Indian Journal of Chemistry
Vol. 45B, December 2006, pp. 2770-2772

Note

Electroreductive generation of (*S*)-(+)-N,N-dimethyl-2-(hydroxymethyl)- pyrrolidinium mercury compound for enantioselective synthesis of 2-amino-1-alkyl/aryl ethanols

Ashok K Yadav* & Meera Manju

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

E-mail: drakyada@sancharnet.in

Received 21 September 2005; accepted (revised) 7August 2006

(*S*)-(+)-N, N - Dimethyl-2-(hydroxymethyl)-pyrrolidinium ($DMHP^+$)-mercury compound mediated enantioselective reduction of aminomethyl alkyl/aryl ketones in dimethyl-formamide-2-propanol (9:1) has been carried out using tetra-butylammonium tetrafluoroborate as a supporting electrolyte. The products viz. 2-amino-1-alkyl/aryl ethanols have been obtained in good yield (68-92%) with 35-91% optical purity and have been assigned (*S*)-configuration. The pinacol (racemic/meso) derivatives are also isolated as minor products (yield 5-20%) via dimerization of radical anion followed by protonation.

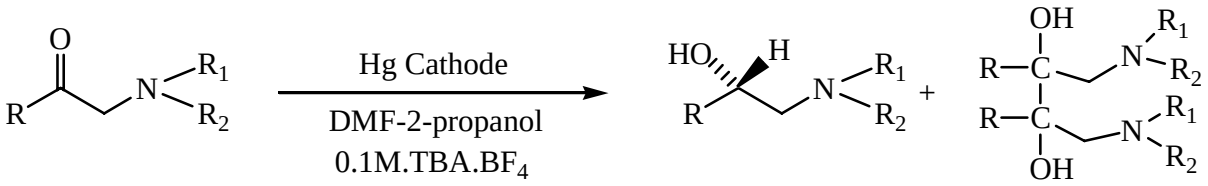
Keywords: Enantioselective synthesis, aminoalkyl/aryl ethanols, cathodic reduction, quaternary ammonium amalgams

IPC Code: Int.Cl.[8]C07D

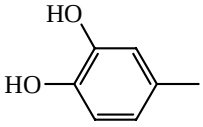
Optically active 2-amino-1-alkyl/arylethanols have been reported to possess diverse biological and pharmacological activities[1-3]. In addition to it, these compounds have been successfully exploited as a catalyst for asymmetric carbon-carbon bond formation reactions[4]. The optical isomers of β-amino alcohols have been obtained through resolution of racemates[2,3], from optically active precursors by utilizing chemical reaction(s)[4], microbiological conversions[5], etc. The chemical conversions to β-amino alcohols have been accomplished by hydrogenation in the presence of chiral phosphine-rhodium[6] or ruthenium[7] catalyst or by using chiral borohydride K glucoride[8]. Our recent work on stereocontrolled electrosynthesis, viz. cathodic reduction of some unconjugated ketones to afford regio- and stereoselective intramolecular cyclization in the catalytic presence of (-)-N,N′-dimethyl-quininium tetrafluoroborate[9], enantioselective cathodic reduction of some prochiral ketones in the presence of catalytic amount of (1*R*,2*S*)-(-)-N,N-dimethylephedrinium tetrafluoroborate[10], (-)-N,N′-dimethylquininium tetra- fluoroborate[11], inspired us to undertake the cathodic reduction of some α-aminoketones. In this communication, we report enantioselective cathodic reduction of some α-aminoketones[12] at mercury cathode in DMF-2-propanol (9:1) in the presence of 0.1*M* $TBA.BF_4$ as supporting electrolyte and catalytic amount of (*S*)-(+)-N,N-dimethyl 2-(hydroxymethyl)pyrrolidinium tetrafluoro-borate. The products obtained were (*S*)-2-amino-1-alkyl/arylethanols quantitatively (68-92% yield) with 35-91% optical purity along with pincols (racemic/ meso) as minor products (5-20%).

In the present investigations, the cathodic reduction of aminomethyl alkyl/aryl ketones[12] has been attempted, **1a-l** under nitrogen atmosphere at mercury pool cathode in DMF-2-propanol (9:1) using 0.1*M* $TBA.BF_4$ as supporting electrolyte in the presence of 10 m*M* (*S*)-(+)-$DMHP^+$ and obtained corresponding optically active 2-amino-1-alkyl/aryl ethanols **2a-l** in quantitative yield (68-92%) with 35-91% optical purity alongwith pinacols **3a-l** (meso/racemic) in 5-20% yield (**Table I**). It is important to note that no enantioselectivity was observed when the reaction was carried out in the absence of $DMHP^+$. Further, during preparative scale experiment, a black coloured substance was observed at the surface of mercury cathode. This black deposit disappeared, when the current was cut off or the solid was exposed to air. Such observations were not noticed in the enantioselective reduction by some ketones at mercury cathode desered earlier[10,11], which occurred at lower cathode potential (–1.48 to –2.10 V vs Ag/AgCl). To visualize the present observation, the cathodic reduction of $DMHP^+$ polarographically at mercury has been investigated and it has been found that the reduction potential $DMHP^+$ at E^0 = –2.60 V and the number of electron per reactant molecule is one. To further look into the insight of the reaction mechanism, the cathodic reduction of a concentrated solution of $DMHP^+$ (0.5 *M*) in DMF at mercury cathode was studied by anodic stripping voltammetry. An attempt was made for cathodic half cycle begining from –2.50V vs Ag/AgCl and the potential of the

