Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 15, pp. 2649–2653, 1997

Printed in Great Britain
PII: S0957-4166(97)00280-2 0957-4166/97 $17.00 + 0.00

Baker's yeast reduction of (*E*)-1-phenyl-1,2-propanedione 2-(O-methyloxime). A key step for a (−)-norephedrine synthesis

Olyr C. Kreutz, Paulo J. S. Moran * and J. Augusto R. Rodrigues
Universidade Estadual de Campinas, Instituto de Química, 13081-970 Campinas-SP, Brazil

Abstract: The enantioselective Baker's yeast reduction of (*E*)-1-phenyl-1,2-propanedione 2-(O-methyloxime) **1** afforded (−)-(*R*)-1-hydroxy-1-phenyl-2-propanone 2-(O-methyloxime) **2** with 97% of enantiomeric excess (ee) which was diastereoselectively reduced by $LiAlH_4$ to obtain the (−)-(*R,S*)-norephedrine with ee=82% and (−)-(*R,R*)-norpseudoephedrine with ee=93% in a ratio 4:1 respectively. © 1997 Elsevier Science Ltd

Introduction

Due to the importance of optically pure 1,2-aminoalcohols as chemotherapeutic drugs, chiral auxiliaries and chiral building blocks in organic syntheses, their stereoselective synthesis has became a goal for many research groups.[1] Considerable effort has been expended in the last ten years to find alternative routes for the enantioselective syntheses of norephedrine and norpseudoephedrine. During this period, methods involving organolithium addition to aldehyde dimethylhydrazones,[2] Friedel–Crafts of L-aminoacid chloride,[3] natural aminoacid,[4] a chiral intermediate of chloramphenicol synthesis,[5] reaction of benzaldehyde and acetyl-CoA promoted by brewers' yeast,[6] optically active cyanohydrins,[7] asymmetric α-amination of ketone enolates by chiral α-chloro-α-nitroso reagents[8] and Baker's yeast reduction of α-azidopropiophenone[9] have been investigated.

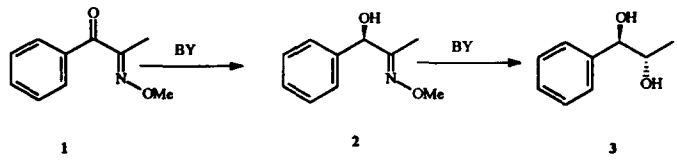
As part of our studies on the use of Baker's yeast reduction of prochiral ketones to produce chiral alcohols, which can be used as building blocks for preparing optically active 1,2-aminoalcohols,[10] we describe in this work the Baker's yeast reduction of (*E*)-1-phenyl-1,2-propanedione 2-(O-methyloxime) **1**, in order to obtain (−)-(*R*)-1-hydroxy-1-phenyl-2-propanone 2-(O-methyloxime) **2**, which can be reduced by $LiAlH_4$ to (−)-(1*R*,2*S*)-norephedrine. As far as we know, there is no report in the literature about Baker's yeast reduction of α-oxo-O-methyloxime.

Results and discussion

The Baker's yeast reductions of **1** gave (1*R*,2*S*)-1-phenyl-1,2-propanediol **3** as a major product after 120 hours of reaction. We observed that **2** is an intermediate of this reaction (see Scheme 1). As our interest is in the use of this intermediate as a chiral building block, we performed a study of this reaction to maximize the yield of **2**. Thus, samples were withdrawn from the reaction mixture at appropriate intervals and analyzed by gas chromatography. The results presented in Figure 1 indicate that the best time to isolate **2** was after 24 hours of reaction which gave **2** in 79% yield (ee=97%), **3** in 7% yield and a 14% recovery of **1**.

