Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4343–4347

TETRAHEDRON: *ASYMMETRY*

Asymmetric reduction of 2-bromo-1-phenylethylidenemalononitrile with chiral NAD(P)H models

Jing Li,[a] You-Cheng Liu [a,c,*] and Jin-Gen Deng [b]

[a]*Department of Chemistry, University of Science and Technology of China, Hefei 230026, PR China*
[b]*Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China*
[c]*National Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, PR China*

Received 27 September 1999; accepted 25 October 1999

Abstract

Reduction of 2-bromo-1-phenylethylidenemalononitrile **1** with the chiral NAD(P)H model (S_S)-1-benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **2** gives the cyclopropane ring product (*S*)-2-phenylcyclopropane-1,1-dicarbonitrile **3** with 54.5% enantiomeric purity.

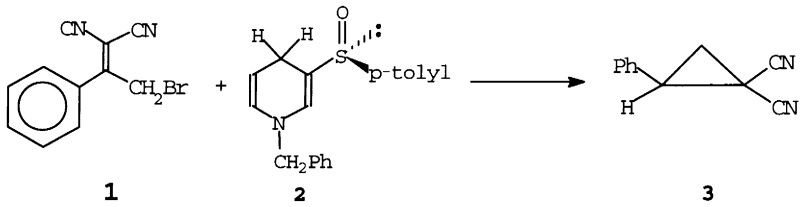
1. Introduction

In the field of asymmetric reduction reactions, chiral models of co-enzyme NAD(P)H have been extensively studied and continue to be of interest. Since the first paper[1] on the asymmetric reduction of α-keto esters by a chiral model of NAD(P)H appeared, numerous asymmetric reductions by chiral NAD(P)H mimics have been reported.[2] The highly enantioselective reductions of some carbonyl and unsaturated compounds have been achieved with a number of such chiral models.[3]

In our previous papers, we[4] reported that the co-enzyme NAD(P)H model 1-benzyl-1,4-dihydronicotinamide (BNAH) can reduce 2-bromo-1-phenylethylidenemalononitrile **1** in CH_3CN to give 2-phenylcyclopropane-1,1-dicarbonitrile **3** in high yield. In order to investigate the stereoselectivity of this reaction, we have studied the reaction using the chiral NAD(P)H model (S_S)-1-benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **2**.[5] Herein we report the results.

* Corresponding author. E-mail: ycliu@ustc.edu.cn

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00481-4



1 2 3

2. Results and discussion

Owing to the low reactivity of compound **2**, the reduction was carried out at 30°C for 12 h in acetonitrile. The desired cyclopropane product with moderate enantioselectivity (52.1% e.e.) was obtained in 35% chemical yield (Table 1). The absolute configuration of product **3** {$[\alpha]_D^{24}=-103.7$ (c=0.30, CH_3COCH_3)} was assigned as (*S*) by comparing its specific rotation to that of standard compound {(*S*)-**3**: $[\alpha]_{546}^{25}=-10.1$ (c=3.77, CH_3COCH_3)}.[6] The results in Table 1 show that the chemical yield of product **3** changed little with time while the enantiopurity of product **3** decreased remarkably (12 h, 52.1% e.e.; 36 h, 42.6% e.e.; 96 h, 16.0% e.e.), which implied that the cyclopropane product partially racemized in the reaction system. When pure product **3** (52.1% e.e.) was stirred in acetonitrile for 72 h and also a mixture of product **3** (52.1% e.e.) and (S_S)-1-benzyl-3-(*p*-tolylsulfinyl)pyridinium bromide (100% e.e.) was stirred in acetonitrile for 72 h, the enantiopurity of **3** dropped to 47.7% e.e. and 42.0% e.e., respectively. The mechanism of epimerization of cyclopropane compounds has been reported by Cram.[6] In the present case, the racemization of product **3** could be explained by the ring-opening mechanism.[7]

Table 1
Reduction of compound **1** with chiral NAD(P)H model **2**[a]

Time(h)	12	24	36	48	96
Ee%[b]	52.1	41.0	42.6	17.4	16.0
Yield%[c]	35.3	40.7	36.7	37.1	28.6

[a] See experimental part.
[b] Enantiomeric excess was determined by chiral GC.[8]
[c] Isolated yields.