Table I — Enantioselective cathodic reduction of aminomethyl alkyl/aryl ketones **1** at mercury cathode in DMF-2-propanol containing 0.1M TBA.BF_4 and 10m*M* (*S*)-(+)-DMHP.2BF_4. Cell divider-ceramic diaphragm, anode –Pt foil



1a-l **2a-l** **3a-l**

Compound	Aminomethyl-alkyl/aryl ketone **1**			yield (%)		2-Amino-1-alkyl/arylethanol **2**		Abs. config.
	R	R^1	R^2	**2a-l**	**3a-l**	$[\alpha]_D^{25}$, degree	% ee	
1a	Me	Me	Me	88	8	8.02 (*c* 0.99, MeOH)	35[a′]	S
1b	Ph	Me	Me	92	5	33.60 (*c* 1.59, MeOH)	67[b′]	S
1c	Ph	Et	Et	80	15	50.10 (*c* 5.0, H_2O)	77[c′]	S
1d	Ph	Bu	H	72	22	10.20 (*c* 4.78, H_2O)	37[d′]	S
1e	Ph	Bu	Me	68	25	30.30 (*c* 2.36, EtOH)	53[e′]	S
1f	Ph	-$(CH_2)_5$-		83	12	37.24 (*c* 1.10, EtOH)	70[f′]	S
1g	Bu^t	-$(CH_2)_5$-		81	13	30.70 (*c* 1.98, EtOH)	42[g′]	S
1h	Me	Et	Et	86	10	29.10 (*c* 4.0, EtOH)	63[h′]	S
1i	Ph	H	H	85	9	26.20 (*c* 2.0, EtOH)	58[i′]	S
1j		H	Me	90	5	48.20 (*c* 1.2, 0. NHCl)	91[j′]	S
1k	Ph	–CH_2OCH_2–		90	5	27.55 (*c* 3.62,MeOH)	44[k′]	S
1l	Ph	Me	Et	90	4	19.25 (*c* 5.0,EtOH)	62[k′]	S

%*ee* Based on reported value for optically pure compounds **2** : **a′** = $[\alpha]_D^{22}$ 22.85° (*c* 1.02, MeOH) ; ref. 13. **b′** = $[\alpha]_D^{20}$ –50.27° *c* 1.61, MeOH) ; ref. 13. **c′** = $[\alpha]_D$ 64.6° (*c* 5.0, H_2O) also calculated by ^{1}H NMR of acetates of alcohols using Eu(hfc)$_3$; ref. 6. **d′** = $[\alpha]_D^{22}$ 27.8° (C 5.0, H_2O) ; ref. 6. **e′** = $[\alpha]_D^{20}$ 57.21° (*c* 2.3, EtOH) ; ref. 13. **f′** = $[\alpha]_D^{20}$ 52.89° (*c* 1.12, EtOH) also calculated by ^{1}H NMR of acetates of alcohols using Eu(hfc)$_3$; ref. 13.**g′** = $[\alpha]_D^{22}$ 72.96° (*c* 1.91, EtOH) ; ref. 4. **h′** = $[\alpha]_D^{24}$ 46.2° (*c* 4.0, EtOH) ; ref. 14. **i′** = $[\alpha]_D^{23}$ 44.8° (*c* 2, EtOH) ; ref. 15. **j′** = $[\alpha]_D^{22\text{-}25}$ –53.2° (*c* 1.2, 0.5 NHCl) ; ref. 16. **k′** = HPLC analysis on chiral column (Chiracel OD, Diacel Co.).

cathode was held at –2.65 V vs Ag/AgCl for sometime and then the anodic scan was applied in order to strip the product formed at mercury surface of the cathodes. Accumulation and stripping of (*S*)-(+)-$DMHP^+$-mercury were performed for the films from 200 to 40 mC. cm^{-2}. The decrease in stripping peak of (*S*)-(+)-$DMHP^+$-mercury is observed for Q_{Hg} < 150 mC. cm^{-2}. The plot of charge Q_{DHMP^+} vs Q_{Hg} shows that the amount of electrogenerated DMHP-Hg amalgam is linearly proportional to the amount of mercury constituting the cathode's (Q_{Hg}). The experimental value follows very closely the line drawn for $Q_{DMHP^+} = 5Q_{Hg}$.

