Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Study of the Effect of Catalyst on Stereochemistry in the Hydrogenation of N-(Menthyloxycarbonyl)-N-Methyl-2-(N-Pyrrolidinyl)-1-cyclohexenamine

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Published online: 23 Sep 2006.

To cite this article: Dorota Matecka & Brian R. de Costa (1994) A Study of the Effect of Catalyst on Stereochemistry in the Hydrogenation of N-(Menthyloxycarbonyl)-N-Methyl-2-(N-Pyrrolidinyl)-1-cyclohexenamine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:11, 1531-1540, DOI: 10.1080/00397919408010153

To link to this article: http://dx.doi.org/10.1080/00397919408010153

SYNTHETIC COMMUNICATIONS, 24(11), 1531-1540 (1994)

A STUDY OF THE EFFECT OF CATALYST ON STEREOCHEMISTRY IN THE HYDROGENATION OF N-(MENTHYLOXYCARBONYL)-N-METHYL-2-(N-PYRROLIDINYL)-1-CYCLOHEXENAMINE.

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Abstract: Catalytic hydrogenation of N-(menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl)-1-cyclohexenamine (**3**) gave mainly 1R,2S-*cis*-N-(menthyloxycarbonyl)- and 1S,2R-*cis*-N-(menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl)cyclohexylamines **7** and **8** with diastereoselectivity favoring the 1S,2R-isomer **8**.

Chiral *cis* and *trans* 2-(1-pyrrolidinyl)cyclohexylamines are important intermediates in medicinal chemistry. The 1S,2S-(+)-*trans* diamine [(+)-**1**] is the main intermediate in the synthesis of novel kappa opioid receptor analgesics.[1] The *cis* diastereoisomers of 1R,2S-(-)-**2** and 1S,2R-(+)-**2** of **1** are important intermediates in the development of novel sigma receptor ligands.[2] Sigma receptors[3] have been implicated in psychoses, as well as motor[3] and neurodegenerative disorders.[4] The synthesis of the enantiomers of these diamines is therefore of considerable interest in the development of new therapeutic agents.

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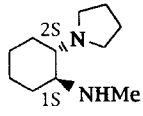
Our approaches to enantiomerically pure 1 or 2 utilized fractional crystallization of optically active salts of racemic 1 or 2[1,2] More recently, the synthesis of the optical isomers of 1 and 2 has been accomplished through the catalytic hydrogenation of the 1R- and 1S-α-methylbenzylamine imine derivatives of (±)-2-benzamidocyclo hexanone.[5] This approach showed low stereoselectivity (2:1 ratio of *cis/trans* products) but high enantioselectivity.



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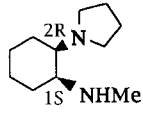

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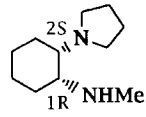
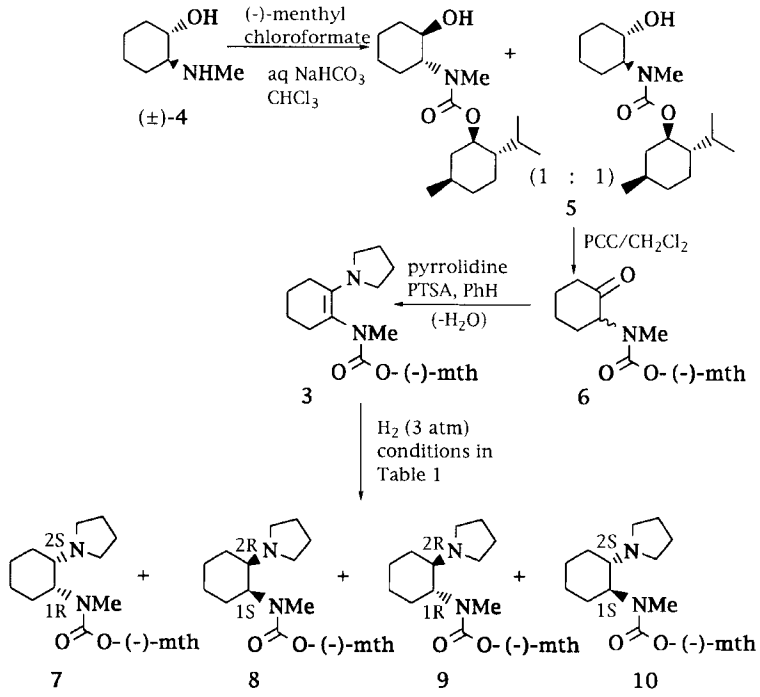