It is well known that solvent polarity can affect the reactivity and stereoselectivity, so a number of solvents were tried in this reaction. In polar solvents, such as DMF, DMSO, HMPA, the substrate decayed very rapidly, and only traces of product could be detected. Because the reaction was slow in acetonitrile, we conducted the reaction in binary solvent systems and the results are shown in Table 2. It can be clearly seen that the chemical yield increased as the ratio of the more polar solvent was raised to 30% for DMF, 40% for DMSO, while the enantiomeric excess remained constant or slightly improved. When the ratio of the more polar solvent was increased further, both the chemical yield and the enantioselectivity decreased. Thus, the rates of consumption of the substrates were measured in DMSO-d_6/CD_3CN by NMR spectroscopy. The second order rate constants (Table 3) indicate that the reaction rates increased as the proportion of DMSO-d_6 increased. By comparing these results with those in Table 2, it is seen that the rate of decomposition of the product and/or the rate of the side reaction became faster as the proportion of the more polar solvent increased.

It is interesting to note that no metal ion was used as catalyst in this reaction while Mg^{2+} or Zn^{2+} was used in most asymmetric reduction reactions with chiral NAD(P)H models reported in the literature,[3]

Table 2
Reduction of compound **1** by chiral NAD(P)H model **2** in binary solvent systems[a]

	DMF/CH_3CN			DMSO/CH_3CN		
Entry	V_{DMF}/V(%)	Ee%[b]	Yield%[c]	V_{DMSO}/V(%)	Ee%	Yield%
1	0	52.1	35.3	0	51.5	28.3
2	10	51.5	51.3	10	49.8	50.9
3	20	48.6	56.4	20	47.0	50.9
4	30	54.6	63.5	30	51.4	63.1
5	40	53.2	56.4	40	49.0	66.4
6	50	54.4	54.3	50	48.2	56.7
7	60	46.8	31.9	60	46.4	44.0
8	80	36.6	14.1	80	42.0	29.3
9	100		trace	100		trace

[a]See experimental part.
[b]Enantiomeric excess was determined by chiral GC.[8]
[c] Isolated yields.

Table 3
Second order reaction rate constants in DMSO-d_6/CD_3CN

Entry	1	2	3	4	5
V_{DMSO}/V(%)	20	40	60	80	100
k($10^{-3}M^{-1}S^{-1}$)	1.73	2.56	2.40	4.08	4.65

hence, no ‘ternary complex’ existed in this reaction. Although it is reported that the stereoselectivity of this reaction originates in the only stable conformation of compound **2**,[3b] the details of the mechanism need to be further investigated.

In summary, we have investigated the stereoselectivity of a new asymmetric reduction reaction by a chiral NAD(P)H model. Albeit the enantioselectivity of cyclopropane product is not as high as that obtained by carbenoid method,[9] this is the first report on asymmetric cyclopropanation of allylic bromide and the reaction condition is mild. Further work on the improvement of the enantioselectivity and an elucidation of the mechanism are in progress.

3. Experimental

3.1. Materials

(S_S)-1-Benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **2**[10] was prepared according to the literature method[5] with some modification. In the preparation of the intermediate (S_S)-3-(*p*-tolylsulfinyl)pyridine,[11] the reaction temperature was slowly raised to –30°C. The reduction of the pyridinium bromide to **2** was carried out according to the literature procedure.[12]

3.2. Typical procedure for reduction of **1** with **2**

A mixture of **1** (50 mg) and **2** (44 mg) was stirred in the corresponding solvent at 30°C for 12 h under Ar atmosphere in the dark. The reaction mixture was treated with water and extracted with ether. Usual work-up and purification by SiO_2 column chromatography (hexane:AcOEt, 10:1) gave a light yellow oily product. ^{1}H NMR (200 MHz) δ: 2.27 (2H, d, J=9.0 Hz), 3.31 (1H, t, J=9.0 Hz), 7.28–7.47 (5H, m) ppm.

3.3. Kinetic measurements

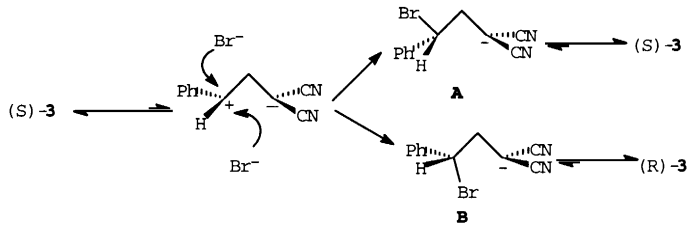
Kinetic measurements were conducted on a Bruker AM 400 NMR spectrometer. The reaction rates were monitored by the decay of peak area of absorption at 4.68 ppm for compound **1** and peak area of absorption at 4.33 ppm for compound **2**.

Acknowledgements

Support from the National Natural Science Foundation of China (grant no. 29672031) is gratefully acknowledged. We would like to thank Ms. Zhi Li and Ms. Fang Min Fu of Chengdu Institute of Organic Chemistry for their help with the GC and HPLC analyses.