The above combined observations suggest that the chirally quaternary-ammonium amalgam DMHP(Hg_5) was formed as black substance on the surface of the mercury cathode, as shown below:

$DMHP^+ + 1e + 5\ Hg \rightarrow DMHP\ (Hg_5)$ Black amalgam

This chirally quaternary ammonium amalgam appears to direct enantioselectivity by hydrogen bonding between the carbonyl group of the substrate and the hydroxy group present in (*S*)–(+)–$DMHP^+$ and then providing conformational rigidity. The formation of DMHP (Hg_5) amalgam at cathodic surface reduces α-aminokeone in such a situation leading to the enantioselectivity in the product **2a-l**. The present method makes a new practical application of catalytic enantioselective synthesis by chirally quaternary amalgam (cf quaternary ammonium amalgams eg. N,N-Dimethyl pyrrolidinium amalgams DMP (Hg_5)[14-19], DMP (Pb_3)[20], DMP(Sn_3)[21], etc).

The mechanistic details of the process will be presented later.

Experimental Section

The cathodic reduction of α-aminoketones **1a-l** has been accomplished under nitrogen atmosphere as

follows– **Catholyte**: 0.1*M* TBA.BF_4 in DMF-proponal (9:1) (70 mL) + 0.01*M* compound **1a-l** + 100 m*M* (*S*)–(+) DMHP.BF_4; **anolyte**: 0.1*M* TBA.BF_4 in DMF-2-propanol in a ceramic diapharagm (30mL); **cathode** mercury pool; **anode**: Pt foil. A constant current of 100 mA (current denly 10 $mA.cm^{-2}$) was passed until the charge corresponding to 2.6 F. mol^{-1} was transferred.

Work Up: From catholyte, DMF-2-propanol was removed by distillation under reduced pressure (50°C at 35 mm of Hg). The products were extracted with ether, dried over anhydrous magnesium sulfate and ether was removed by distillation. The products were separated and purified on a column of silicate gel G and elution was accomplished with pet. ether and ethyl acetate (9:1). The details of results are summarized in **Table I**.

Acknowledgements

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

References

1 Roth H J & Kleemann A, *Pharmaceutical Chemistry Vol. 1 : Drug Synthesis*, Ellis Horwood, **1988**, p. 144.
2 Patil P N & Miller D D Trendelenburg, *Pharmacol Rev* 26, **1975,** 323.
3 Brittain R T, Jack D & Ritchie A C, *Adv Drug Res*, 5, **1970**, 197.
4 Oguni N, Matsuda Y & Kaneko T, *J Am Chem Soc*, 110, **1983**, 7877.
5 Howe R, Moore R H & Rao B S, *J Med Chem*, 16, **1973**, 1020.
6 Takeda H, Tachinami T, Aburatani M, Takahashi H, Morimoto T & Achiwa K, *Tetrahedron Lett*, 30, **1980**, 363.
7 Kitamura M, Okhuma T, Inoue S, Sayo N, Kumobayashi H, Akutagawa S, Ohta T, Takaya H & Noyori R, *J Am Chem Soc* 110, **1988**, 629.
8 Cho Byung Tae & Chun Usung, *Tetrahedron Asymm*, 3, **1992**, 341.
9 Yadav A K & Singh A, *Synlett*, 8, **2000**, 1199.
10 Yadav A K & Singh A, *Bull Chem Soc Jpn*, 75, **2002**, 587.
11 Yadav A K, Manju M & Chimpa P R, *Tetrahedron Asymm*, 14, **2003**, 1079.
12 The α-aminoketones were prepared by reduction of aryl azidomethyl ketone, which was obtained by treatment of aryl halomethyl ketone with sodium azide, see Bretschneider H & Hormann H, *Monatsch Chem*, 84, **1953**, 1021, 1_J was prepared by reported method; See Stolz, F, *Chem Ber*, 37, 1904.
13 Miyano S, Lu L D-L, Viti S M & Sharpless K B, *J Org Chem*, 50**, 1985**, 4350.
14 Raasch M S & Brode W R, *J Am Chem Soc*, 64, **1942**,1112.
15 Nabeya A, Shigemoto T & Iwakura Y, *J Org Chem*, 40, **1975**, 3536.
16 Lyle G G, *J Org Chem*, 25, **1960**, 1779.
17 Kariv-Miller E & Andruzzi R, *J Electroanal Chem*, 187, **1985**, 175.
18 Kariv-Miller E & Vajtner Z, *J Org Chem*, 50, **1985**, 1394.
19 Swartz J E, Mahachi T J & Kariv-Miller E, *J Am Chem Soc*, 110, **1988**, 3622.
20 Lawin P B, Hutson A C & Kariv-Miller E, *J Org Chem*, 54, **1989**, 526.
21 Gunderson E G, Svetlick V & Kariv-Miller E, *J Electrochem Soc*, 140, **1993**, 1842.