Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1079–1081

TETRAHEDRON: *ASYMMETRY*

Enantioselective cathodic reduction of some prochiral ketones in the presence of (−)-*N*,*N*′-dimethylquininium tetrafluoroborate at mercury cathode

Ashok K. Yadav,* Meera Manju and Pukh Raj Chhinpa

Department of Chemistry, University of Rajasthan, Jaipur-302 004, India

Received 31 January 2003; accepted 17 February 2003

Abstract—This work describes preparative scale enantioselective cathodic reduction of some prochiral ketones, viz. 3,4-dihydro-1(2*H*)-naphthaleneone, 2-octanone, 1-phenyl-2-propanone, *E*-3-octen-2-one, 1-octyn-3-one, 1-undecyn-3-one, 1-tetradecyn-3-one at mercury pool in *N*,*N*-dimethyl formamide (DMF)–2-propanol (9.5:0.5), using tetrabutylammonium tetrafluoroborate (TBA·BF_4), as supporting electrolyte and (−)-*N*,*N*′-dimethylquininium tetrafluoroborate (DMQ·2BF_4), as a enantioselective inductor. The products obtained were corresponding (*S*)-alcohols in 24–70% ee.

1. Introduction

Among the variety of methods[1–4] available for stereocontrolled synthesis, the few electrochemical methods are based on the use of chirally modified electrodes,[5–7] the use of a chiral supporting electrolyte,[7] chiral solvent[8] and cathodic reduction in the presence of optically active compounds[2,3,6,9,10] and crown ethers,[11] etc., Schaefer et al.[12] have proposed a refined model for the transition state of the alkaloid induced enantioselective electroreduction of 4-methyl coumarin in the presence of yohimbine. Diastereoselective cathodic reduction of phenylglyoxalic acid attached to chiral auxiliaries[13] and diastereoselective cathodic cyclization of 1-(4- and 1-(3-oxoalkyl)pyridinium salts, etc., have been reported.[14] Our efforts, on the cathodic reduction[15] of unconjugated ketones, resulted in regioselective intramolecular cyclized products, e.g. 6-hepten-2-one, on cathodic reduction, at mercury pool, in the presence of (−)-*N*,*N*′-dimethylquininium tetrafluoroborate (DMQ·2BF_4), in DMF/2-propanol, gave *cis*-1,2-dimethylcyclohexanol.

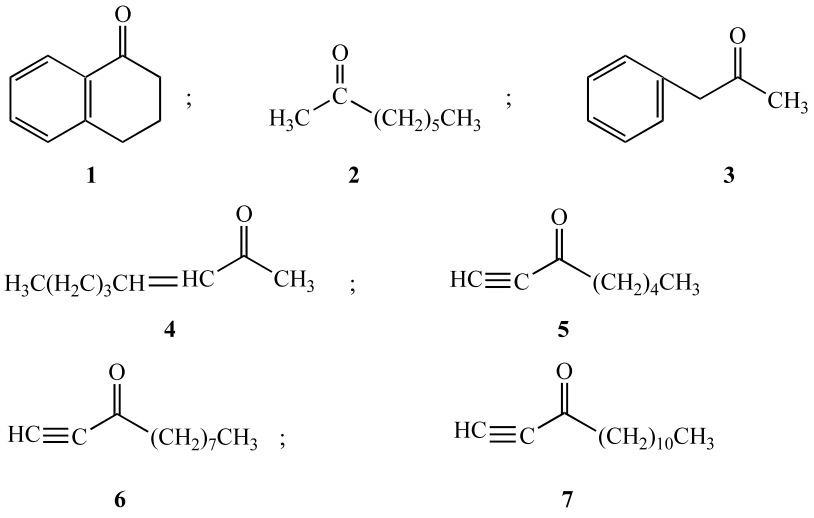
Recently, we have reported[16] the enantioselective cathodic reduction of some prochiral ketones and obtained the corresponding (*S*)-alcohols in 40–55% ee, in the presence of catalytic amounts of (1*R*,2*S*)-(−)-*N*,*N*′-dimethylephedrinium tetrafluoroborate. Our current interest in this area is to explore the cathodic reduction of some prochiral ketones **1**–**7** in the presence of DMQ^{2+} as a chiral inductor, at a mercury pool, in the presence of 0.1 M TBA·BF_4, as supporting electrolyte, in DMF/2-propanol (9.5:0.5). The compounds obtained were (*S*)-1,2,3,4-tetrahydro-1-naphthol **1a**, (*S*)-2-octanol **2a**, (*S*)-phenyl-2-propanol **3a**, (*S*,*E*)-3-octen-2-ol **4a**, (*S*)-1-octyn-3-ol **5a**, (*S*)-1-undecyn-3-ol **6a**, and (*S*)-1-tetradecyn-3-ol **7a**.