In order to isolate the intermediate of this reaction for further use, it was experimentally convenient to perform this reaction with Baker's yeast supported on montmorillonite K10.[11] Until 7 cycles of reuse, the Baker's yeast–montmorillonite was in good condition for further recycling (see Table 1). While the chemical yield remained practically constant, the optical yield decreased slowly with reuse. The configuration of **2** was assumed as *R* since **2** was considered to be the precursor of **3** (see Figure 1) which has the configuration assigned as 1*R*,2*S* by comparison of ^1H NMR and specific optical rotation data described elsewhere.[12] In fact, the transformation of **2** into **3** must involve a hydrolysis of the

* Corresponding author. Email: moran@iqm.unicamp.br



1 2 3

Scheme 1.

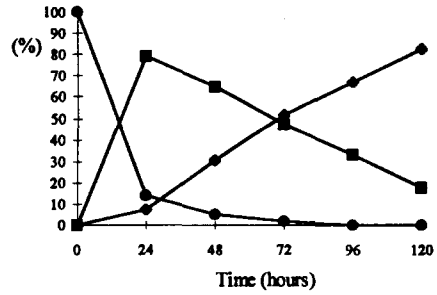


Figure 1. Conversion of 1-phenyl-1,2-propanedione 2-(O-methyloxime) **1** (●) to (−)-(1*R*,2*S*)-1-phenyl-1,2-propanediol **3** (◆) and (−)-(*R*)-1-hydroxy-1-phenyl-2-propanone 2-(O-methyloxime) **2** (■) as reaction intermediate, mediated by Baker's yeast.

Table 1. Reaction mixture composition of Baker's yeast–montmorillonite K10 reduction of **1**, after 24 hours of reaction

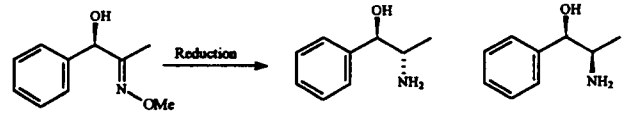
Reuse	1	2		3
	(%)[a]	(%)[a]	$[\alpha]_D^{20}$[b]	(%)[a]
1	12.9	69.7	-115[c]	17.4
2	12.2	68.9	-115	18.9
3	8.8	73.9	-106	17.3
4	10.5	72.2	-106	17.3
5	14.1	71.9	- 97	14.0
6	17.2	68.1	- 97	14.7
7	17.2	69.0	- 97	13.8
8	24.4	65.6	- 88	10.0

a) determined by gas chromatography; b) c= 1.3, $CHCl_3$; c) chiral CG: 97% ee.

O-methyloxime group followed by the reduction of the ketone formed, mediated by Baker's yeast, without any change in the configuration of C-1.

Since Baker's yeast reduction of 1-phenyl-1,2-propanedione provides (2*S*)-2-hydroxy-1-phenylpropanone under pH control[13] and the diol **3** without pH control,[12a,b] the hydrolysis of **2** using the only available methodology[14] is an interesting way to obtain (1*R*)-1-hydroxy-1-phenyl-2-propanone which can be used for the synthesis of (−)-ephedrine.

The reduction of **2** with H_2 and Pd–C in methanol was not accomplished at 2 kgf/cm^2, at room temperature after 16 hours. It is well known that some O-methyloxime needs much longer reaction times for the complete reduction reaction.[15] Also, the reduction of **2** with $LiAlH_4$ in THF at room temperature was not observed. By using more drastic conditions, such as refluxing the mixture of **2** with $LiAlH_4$ in THF for 24 hours, the complete reduction of **2** was possible yielding (−)-(1*R*,2*S*)-norephedrine **4** as a major product and (−)-(1*R*,2*R*)-norpseudoephedrine **5** in a ratio of 4:1, respectively



2 4 5

Scheme 2.