References

1. Ohnishi, Y.; Kagami, M.; Ohno, A. *J. Am. Chem. Soc*. **1975**, *97*, 4766–4768.
2. (a) Inouye, Y.; Oda, J.; Baba, N. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp. 91–124; (b) Burgess, V. A.; Davies, S. G.; Skerlj, R. T. *Tetrahedron: Asymmetry* **1991**, *2*, 299–328 and references cited therein.
3. (a) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc*. **1979**, *101*, 7036–7040; (b) Obika, S.; Nishiyama, T.; Tatematsu, S.; Miyashita, K.; Iwata, C.; Imanishi, T. *Tetrahedron* **1997**, *53*, 593–602; (c) Burgess, V. A.; Davies, S. G.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun*. **1990**, 1759–1762; (d) De Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc*. **1979**, *101*, 2759–2761; (e) Seki, M.; Baba, N.; Oda, J.; Inouye, Y. *J. Am. Chem. Soc*. **1981**, *103*, 4613–4615.
4. (a) Liu, Y. C.; Li, B.; Guo, Q. X. *Tetrahedron Lett*. **1994**, *35*, 8429–8432; (b) Liu, Y. C.; Li, B.; Guo, Q. X. *Tetrahedron* **1995**, *51*, 9671–9680.
5. Imanishi, T.; Bbika, S.; Nishiyama, T.; Nishimoto, M.; Hamano, Y.; Miyashita, K.; Iwata, C. *Chem. Pharm. Bull*. **1996**, *44*, 267–272.
6. Yankee, E. W.; Spencer, B.; Howe, N. E.; Cram, D. J. *J. Am. Chem. Soc*. **1973**, *94*, 4220–4230.
7. There could be an equilibrium between the cyclopropane product **3** and the ring-opened form when only pure **3** was stirred in CH_3CN. The product **3** with reversed configuration could be formed through 180° rotation of the benzyl group about its bond to the methylene and recyclization to the cyclopropane ring. Based on the above equilibrium, in the presence of bromide ion the benzyl carbon might be attacked by bromide ion from both the inner and outer sides. Though intermediate **A** could easily collapse back to (*S*)-**3**, the intermediate **B** must rotate its bond to recyclize to (*R*)-**3**. This process would obviously enhance the chance of racemization.



8. Chiral GC was performed with cp-Cyclodex-236 M column; column temperature: 161°C; retention time of (−)-**3**: 11.82 min; retention time of (+)-**3**: 12.13 min.

9. (a) Denmark, S. E.; O'Connor, S. E. *J. Org. Chem.* **1997**, *62*, 584–594; (b) Denmark, S. E.; O'Connor, S. E. *J. Org. Chem.* **1997**, *62*, 3390–3401; (c) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411–432.
10. (S_S)-1-Benzyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine **2**: 92% yield; ^{1}H NMR (200 MHz) δ: 2.34 (3H, s), 2.38 (1H, dm, J=17.6 Hz), 3.06 (1H, dm, J=17.6 Hz), 4.24 (2H, s), 4.54 (1H, dt, J=8.0, 3.5 Hz), 5.63 (1H, dq, J=8.0, 1.6 Hz), 6.71 (1H, d, J=1.3 Hz), 7.21 (5H, brs), 7.31, 7.41 (4H, AA′BB′ type, J=6.4 Hz) ppm. Anal. calcd for $C_{19}H_{19}NOS$: C, 73.98; H, 6.12; N, 4.53; found: C, 74.03; H, 6.17; N, 4.62. $[\alpha]_D^{24}$=+208.7 ($CHCl_3$, c=0.25) (lit.[5] $[\alpha]_D^{24}$=+160.8 ($CHCl_3$, c=0.25).
11. (S_S)-3-(*p*-Tolylsulfinyl)pyridine: 63% yield; ^{1}H NMR (200 MHz) δ: 2.38 (3H, s), 7.29, 7.55 (4H, AA′BB′ type, J=8 Hz), 7.42 (1H, m), 8.01 (1H, d, J=8 Hz), 8.66 (1H, dd, J=4, 1.1 Hz), 8.76 (1H, d, J=2 Hz); MS m/z: 217 (M^+); 100% e.e., HPLC t_R (+)-isomer: 40.73 min (100%); t_R (−)-isomer: 46.36 min (0%); Daicel OB, *i*-PrOH:hexane, 10:90, 0.8 mL/min.
12. (a) Obika, S.; Nishiyama, T.; Tatematsu, S.; Miyashita, K.; Imanishi, T. *Chem. Lett.* **1996**, 853–854; (b) Obika, S.; Nishiyama, T.; Tatematsu, S.; Miyashita, K.; Imanishi, T. *Tetrahedron* **1997**, *53*, 3073–3082.