2. Results and discussion

In our strategy, we have carried out cathodic reductions of prochiral ketones **1**–**7** in DMF/2-propanol (9.5:0.5) containing 10 mM of DMQ·2BF_4 at a mercury pool cathode, in a divided cell, using a porous diaphragm. A constant current 100 mA (c.d., 10 mA cm^{-2}) was passed, until a charge corresponding to 2.2 F mol^{-1} was transferred. The products obtained were (*S*)-alcohols **1a**–**7a** in 80, 70, 72, 75, 72, 65 and 68% yield, respectively, having enantiomeric excesses of 62, 24, 35, 59, 70, 56 and 50%, respectively. The enantiomeric excess of compounds **1a**–**7a** has been assayed by comparison with this known value of the maximum specific rotation and by HPLC analysis of 2-methoxy-2-trifluoromethyl phenyl acetate (MPTA) ester in petroleum ether–acetonitrile (9.5:0.5), at flow rate 3 mL/min.

* Corresponding author. Fax: +91-0141-2708621; e-mail: draky@sify.com

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00169-1



Compounds **1**–**7** have been cathodically reduced to yield (*S*)-alcohols.

The effect of concentration of the inductor viz. $DMQ{\cdot}2BF_4$, on cathodic reduction of **1**, was studied at 1 ,5, 10, 15 and 25 mM. Product **1a** was obtained in 75–80% yield with 50, 55, 62, 64 and 66% ee's, respectively, establishing that the inductor concentration has no significant effect on ee and thus suggests strong adsorption on the surface of electrode.[17]

In conclusion, the present procedure provides a novel general methodology for synthesis of (*S*)-alcohols **1a**–**7a** in 24–70% ee. These are preliminary investigations and the mechanistic pathway of the process is under study and will be addressed later.

3. Experimental

3.1. General

The electrosynthesis has been performed on a Autolab PGSTAT 100 electrochemical system. $TBA{\cdot}BF_4$ and $DMQ{\cdot}2BF_4$ were synthesized according to reported methods[15,18] and were dried under vacuum and kept in a desiccator. DMF was dried by a reported method[19] and kept over activated molecular sieves (4 Å) under nitrogen gas. 2-Propanol (A.R. grade) and other chemicals (L.R. grade) were used as such.

The electrosynthesis has been carried out as follows: **Catholyte**: 0.1 M tetrabutylammonium tetrafluoroborate ($TBA{\cdot}BF_4$) in DMF/2-propanol (9.5:0.5) and 10 mM $DMQ{\cdot}2BF_4$ (70 ml); **Anolyte**: 0.1 M $TBA{\cdot}BF_4$ in DMF/2-propanol (9.5:0.5) in porous diaphragm (30 ml); **Cathode**: Mercury pool; **Anode**: Pt foil.

0.01 M of ketone **1**–**7** was added to the catholyte. A constant current of 100 mA (current density 10 mA cm^{-2}) was passed until charge corresponding to 2.2 F mol^{-1} was transferred.

3.2. Work-up

DMF was removed under reduced pressure (50°C at 35 mmHg). About 60 mL water was added and the products were extracted with ether, dried over anhydrous sodium sulfate and filtered. The solvent was removed and products **1a**–**7a** were further purified by distillation/column chromatography over silica gel (G).

3.3. Purification and ee determination of chiral alcohols 1a–7a

3.3.1. (*S*)-1,2,3,4-Tetrahydro-1-naphthol, 1a. The product was purified, on silica gel, using a 5:1 mixture of benzene and ethyl acetate. 80% yield; colourless oil; $[\alpha]_D^{24} = -22.2$ (*c* 3.06, $CHCl_3$) 62% ee based on its maximum rotation[20] $[\alpha]_D^{17} = +32.7$.

3.3.2. (*S*)-2-Octanol, 2a. Distillation at 120–140°C at 100 mmHg afforded (*S*)-2-octanol (and remaining starting material **1**) 70% yield; colourless oil; $[\alpha]_D^{21} = -2.4$ (*c* 5.53, ethanol), 24% ee based on the highest reported[21] value for (*S*)-2-octanol $[\alpha]_D^{21} = +10.1$ (*c* 5.57, ethanol).

3.3.3. (*S*)-Phenyl-2-propanol, 3a. Distillation at 120–135°C (17 mmHg) gave a mixture of starting ketone and (*S*)-phenyl-2-propanol in 72% yield; colourless oil; $[\alpha]_D^{25} = +14.7$ (*c* 5.28, benzene) in 35% ee based on highest reported value[22] of (*S*)-**3a**, lit. $[\alpha]_D^{25} = +41.8$ (*c* 5.26, benzene).

3.3.4. (*S*,*E*)-3-Octen-2-ol, 4a. Column chromatography on silica gel using a 5:1 mixture of pentane–ether followed by distillation [103–118°C, 17 mmHg] gave (*S*,*E*)-3-octen-2-ol; colourless oil; 75% yield. The enantiomeric excess, as well as absolute configuration, was determined on the basis of the specific rotation value of saturated derivative. The above obtained alcohol (30 mg, 0.22 mM) was reduced by treatment with potassium azodicarboxylate (450 mg, 2.3 mM) and acetic acid (140 mg, 2.3 mM) in methanol (5 mL). Column chromatography, using pentane–ether (4:1), followed by distillation gave (*S*)-2-octanol, as colourless oil $[\alpha]_D^{22} = -6.0$ (*c* 5.5, ethanol) in 59% ee, lit.[21] $[\alpha]_D^{21} = +10.1$ (*c* 5.57, ethanol).