Table 2. Reduction of (*R*)-(−)-1-hydroxy-1-phenyl-2-propanone 2-(O-methyloxime) **2**

Reagent	Yield (%)	Diastereomeric ratio* *syn* : *anti*
$LiAlH_4$,THF, 24hs, r.t.	-	-
$LiAlH_4$,THF, 24hs, reflux	93	1 : 4
Ni/Raney, H_2, 2 atm, MeOH, 8 hs, r.t.	90	1 : 1
Pd/C, H_2, 2 atm, MeOH, 16 hs, r.t.	-	-
$NaBH_4/FeCl_3$, THF, 24 hs, r.t.[16]	93	1 : 1

* inferred by ^{1}H NMR based on previously published data[17]

(Scheme 2). The reduction reactions with Ni/Raney and with $NaBH_4/FeCl_3$ were accomplished but without diastereoselectivity (see Table 2).

Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FT spectrophotometer. NMR spectra were recorded on a Bruker AC 300P or Varian Gemini 300 spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Gas chromatographic analyses were performed on an HP 5890 spectrometer with an HP-5 column (crosslinked 5% Ph Me Silicone, ID 0.53 mm, 30 m length). The GC analysis of reaction mixtures (used in Figure 1) was based on the calibration curves of each component. Enantiomeric excess was determined by GC analysis using a chiral column [stationary phase: heptakis-(2,6-methyl-3-penthyl)-β-cyclodextrine]. Chromatography columns were prepared with Silica gel-60. Mass spectra were obtained on a GC-MS HP 5988A spectrometer. Specific rotation were measured on a Carl Zeis Polamat A polarimeter. Commercially available chemicals and solvents were used without further purification. Commercially available dry Baker's yeast from N. V. Algist-Bruggeman S. A. was used in this work.

(E)-1-Phenyl-1,2-propanedione 2-oxime

Propiophenone was nitrosated by Slater's method[18] to give the required product as needles in 77% yield. mp 113–114°C (lit.[19] 115°C); IR (KBr) 1660, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.0 (bs, OH), 7.86 (m, 2H), 7.57 (m, 1H), 7.43 (m, 2H) and 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 10.2, 128.2, 130.2, 132.8, 136.7, 156.2, 191.9; HRMS calcd for $C_9H_9NO_2$: 163.0633. Found: 163.0633. The evidence for the *E*-isomer is based on the ^{13}C NMR spectrum of a mixture of *Z*- and *E*-isomers which was obtained by reaction of 1-phenyl-1,2-propanedione with hydroxylamine. It is known[20] that the methyl carbon chemical shift *syn* to the OH group in the oximes result an upfield shift due to the steric compression. We found a δ(CH_3) 17.1 for the *Z*-isomer and 10.2 for the *E*-isomer.

(E)-1-Phenyl-1,2-propanedione 2-(O-methyloxime) 1

The following modified Buehler[21] method was used: Ag_2O (3.2 g, 13.8 mmol) was slowly added with stirring to a solution of 1-phenyl-1,2-propanedione 2-oxime (2.0 g, 12.3 mmol) and MeI (4.0 mL, 61.5 mmol) in 15 mL of CH_2Cl_2 cooled in an ice–water bath. After half hour of reaction, the green precipitate was filtered and washed with CH_2Cl_2. The CH_2Cl_2 was evaporated from the filtrate yielding 2.1 g (96%) of a yellow oil. IR (neat): 1661, 1597, 1325 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300

MHz), δ: 7.96 (m, 2H), 7.53 (m, 1H), 7.41 (m, 2H), 4.04 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 10.7, 63.1, 127.9, 130.7, 132.6, 136.5, 155.3, 191.2; MS (70 eV) m/e 177(M^+,7), 105(100), 77(57), 51(18). In the same manner as above, we prepare the mixture of *Z*- and *E*-isomers which was obtained by reaction of 1-phenyl-1,2-propanedione with O-methylhydroxylamine. We found a δ ^{13}C NMR (CH_3) 17.0 for the *Z*-isomer and 10.7 for the *E*-isomer. After a few days, the *Z*-isomer was totally converted to the *E*-isomer in $CDCl_3$ at room temperature.

