Tetrahedron: Asymmetry Vol. 1, No. 3, pp. 163-166, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Magnesium Ion Mediated Stereospecific Formation of N-Substituted Ethanolamines During Reductive Amination.

Johannes Brussee*, Rolf A.T.M. van Benthem, C.G. Kruse# and Arne van der Gen.

Department of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands.

#. Duphar B.V., P.O. Box 2, 1380 AA Weesp, The Netherlands.

(*Received* 31 *January* 1990)

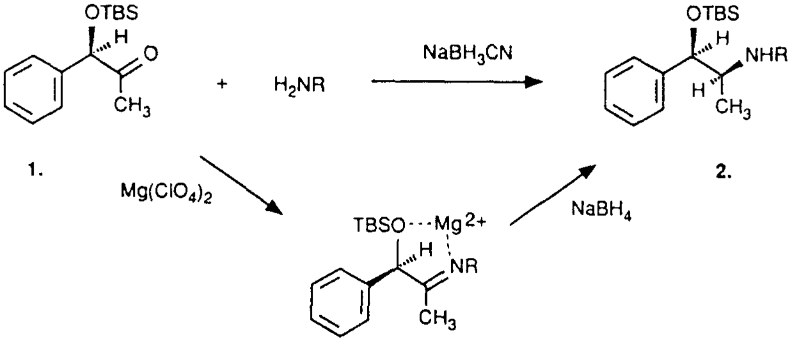
Abstract: Reductive amination of (*R*)-O-protected-α-hydroxyketone **1** with primary amines by $NaBH_4$ in the presence of $Mg(ClO_4)_2$ led to the exclusive formation of erythro (1*R*,2*S*)-O-protected-N-substituted ethanolamines **2**. (R = methyl, ethyl, *i*-propyl, benzyl, phenylethyl).

The use of optically active β-ethanolamines as chiral auxiliaries and chiral building blocks is well known. In a previous paper we reported the synthesis of optically active ethanolamines from O-protected cyanohydrins by a Grignard reaction followed by *in situ* reduction of the intermediary imines. N-unsubstituted ethanolamines of high optical purity could be prepared in this way in high yield[1].

Synthesis of N-substituted ethanolamines by reduction of α-aminocarbonyl compounds has been extensively investigated[2]. We have explored a different approach, based on the reductive amination of an aldehyde or ketone through $NaBH_3CN$ reduction of its imine, formed *in situ* by reaction with an alkylamine. It has been established that reduction of imines is rapid at pH 6-7 in contrast to aldehydes or ketones that are hardly affected in this pH range[3,4].

Our first attempts to try this type of reaction on unprotected α-hydroxyketones (acyloins) met with little success. Side reactions lowered the yields and, when starting with optically active compounds, substantial racemization occurred. Isomerization of the acyloin during imine formation is the most probable cause. This phenomenon was earlier observed for benzoins[5,6].

O-*t*-butyldimethylsilyl (TBS) protected acyloins, prepared as recently described[7], turned out to be ideal starting materials for reductive amination and did not have any of the disadvantages described above.



Reductive amination with $NaBH_3CN$ was performed as described in literature[7]. (*R*)-(+)-1-[(*t*-butyldimethylsilyl)oxy]-1-phenyl-2-propane (**1**) was used and a number of primary amines were tested (Table I). During the reduction a second chiral centre is created which will give rise to formation of mixtures of erythro- and threo-compounds. Appreciable chiral induction was observed. Erythro/threo ratios were conveniently determined by NMR by a procedure described for unprotected ethanolamines[8]. In our case, with O-TBS-protected ethanolamines, we found for erythro $J_{\alpha,\beta}$ = 3.6-4.1 Hz and for threo $J_{\alpha,\beta}$ = 8.8-9.2 Hz. Reactions were allowed to proceed to 95% conversion. Bulky groups directly attached to nitrogen lengthened the reaction times. For R = *t*-butyl 95% conversion was not reached even after 14 days. The steric hindrance in this case is also reflected by a completely different erythro/threo ratio.

Table I. Reductive amination of **1** with primary amines and $NaBH_3CN$.

	R	t	E/T		R	t	E/T
a.	CH_3	1.5h	82/18	d.	t-C_4H_9	14d	34/66
b.	C_2H_5	5.0h	75/25	e.	$CH_2C_6H_5$	1h	76/24
c.	i-C_3H_7	3d	81/19	f.	$C_2H_4C_6H_5$	1h	81/19

t: reaction time for 95% conversion. h: hour. d: day.