(-)-2

In the present study, we investigate the effect of catalyst on the the *cis/trans* stereoselectivity/diastereoselectivity during hydrogenation of enamine 3 (Scheme 1) containing the (-)-menthoxy group as a chiral auxiliary.

Reaction of (±)-*trans*-2-(methylamino)cyclohexanol [(±)-4][2a] with (-)-menthyl chloroformate (Aldrich Chemical Co., Milwaukee, WI) in the presence of aqueous $NaHCO_3$ under Schotten-Baumann conditions furnished the 1:1 diastereoisomeric mixture 5 as an oil (88%) (Scheme 1). PCC oxidation of 5 afforded the diastereoisomeric ketone mixture 6 as an oil (89%). Condensation of 6 with pyrrolidine gave enamine 3 (97%). This enamine was subjected to catalytic hydrogenation at 3 atm pressure under 12 different conditions as depicted in Table 1. In addition to investigating the effect of different catalysts, the effect of solvent was also examined in certain cases. The four possible diastereoisomers 7-10 thus formed (Scheme 1) proved to be separable by gas chromatography (GC). The relative proportions and diastereoisomeric excesses of 7-10



Scheme 1

were readily quantified by integration of the GC peaks (Table 1). The absolute stereochemistry of these isomers was determined by GC chromatographic and ^{1}H NMR spectral comparison to references of known absolute configuration.

Thus, reference **7** was obtained by treatment of 1R,2S-(-)-**2**[2] with (-)-menthyl chloroformate in the presence of Et_3N. References **8**, **9**, and **10** were similarly obtained from 1S,2R-(+)-**2**[2], 1R,2R-(-)-**1**[1] and 1S,2S-(+)-**1**[1], respectively.

The preferential formation (Scheme 1) of enamine **3** (tetra substituted double bond) as opposed to the isomeric trisubstituted

Table 1

Expt No.[a,b]	Catalyst	Time (h)[c]	Ratio % *cis/trans*	de % for **8** (*cis*)[d]	de % for **10** (*trans*)[d]
1	10% Pd/C	4	>99 *cis*	16	-
2	5% Pd/$BaSO_4$	48	>99 *cis*	8	-
3	PtO_2[e]	4	87:13	19	20
4	10% Pt/C[f]	24	88:12	14	21
5	10% Pt/alumina	24	84:16	13	15
6	5% Ru/C	24	>99 *cis*	7	-
7	5% Rh/C	4	98:2	9	14
8	Raney Ni[g]	48	>99 *cis*	2	-
9	Raney Ni[g]	48	>99 *cis*	0.5	-
10	$RhCl_2(PPh_3)_3$	24	>99 *cis*	20	-
11	$RhCl_2(PPh_3)_3$[h]	72	>99 *cis*	14	-
12	10%Pd/C[i]	48	>99 *cis*	16	-