*Reduction of (E)-1-phenyl-1,2-propanedione 2-(O-methyloxime) **1** by free Baker's yeast*

The O-methyloxime (0.53 g, 3 mmol) was added with stirring at 30°C to a suspension of 30 g of fresh Baker's yeast and 30 g of sucrose in 1 L of a solution 2% KCl in water. After continuous stirring for the specified time indicated, the reaction mixture was saturated with sodium chloride and the products were extracted with chloroform in a liquid–liquid continuous extractor for 72 hours. After solvent evaporation, the residue was subjected to a chromatography column with hexane/ethyl acetate (5:1) as eluent in order to separate the two products and the unreacted O-methyloxime.

Yeast immobilization

We used the same method described by Sorrilha *et al.*;[11] 30 g of fresh Baker's yeast was added to a suspension of 30 g of montmorillonite K10 in 1 L of water and then the resultant suspension was gently shaken for one and a half hours. After vacuum filtration, the immobilized Baker's yeast (IMBY) was suspended in 1 L of an aqueous solution of KCl 2%.

*Reduction of (E)-1-phenyl-1,2-propanedione 2-(O-methyloxime) **1** by IMBY*

Sucrose (30 g) was added to 1 L of the previous prepared suspension of IMBY. After 30 minutes of mechanical stirring at 30°C, **1** (0.53 g, 3.0 mmol) was added and the stirring continued for an additional 24 hours. The IMBY was then filtered off and the filtrate was extracted with ethyl acetate. After solvent evaporation, the residue was subjected to the same procedure described above. The IMBY was reused. The results are presented in Table 1 and Figure 1.

*(−)-(R)-1-Hydroxy-1-phenyl-2-propanone 2-(O-methyloxime) **2***

After 24 hours, the procedures using free or immobilized Baker's yeast gave same results for reduction of **1**. IR (neat): 3404, 2987, 1451, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ: 7.35 (m, 5H), 5.18 (s, 1H), 3.92 (s, 3H), 3.75 (bs, OH), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 11.3, 61.9, 75.3, 126.0, 128.1, 140.0, 157.0; MS (70 eV) m/e 179(M^+,8), 150(40), 118(20), 107(100), 105(43) 79(85), 77(63), 51(14); $[\alpha]_D^{20}=-115$ (c 1.3, $CHCl_3$). Chiral GC gave ee 97%.

*(−)-(1R,2S)-1-Phenyl-1,2-propanediol **3***

After 120 hours, the procedures using free or immobilized Baker's yeast gave same results for reduction of **1**. IR (neat) 3386, 1451, 1077, 1044 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz), δ: 7.28 (m, 5H), 4.61 (d, J=3.82 Hz, 1H), 3.92 (m, 1H), 3.4 (bs, OH), 0.98 (d, J=6,39 Hz, 3H); $[\alpha]_D^{20}=-35$ (c 1, $CHCl_3$), lit.[12c] $[\alpha]_D^{20}=-40$ (c 1.3, $CHCl_3$).

*Reduction of (−)-(R)-1-hydroxy-1-phenyl-2-propanone 2-(O-methyloxime) **2** by $LiAlH_4$*

Powder $LiAlH_4$ (0.25 g, 6.6 mmol) was slowly added to a solution of **2** (0.36 g, 2.0 mmol) in 15 mL of dry THF under Ar atmosphere and cooled in an ice–water bath. After the addition, the resulting mixture was refluxed for 24 hours. Then the solution was treated with an aqueous saturated solution of $MgSO_4$ and the precipitate formed was filtered off. The filtrate was extracted three times with ethyl ether and the extract dried with $MgSO_4$. The ethyl ether was evaporated yielding 0.28 g (93%) of a pale yellow oil. IR (neat): 3355, 2968, 1451 cm^{-1}. The ^1H NMR ($CDCl_3$, 300 MHz) show a mixture of **4** and **5** in a ratio of 4:1, respectively. The signals of the major product were δ 7.28 (m, 5H), 4.45 (d, J=4.76 Hz, 1H), 3.08 (m, 1H), 2.5 (bs, OH, NH_2), 0.93 (d, J=6.51, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 18.2, 52.0, 77.5, 126.6, 127.4, 141.6. $[\alpha]_D^{20}=-15.1$ (c 3.4, ethanol), lit.[22] $[\alpha]_D^{20}=-14.6$ (c 3.4, alcohol) for 1*R*,2*S* isomer and $[\alpha]_D^{20}=-32.6$ (c 3.5, alcohol) for 1*R*,2*R* isomer.