In order to optimize the reaction in favour of the erythro isomer we decided to use a magnesium salt as a complexing agent. Reduction of imines in the presence of magnesium perchlorate, by *Hantzsch* ester in acetonitrile, has been demonstrated to proceed via iminium salt complexes[9]. Formation of a magnesium bidentate complex should convey a more rigid conformation to the imine intermediate, which was expected to result in a higher percentage of the erythro diastereomer(**2**)[10].

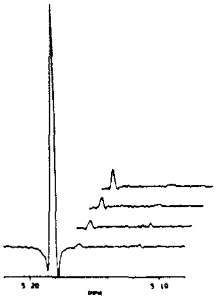
Table II. Magnesium perchlorate mediated imine formation and reduction with $NaBH_4$.

	R	t	E/T		R	t	E/T
a.	CH_3	30m	100/0	d.	t-C_4H_9	14d	-
b.	C_2H_5	30m	100/0	e.	$CH_2C_6H_5$	15m	100/0
c.	i-C_3H_7	150m	100/0	f.	$C_2H_4C_6H_5$	15m	100/0

t: reaction time for imine formation. m: minute. d: day.

In our first experiments with magnesium perchlorate and acetonitrile we noticed that, except for *t*-butylamine, formation of the imine was greatly accelerated and quantitative (GC). Use of $NaBH_3CN$ was therefore not mandatory and the more reactive $NaBH_4$ could be used instead. As a consequence, much lower reaction temperatures could be applied. The combination of magnesium perchlorate and low temperatures afforded a shift to the erythro compound, (Table II) to the extent that the threo compound could not be detected anymore in the NMR spectra (detection limit 0.5%).

The isolated products were subjected to enantiomeric excess determination by use of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid.



Free amine and an equivalent amount of a mixture of 60% *R* and 40% of *S* of this acid gave two signals with baseline separation in ^{19}F NMR with a ratio of 60 : 40. Detection limits were determined by using 95% *R*, 5% *S*; 98% *R*, 2% *S*; 99% *R*, 1% *S* and 100% *R* mixtures (see figure). The limit of detection was approximately 0.5%. Taking into account that (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid itself contains a trace of the *S*-enantiomer it was established that the e.e. of the products is 99% or more in all cases. Compound **2a** was deprotected with $LiAlH_4$[1]. The product was identical in spectral and optical properties with (1*R*,2*S*)-(-)-ephedrine.

Experimental:

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL FX-200 and ^{19}F NMR spectra on a Bruker WM 300 instrument. The optical purity of the ethanolamines was determined with the aid of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (see text). Optical rotations were measured using a Perkin Elmer 141 polarimeter. IR spectra (KBr) were recorded on a PYE UNICAM SP3 200 instrument. (*R*)-(+)-1-[(*t*-butyldimethylsilyl)oxy]-1-phenyl-2-propane (**1**) was as described earlier[7]. The crude product was purified by distillation (0.15 mm Hg, 99-101°C) and crystallization.
$[\alpha]^{20}_D$ +67.0°, (*c* 1, $CHCl_3$), e.e. >99%, mp 36-38°C.

Magnesium perchlorate mediated reductive amination. General procedure.

(*R*)-(+)-1-[(*t*-Butyldimethylsilyl)oxy]-1-phenyl-2-propanone (**1**), 5g (19 mmol) was dissolved in 200 mL of dry acetonitrile and 5g of $Mg(ClO_4)_2$ (22 mmol) was added. After 5 min 115 mmol of the desired N-alkylamine was added. The reaction mixture was magnetically stirred at room temperature. When imine formation was completed (see Table II) the reaction mixture was cooled to -18°C. This cooled solution was poured onto a frozen solution (-70°C) of 0.83 g (22 mmol) $NaBH_4$ in 100 mL acetonitrile. The reaction flask was isolated to prevent a quick warming up. During 1 hour the reaction mixture was stirred and the temperature raised to -20°C. The mixture was poured into 1L 1N HCl and extracted with CH_2Cl_2. The organic layer was washed with 1N NaOH (2x), 1N HCl (2x) and brine (2x). After drying on Na_2SO_4 the solvent was evaporated under reduced pressure. The isolated silyl derivatives were obtained, as HCl salt, in quantitative yield.

