ed*., 2005, vol. 44, p. 5516.
8. Duguet, N., Harrison-Marchand, A., Maddaluno, J., and Tomioka, K., *Org. Lett*., 2006, vol. 8, p. 5745.
9. Zheng, V. and Avery, M.A., *Tetrahedron*, 2004, vol. 60, p. 2091.
10. Ward, D.E., Jheengut, V., and Akinnusi, O.T., *Org. Lett*., 2005, vol. 7, p. 1181.
11. Achiwa, K., *J. Am. Chem. Soc*., 1976, vol. 98, p. 8265.
12. Achiwa, K., *Chem. Lett*., 1978, vol. 7, p. 561.
13. Mukaiyama, T., Soai, K., Sato, T., Shimizu, H., and Suzuki, K., *J. Am. Chem. Soc*., 1979, vol. 101, p. 1455.
14. Kolb, H.C., Van Nieuwenhze, M.S., and Sharpless, K.B., *Chem. Rev*., 1994, vol. 94, p. 2483.
15. Kim, J.N., Lee, H.J., and Jong, J.H., *Tetrahedron Lett*., 2002, vol. 43, p. 9141.
16. Pellissier, H., *Tetrahedron*, 2007, vol. 63, p. 3235.
17. Najera, C. and Sansano, J., *Org Biomol. Chem*., 2009, vol. 7, p. 4567.
18. Sair, C.P., Hideg, E., Vass, I., and Hideg, K., *Bioorg. Med. Chem. Lett*., 1998, vol. 8, p. 379.