Chiral GC shows ee=82% for (1*R*,2*S*)-norephedrine and ee=93%. for (1*R*,2*R*)-norpseudoephedrine. The absolute configuration was determined by comparison with the chiral GC of an authentic sample of (+)-(*S*,*R*)-norephedrine and with a racemic mixture.

Acknowledgements

We thank FAPESP (96/4883-7) for financial support, CNPq for a scholarship for OCK and Dr F. Y. Fujiwara for his assistance in the manuscript elaboration.

References

1. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996.** *96*, 835; (b) Kanerva, L. T. *Acta Chem. Scand.* **1996**, 50, 234.
2. Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265.
3. Mazaki, M.; Morifuji, N.; Takahashi, T.; Hashimoto, K.; Takeda, H. *Jpn. Kokai Tokkyo Hoho* JP 62209047, **1987**, CA **1988,** *108*:150043d.
4. Lamant, M.; Guignard, A. *Helv. Chim. Acta* **1987**, *70*, 1279.
5. Boerner, A.; Krause, H. *Tetrahedron Lett.* **1989**, *30*, 929.
6. Kheradmandy, M. *Amirkabir* **1990**, 4, 10, CA **1990**, *113*:170361n.
7. (a)Effenberger, F.; Gutterer, B.; Hopf, M.; Hoersch, B.; Ziegler, T. *Biochem. Eng.—Stuttgart [Proc. Int. Symp.] 2nd* **1990**, 130; (b) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045.
8. Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900.
9. Moran, P. J. S.; Rodrigues, J. A. R.; Joekes, I.; Brenelli, E. C. S.; Leite, R. A. *Biocatalysis* **1994**, *9*, 321.
10. Brenelli, E. C. S.; Carvalho, M.; Okubo, M. T.; Marques, M.; Moran, P. J. S.; Rodrigues, J. A. R.; Sorrilha, E. P. M. *Indian J. Chem. Sec. B* **1992**, *31B*, 821.
11. Sorrilha, A. E. P. M.; Marques, M.; Joekes, I.; Moran, P. J. S.; Rodrigues, J. A. R.. *BioMed Chem. Lett.* **1992**, *2*, 191.
12. (a) Takesshita, M.; Sato, T. *Chem. Pharm. Bull.* **1989**, *37*, 1085; (b) Brenelli, E. C. S.; Moran, P. J. S.; Rodrigues, J. A. R. *Synth. Commun.* **1990**, *20*, 261; (c) Ohta, H.; Yamada, H; Tsuchihashi, G. *Chem. Lett.* **1987**, 2325.
13. Chênevert, R.; Thiboutot, S. *Chem. Lett.* **1988**, 1191.
14. (a) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199; (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed. John Wiley, New York, 1991; pp. 216.
15. Munegumi, T.; Harada, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1425.
16. Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans 1* **1990**, 1859.
17. Hamman, S.; Benaissa, T.; Beguin, C. G. *Magn. Reson. Chem.* **1988**, *26*, 621.
18. Slater, W. K. *J. Chem. Soc.* **1920**, *117*, 587.
19. Beilstein's "Handbuch der Organischen Chemie", **1925**, *7*, 677.
20. (a) Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 4897; (b) Olivato, P. R.; Ribeiro, D. S.; Rittner, R.; Hase, Y.; del Pra, D.; Bombieri, G. *Spectrochim. Acta* **1995**, *51*, 1479.
21. Buehler, E. *J. Org. Chem.* **1967**, *32*, 261.
22. Beilstein's "Handbuch der Organischen Chemie", **1950**, *13*, II, 370.

(Received in USA 18 June 1997)