(1*R*,2*S*)-(-)-2-(Methylamino)-1-phenyl-1-[(*t*-butyldimethylsilyl)oxy]-propane, HCl salt. (**2a**).
$[\alpha]^{20}_D$ -31.1°, (*c* 1, $CHCl_3$). mp 153-155°C. e.e. >99%
^{1}H NMR: ($CDCl_3$) δ 9.35 (br, 2H, NH_2); 7.34 (m, 5H, arom); 5.26 (d, 1H, J = 3.6 Hz, C_6H_5CH); 3.29 (m, 1H CHN); 2.74 (s, 3H, NCH_3); 1.36 (d, 3H, J = 6.7 Hz, CH_3); 0.93 (s, 9H, *t*-bu); 0.19 (s, 3H, CH_3Si); -0.25 (s, 3H, CH_3Si).
^{13}C NMR: 140.2 (C-1); 128.2 (C-3,5); 128.1 (C-4); 126.6 (C-2,6); 74.0 (C-OH); 60.6 (C-N); 30.3 (N-CH_3); 25.8 ($(CH_3)_3$); 17.9 (C-Si); 10.1 (CH_3); -4.49 (Si-CH_3); -4.73 (Si-CH_3).
IR: 2920, 1450, 1400, 1255, 1190, 1130, 1065, 1020, 835, 780, 740, 705 cm^{-1}
$C_{16}H_{30}NOClSi$: Calc.: C 60.82% H 9.57% N 4.43% Found: C 60.56% H 9.56% N 4.62%

(1*R*,2*S*)-(-)-2-(Ethylamino)-1-phenyl-1-[(*t*-butyldimethylsilyl)oxy]-propane. HCl salt. (**2b**).
$[\alpha]^{20}_{D}$ -33.0°, (*c* 1, $CHCl_3$). mp 188-189°C. e.e. >99%
^{1}H NMR: ($CDCl_3$) δ 9.01 (br, 2H, NH_2); 7.31 (m, 5H, arom); 5.37 (d, 1H, J = 3.9 Hz, C_6H_5CH); 3.36 (m, 1H CHN); 3.10 and 2.88 (m, 2H, CH_2CH_3); 1.41 (t, 3H, J = 7.0 Hz, CH_2CH_3); 1.38 (d, 3H, J = 6.9 Hz, CH_3); 0.94 (s, 9H, *t*-bu); 0.18 (s, 3H, CH_3Si); -0.25 (s, 3H, CH_3Si).
^{13}C NMR: 140.5 (C-1); 128.2 (C-3,5); 128.0 (C-4); 126.5 (C-2,6); 73.8 (C-OH); 58.7 (C-N); 39.2 (NCH_2); 25.7 ($(CH_3)_3$); 17.8 (C-Si); 11.4 (CH_2CH_3); 10.5 (CH_3); -4.55 (Si-CH_3); -5.02 (Si-CH_3).
IR: 2950, 1460, 1400, 1390, 1250, 1200, 1120, 1075, 1030, 830, 780, 750, 700 cm^{-1}
$C_{17}H_{32}NOClSi$: Calc.: C 61.88% H 9.77% N 4.25% Found: C 61.88% H 9.88% N 4.38%

(1*R*,2*S*)-(-)-2-(*iso*-Propylamino)-1-phenyl-1-[(*t*-butyldimethylsilyl)oxy]-propane. HCl salt. (2c).
$[\alpha]^{20}_{D}$ -0.1°, (*c* 1, $CHCl_3$). mp 184-186°C. e.e. >99%
^{1}H NMR: ($CDCl_3$) δ 8.78 (br, 2H, NH_2); 7.34 (m, 5H, arom); 5.24 (d, 1H, J = 5.6 Hz, C_6H_5CH); 3.36 (m, 1H CHN); 2.97 (m, 2H, $CH(CH_3)_2$); 1.51 (d,3H, J = 6.7 Hz, CH_3); 1.47 (d, 3H, J = 6.7 Hz, $CHCH_3$); 1.37 (d, 3H, J = 6.7 Hz, $CHCH_3$); 0.91 (s, 9H, *t*-bu); 0.13 (s, 3H, CH_3Si); -0.21 (s, 3H, CH_3Si).
^{13}C NMR: 140.7 (C-1); 128.5 (C-3,5); 128.4 (C-4); 127.0 (C-2,6); 74.0 (C-OH); 58.0 (C-N); 48.9 ($NCH(CH_3)_2$); 25.7 ($(CH_3)_3$); 19.8 ($NCHCH_3$); 18.2 ($NCHCH_3$) 17.9 (C-Si); 14.7 (CH_3); -4.52 (Si-CH_3); -4.99 (Si-CH_3).
IR: 2950, 1450, 1390, 1250, 1190, 1135, 1080, 1030, 840, 775, 735, 695 cm^{-1}
$C_{18}H_{34}NOClSi$: Calc.: C 62.85% H 9.96% N 4.07% Found: C 62.85% H 10.00% N 4.20%

