Tetrahedron Vol 45, No 22, pp 6999 to 7002, 1989
Printed in Great Britain

0040-4020/89 $3 00+ 00
Pergamon Press plc

A STUDY OF SELECTIVE OXIME REDUCTION METHODS

H. Spreitzer*, G. Buchbauer and Ch. Püringer
Institute of Pharmaceutical Chemistry
University of Vienna, Währingerstrasse 10
A-1090 Vienna

(*Received in Germany* 3 *July* 1989)

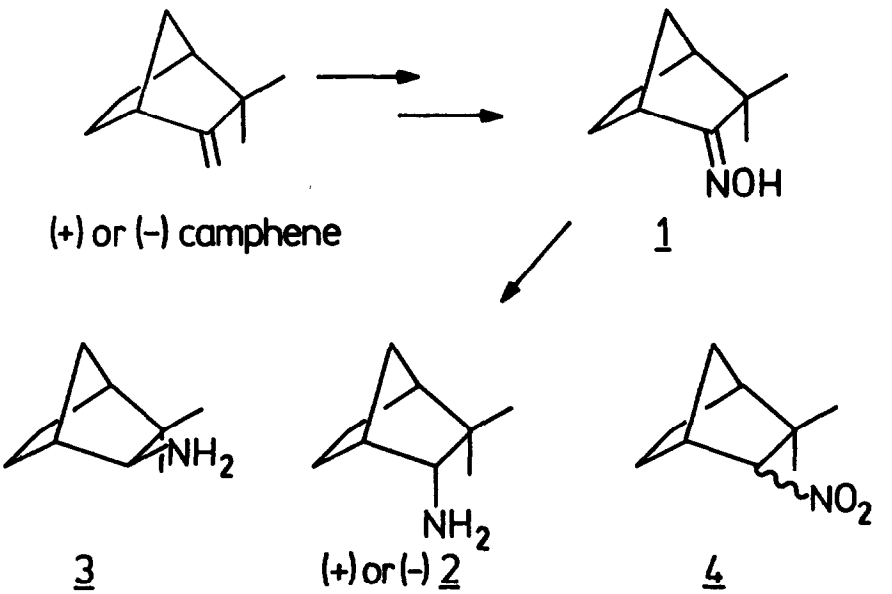
Summary: The title compound **2** is easily available in good yields by selective reduction of oxime **1** with $TiCl_4/NaBH_4$ or $Na^0/n\text{-}C_3H_7OH$. The selectivities of numerous reduction methods are compared.

In our laboratory we are mainly interested in studying structure/activity relationships of bicyclic compounds.[1] For this reason and especially for the syntheses of fungicidal, insecticidal and herbicidal derivatives of urea[2] we were in need of endo-2-camphenylylamine (**2**). Until now this compound is only available by fractionated crystallisation of the benzoates[3] or hydrochlorides[4] of the desired amine **2** and the isomeric amine **3**, both resulting from an unselective reduction of oxime[3] **1** or nitro-compound **4**.[5] These methods are uneconomical and lead to **2** only in small yields. Therefore we were forced to develop a short and selective route to endo-2-camphenilylamine (**2**).
Camphenilonoxime (**1**) seems to us to be an ideal starting material, particularly because both enantiomers of the corresponding ketone[6] are easily available via (+) or (-) camphene. Moreover until now no examinations of diastereoselective reductions of oximes to amines were published.
Table 1 summarizes the series of tests of reducing the sterically highly hindered camphenilone oxime (**1**) to endo-2-camphenilylamine (**2**).
We classified the reductive methods into three groups:

1. Hydride reductions.
2. Hydrogenation by catalysts.
3. Other methods.

Unexpectedly sterically highly hindered hydride donors were of low selectivity just as the use of catalysts for hydrogenation exhibited no favoured attack.

Not only substituted aluminium hydride complexes but also trisiamyl-borohydride - well known for excellent selectivity at reductions of carbonyl compounds to diastereomeric alcohols - failed. Modifying the reactivity of $NaBH_4$ by adding $TiCl_4$ in glyme* leads[7] to a high selective hydride transfer from the less hindered direction leading to the endo configurated amino group. Surprisingly diastereoselective reduction succeeds by a dissoving metal reaction ($Na^0/n\text{-}C_3H_7OH$)[8] simply by changing the solvent. Using EtOH as solvent one obtaines 2 and 3.[3]



These two selective reduction methods make it possible to furnish both enantiomers of the bicyclic amine 2 in a short rection sequence starting from (+) or (-) camphene from the chiral pool. Perhaps the reduction with Na^0 in $n\text{-}C_3H_7OH$ may be fortuitous but the selectivity of the $TiCl_4$ modified $NaBH_4$ seems remarkable. Possible general application to other diastereotopic oximes will be investigated.