[a] See Experimental Section for General Experimental Method. [b] Solvent is EtOAc, unless stated otherwise. [c] All reactions were performed at room temperature (23 °C) and went to completion. [d] The diastereoisomeric excesses (de) of **8** and **10** were determined by GC analysis of the reaction mixture at 200 °C-280 °C gradient (20 °C/min) using a 30m SE-30 column. Under these conditions, the isomers appeared as follows: **7** (11.8 min), **8** (12.0 min), **9** (10.9 min) and **10** (11.1 min). These isomers co-chromatographed with authentic samples prepared as described in the Experimental Section. [e] 1:20 w/w ratio of catalyst to substrate was employed. [f] 1:5 w/w ratio of catalyst to substrate was employed. [g] 1:1 w/w ratio of catalyst to substrate was employed; EtOH solvent. [h] 1:2 w/w ratio of catalyst to substrate was employed; CH_2Cl_2solvent. [i] 1:3 w/w ratio of catalyst to substrate and $NH_4 \bullet HCO_2$ (1.1 eq) was employed; solvent MeOH. The reaction mixture was filtered through celite, and the filtrate was evaporated *in vacuo*. The residue was partitioned between ether and water and the ether layer was evaporated *in vacuo* to give the product (quantitative).

enamine under equilibrium conditions suggests that the former is the thermodynamically more stable isomer. The results of the catalytic hydrogenation (Table 1) indicate that the *cis* diastereoisomers **7/8** predominate under all conditions as would be expected from attack of hydrogen from the same face of the enamine double bond. The *cis* products **7/8** typically constituted >99% of the product mixture. Interestingly, the more reactive Pt and Rh containing heterogeneous catalysts gave from 2-16% of the *trans* isomers **9/10** suggesting catalyst-induced rearrangement of the enamine double bond of **3**. In all other cases, the proportion of *trans* isomer was <1% of the total product mixture. This reaction also proved to be diastereoselective with de ranging from 0.5-20% in favor of **8** (1S,2R absolute configuration) and de 13-21% for **10** (1S,2S). The stereoselective nature of these hydrogenations in favor of the *cis* isomers identifies this as a promising route to (+)- and (-)-**2**. The moderate de's suggests that the (-)-menthyl chiral auxiliary is too distant from the double bond of **3** to allow for efficient chiral induction.

Experimental Section

^{1}H NMR spectra are were obtained from $CDCl_3$ solutions of compounds using a Varian Gemini 300 NMR spectrometer. Infrared (IR) spectra were obtained using a Bio-Rad FTS-45 FTIR spectrometer. Gas chromatography (GC) was determined with a Hewlett-Packard 5890A instrument fitted with a 30m SE30 capillary column and flame ionization detector. Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA. Thin layer chromatography was performed on 250 μm

Analtech GHLF silica-gel plates. High resolution mass measurements (HRMS) were determined a VG Micromass 1070 mass spectrometer

***trans*-2-(N-Menthyloxycarbonyl)-N-(methylamino) cyclohexanols (5).** To a stirred and cooled (ice-bath) solution of (±)-*trans*-2-(methylamino)cyclohexanol [(±)-**4**][6] (13.7 g, 0.1 mol, 1.1 eq) in $CHCl_3$ (100 mL) was added Et_3N (43 mL, 0.27 mol, 3 eq), followed by (-)-menthyl chloroformate (19.9 g, 0.09 mol) and stirring was continued until the reaction was complete (TLC, conc aqueous NH_3/MeOH/$CHCl_3$ 2:18:80). The volatiles were evaporated *in vacuo* and the residue was partitioned between 5% aqueous citric acid (300 mL) and EtOAc (300 mL). The organic phase was washed with $NaHCO_3$ (75 mL), water, dried (Na_2SO_4) and the solvent was evaporated *in vacuo* to give the 1:1 diastereomeric mixture (as determined using ^1H NMR and GC) **5** (25.0 g, 88%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.79 (d, J=7.1Hz, 3H), 0.91 (d, J=7.3Hz, 6H), 0.95-1.79 (m complex, 13H), 1.92-1.98 (m, 1H), 2.02-2.16 (m, 4H), 2.80 (s, 3H), 3.44-3.58 (m, 1H), 3.89 (s broad, 1H), 4.59 (m, 1H); HRMS (MH^+ calcd for $C_{18}H_{34}NO_3$): 312.2539. MH^+(found)=312.2544.