3.3.5. (*S*)-1-Octyn-3-ol, 5a. The product, on separation by column chromatography on silica gel, using a 5:1 mixture of pentane–ether as a eluent, gave oily 1-octyn-3-ol; 72% yield. Distillation at 120–125°C (25 mmHg), afforded a pure sample of **5a** $[\alpha]_D^{22} = -14.4$ (*c* 0.85, ether) and 70% ee, based on HPLC analysis of MTPA esters. Petroleum ether and acetonitrile (99.5:0.5) was used in HPLC, at flow rate of 3 mL/min, which afforded peak of esters of (*S*)-1-octyn-3-ol (t_R 3.6 min, 85.6%) and (*R*)-1-octyn-3-ol (t_R 4.1 min, 15.4%).

3.3.6. (*S*)-1-Undecyn-3-ol, 6a. Column chromatography on silica gel gave (*S*)-(−)-undecyn-3-ol in 65% yield. Distillation (130–145°C, 5 mmHg) gave, **6a** $[\alpha]_D^{22} = -8.6$ (*c* 0.86 ether) in 56% ee, based on HPLC analysis of MTPA ester in petroleum–acetonitrile (99.5:0.5), at flow rate 3 mL/min. (*S*)-esters (t_R 3.7 min, 78%), (*R*)-esters (t_R 4.1 min, 22%).

3.3.7. (*S*)-1-Tetradecyn-3-ol, 7a. Column chromatography on silica gel gave (*S*)-1-tetradecyn-3-ol in 68% yield. Distillation [130–145°C, 3 mmHg] gave **7a** $[\alpha]_D^{22} = -6.4$ (*c* 0.78 ether) in 50% ee, based on HPLC analysis of MTPA esters in petroleum–acetonitrile (99.5:0.5), at flow rate 3 mL/min (t_R 3.8 min, 75%), (*R*)-esters (t_R 4.2 min, 25%).

All products **1a**–**7a** were characterized by ^{1}H NMR and IR spectra.

Acknowledgements

Financial support from DST, New Delhi, is gratefully acknowledged.

References

1. Blaser, H. U. *Tetrahedron: Asymmetry* **1991**, *2*, 843–866.
2. Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935–952.
3. Nogradi, M. *Stereoselective Synthesis*; VCH: New York, Weinheim, 1995.
4. Murray, R. W. *Acc. Chem. Res.* **1980**, *13*, 135–141.
5. Brunner, H. *Top. Sterochem.* **1988**, *18*, 129.
6. Komori, T.; Nonaka, T. *J. Am. Chem. Soc.* **1984**, *106*, 56–59.
7. Tellac, A. *Bull. Soc. Chem. Fr.* **1985**, 743–761.
8. Seebach, D.; Dei, H. A. *Angew. Chem., Int Ed. Engl.* **1975**, *87*, 629–630.
9. Horner, L.; Brich, W. *Justus Liebigs Ann. Chem.* **1978**, 1354–1364.
10. Nielsen, M. F.; Batanero, B.; Lohl, T.; Schaefer, H. J.; Wurthwein, E. U.; Froehlich, R. *Eur. J. Chem.* **1997**, *3*, 2011–2024.
11. Horner, L.; Brich, W. *Chem. Ber.* **1978**, *111*, 574–578.
12. Hoeweler, U.; Schoo, N.; Schaefer, H. J. *Liebigs Ann. Chem.* **1993**, *6*, 609–614.
13. Reufer, C.; Zielinski, C.; Schaefer, H. J.; Froehlich, R. *Acta. Chem. Scand.* **1999**, *53*, 1023–1037.
14. Gorny, R.; Ruediger, Schaefer, H. J.; Froehlich, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2007–2009.
15. Yadav, A. K.; Singh, A. *Synlett* **2000**, *8*, 1199–1201.
16. Yadav, A. K.; Singh, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 587–588.
17. For example, see: (a) Jubault, M.; Raoult, E.; Pletier, D. *J. Chem. Soc., Chem. Commun.* **1980**, 953; (b) Kopilov, J.; Kariv, E.; Miller, L. L. *J. Am. Chem. Soc.* **1977**, *99*, 3450–3454.
18. For example, see: Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299.
19. *Practical Organic Chemistry*; Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., ed.; 1996, p. 409.
20. Davies, A. G.; White, A. M. *J. Chem. Soc.* **1952**, 3300–3303.
21. Hill, R. K. *J. Am. Chem. Soc.* **1958**, *80*, 1611–1613.
22. Arcus, C. L.; Hallgarten, P. A. *J. Chem. Soc.* **1956**, 2987–2991.