TABLE 1:

	Yield (%)	endo/exo[a)]
1. Hydride Reductions:		
1.1. $LiAlH_4$/Ether	71.7	1.533
1.2. $LiAlH_4$/THF	71.7	5.279
1.3. Redal®/Toluene	43.5	3.378
1.4. Superhydride®/THF	0	0
1.5. $NaBH_4/TiCl_4$/Glyme	76.4	100% endo
1.6. $NaBH_4/TiCl_3/NH_4OAc$ /MeOH	32.2	100% endo
1.7. $LiSia_3BH$/THF	0	0
1.8. 20% DIBAH/N-Hexane/THF	51.1	0.177
1.9. Diborane/THF	25.6	3.112
1.10. Palladiumphthalocyanine/ $NaBH_4$/EtOH	6.4	0.286
2. Hydrogenation by Catalytic Reductions:		
2.1. $H_2/Pd/C$/EtOH absol.	0	0
2.2. Raney-Ni/10% NaOH	34.0	26.96
2.3. Raney-Ni/NaH_2PO_2/H_2O/ 2 N NaOH/EtOH	14.9	2.71
2.4. Raney-Ni/$NH_2NH_2.H_2O$/EtOH	36.2	0.110
2.5. H_2/PtO_2/EtOH absol. 70 atm	0	0
2.6. H_2/PtO_2/EtOH absol.	4.0	100% endo
3. Others Methods:		
3.1. Na^o/n-Propanol	77.7	100% endo
3.2. $SnCl_2/HCl_{conc.}$	0	0
3.3. Mg/CH_3COONH_4/MeOH	0	0

[a)] Determination of the ratio by capillary GC (VAE-3700, Fused Silica Capillary SPB 1, 15m, 0.32mm ID, 0.25µm df, Shimadzu Int. C-R1B).

Experimental:

1. A solution of 0.383 (2.5 mmol) **2** in 2.5 ml glyme^R is slowly added under stirring to a cooled (0° C) mixture of 0.998 g (5.25 mmol) $TiCl_4$ and 0.388 g (10.5 mmol) $NaBH_4$ in 10 ml glyme^R. After stirring 20 h at r.t. H_2O is added. The mixture is alkalised by adding 25% NH_3 and subsequently filtered through a Buchner funnel and extracted with ether. The combined organic layers are washed with brine, dried and evaporated.
2. A solution 0.5 g (3.3 mmol) **2** in 11 ml abs. n-propanol is treated with 0.76 g (3.3 mmol) of sodium and subsequently refluxed for 1 h. After cooling 15 ml H_2O is added and the mixture is extracted with ether. The combined ether layers are extracted with 2 N HCl and after alkalisation with KOH the aqueous solution is extracted with ether and worked up as described.
Kp_2:115°C; Fp: 133° C (after sublimation). IR (KBr): 3400, 2920, 1620, 1470, 1360 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): 0.82 (s,3H); 0.97 (s,3H); 2.76 (d,J= ,1H). - ^{13}C-NMR ($CDCl_3$): 19.58 (C_6); 20.72 (C_9); 25.41 (C_5); 31.55 (C_8); 36.00 (C_7); 38.24 (C_3); 45.02 (C_4); 49.96 (C_1); 62.69 (C_2). - MS (m/z, r.i.): 139 (M^+, 17); 107 (17); 96 (31); 70 (68); 56 (100); 43 (32); 42 (16); 41 (45); 39 (40). H.R.: Calc. 139.136[1]; Found: 139.136[3]$\pm$0.0007.

Acknowledgement: We acknowledge with gratitude the interest of Dragoco-Vienna in our work.

Literature:

1. Spreitzer H.; Buchbauer G.; Reisinger S.; Helv. Chim. Acta. **1989** (72), 806-810. Buchbauer G.; Spreitzer H.; Zechmeister-Machhart F.; Pleßl M.; Monatsh. Chem. **1989** (120), 299-310.
2. Buchbauer G.; Spreitzer H.; Püringer Ch.; Arch. Pharm. in press.
3. Hückel W.; Tappe W.; Ber. dtsch. Chem. Ges. **1936** (69), 2769-2772.
4. Püringer Ch.; Thesis, University of Vienna **1989**.
5. Noyce D.S.; J. Am. Chem. Soc. **1951** (73), 20-21.
6. Bartlett P.D.; Webster E.R.; Dills Ch.E.; Richey H.G.; Liebigs Ann. Chem. **1959** (623), 217-248.
7. Kano S.; Tanaka Y.; Sugino E.; Hibino S; Synthesis **1980**, 695-697.
8. Sugden J.K.; Patel J.J.K.; Chem. and Ind. **1972**, 683.