(1*R*,2*S*)-(-)-2-(Benzylamino)-1-phenyl-1-[(*t*-butyldimethylsilyl)oxy]-propane. HCl salt. (2e).
$[\alpha]^{20}_{D}$ -24.6°, (*c* 1, $CHCl_3$). mp 202-205°C. (dec.) e.e. >99%
^{1}H NMR: ($CDCl_3$) δ 9.24 (br, 2H, NH_2); 7.30 (m, 10H, arom); 5.26 (d, 1H, J = 4.1 Hz, C_6H_5CHOH); 4.01 (d, 1H, J = 15 Hz, $C_6H_5CH_2$); 3.92 (d, 1H, J = 15 Hz, $C_6H_5CH_2$); 3.21 (m, 1H CHN); 1.38 (d, 3H, J = 6.6 Hz, CH_3); 0.89 (s, 9H, *t*-bu); 0.15 (s, 3H, CH_3Si); -0.26 (s, 3H, CH_3Si).
^{13}C NMR: 139.9; 130.7; 130.2; 129.0; 128.9; 128.4; 128.3; 127.1; (arom) 74.4 (C-OH); 57.8 (C-N); 47.6 ($NCH_2C_6H_5$); 25.8 ($(CH_3)_3$); 18.0 (C-Si); 11.3 (CH_3); -4.41 (Si-CH_3); -4.73 (Si-CH_3).
IR: 2940, 1450, 1380, 1250, 1190, 1135, 1080, 1030, 840, 775, 735, 695 cm^{-1}
$C_{22}H_{34}NOClSi$: Calc.: C 67.40% H 8.74% N 3.57% Found: C 67.62% H 8.84% N 3.80%

(1*R*,2*S*)-(-)-2-(2-Phenylethylamino)-1-phenyl-1-[(*t*-butyldimethylsilyl)oxy]-propane. HCl salt. (2f).
$[\alpha]^{20}_{D}$ -5.3°, (*c* 1, $CHCl_3$). mp 176-177°C. e.e. >99%
^{1}H NMR: ($CDCl_3$) δ 9.33 (br, 2H, NH_2); 7.27 (m, 10H, arom); 5.34 (d, 1H, J = 3.9 Hz, C_6H_5CHOH); 3.2 (m, 4H, $C_6H_5CH_2CH_2$); 3.2 (m, 1H CHN); 1.40 (d, 3H, J = 6.7Hz, CH_3); 0.84 (s, 9H, *t*-bu); 0.16 (s, 3H, CH_3Si); -0.22 (s, 3H, CH_3Si).
^{13}C NMR: 140.1; 136.2; 128.6; 128.5; 128.3; 128.1; 126.8; 126.5 (arom); 73.9 (C-OH); 59.4 (C-N); 45.7 ($NCH_2CH_2C_6H_5$); 32.4 ($NCH_2CH_2C_6H_5$); 25.6 ($(CH_3)_3$); 17.8 (C-Si); 10.6 (CH_3); -4.52 (Si-CH_3); -4.93 (Si-CH_3).
IR: 2950, 1450, 1390, 1255, 1200, 1130, 1050, 850, 780, 755, 700 cm^{-1}
$C_{23}H_{36}NOClSi$: Calc.: C 68.03% H 8.94% N 3.45% Found: C 67.40% H 9.08% N 3.45%

References.

1. Brussee, J.; Dofferhoff, F.; Kruse, C.G.; Van der Gen, A. *Tetrahedron*, **1990**, in press.
2. Tramontini, M. *Synthesis*, **1982**, 605, and references cited therein.
3. Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
4. Garry S.W.; Neilson, D.G. *J. Chem. Soc. Perkin Trans. I* **1987**, 601.
5. Armesto, D.; Horspool, W.M.; Ortiz, M.J.; Perez-Ossorio, R. *Synthesis*, **1988**, 799.
6. Davis, F.A.; Haque, M.S.; Przeslawski, R.M. *J. Org. Chem.* **1989**, *54*, 2021.
7. Brussee, J.; Roos, E.C.; Van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485.
8. Lövgren, K.; Nilsson, J.L.G. *Acta Pharm. Suec.* **1977**, *14*, 30.
9. Van Niel, J.C.G.; Kort, C.W.F.; Pandit, U.K. *Recl. Trav. Chim. Pays-Bas*, **1986**, *105*, 262.
10. Cram, D.J.; Kopecky, K.R.; *J. Amer. Chem. Soc.* **1959**, *81*, 2748.