2-(N-Menthyloxycarbonyl-N-methylamino)cyclo hexanones (6). To a stirred solution of **5** (25.0 g, 0.08 mol) in CH_2Cl_2 (50 mL) at rt was added dropwise during 20 min PCC (26.0 g, 0.12 mol, 1.5 eq) in CH_2Cl_2 (80 mL). Thin layer chromatography ($CHCl_3$/MeOH 19:1) indicated that the reaction was complete after 3h at rt. The reaction mixture was diluted with ether (120 mL) and then filtered through a short column of Florisil. Evaporation of the filtrate gave the product (22.1 g, 89%) as a pale green oil which was further purified by distillation (bp 143-144 °C/0.025mmHg). Diastereoisomeric mixture **6** (1:1

as confirmed by ^{1}H NMR) exhibited the following characteristics: ^{1}H-NMR δ 0.79 (d, J=6.8Hz, 3H), 0.89 and 0.91 (2d, J=6.3Hz, 6H), 0.99-1.08 (m, 2H), 1.64-2.11 (m, 11H), 2.22-2.54 (m, 4H), 2.82 (s, 3H), 4.52-4.64 (m complex, 1H), 4.72-4.82 (m, 1H); IR (cm^{-1}): 1693 (C=O), 1723; HRMS (M^+ (calcd for $C_{18}H_{31}NO_3$): 309.2304. M^+(found): 309.2289; Anal (calcd for $C_{18}H_{31}NO_3$): C 69.86, H 10.09, N 4.53%. Found: C 69.57, H 9.99, N 4.50%.

N-(Menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl) -1-cyclohexenamine (3). A solution of **6** (12.1 g, 0.039 mol), *p*-toluenesulfonic acid•monohydrate (0.0023 mol, 0.06 eq) and pyrrolidine 3.53 g, 0.049 mol, 1.27 eq) in benzene (130 mL) was boiled under reflux under a Dean-Stark trap. Analysis of the reaction mixture by GC (200-280 °C; 10 °C/min gradient) indicated the presence of **6** (48%, retention time 9.62 min) and **3** (52%, retention time 14.1 min) after refluxing for 4 h and **6** (18%) and **3** (82%) after 22h. A further 3.53 g of pyrrolidine was added, and the reaction was continued for a total of 48h when GC indicated the reaction to be complete (97% enamine **3**). The reaction mixture was cooled to rt and the solvent was evaporated *in vacuo* to give **3** as an oil which was stored at -30 °C under N_2 until further use ^{1}H NMR δ 0.74-0.79 (m, 3H), 0.82-0.92 (m, 6H), 0.94-1.05 (m, 3H), 1.38-2.37 (m, 19H), 2.92 (s, 3H), 4.46-4.64 (m, 3H), 4.78-4.84 (m,1H); HRMS (MH^+ calcd for $C_{22}H_{39}N_2O_9$): 363.2997. MH^+ (found): 363.3012.

Catalytic Hydrogenation of 3. To a solution of **3** (0.25 g) in EtOAc (10 mL) (or other solvent as indicated in Table 1) was added the appropriate catalyst (25 mg or other proportion as indicated in the footnote to Table 1) and the mixture was shaken at rt under a H_2 atmosphere (3 atm) for 4h or other time (Table 1). Progress of the

reaction was monitored by TLC (concentrated aqueous NH_3/MeOH/$CHCl_3$ 1:9:90). The *cis* diastereoisomers **7** and **8** proved inseparable from each other by TLC. This was also the case for the and *trans* diastereoisomers **9** and **10** ; however, **7** and **8** were readily separable from **9** and **10** by TLC. Complete separation and quantitation of the products was achieved using GC under the conditions indicated in the footnote to Table 1. On completion, the reaction mixtures were filtered through celite and the product distribution of **7-10** (obtained quantitatively) (Scheme 1) was assessed by GC. The identity of the products was confirmed by ^1H NMR and chromatographic comparison (GC) to authentic samples of known absolute configuration prepared as described below.

1R,2S-*cis*-N-(Menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine (7). To a solution of (-)-**2**[2] (98 mg, 0.54 mmol, 1.1 eq) in $CHCl_3$ (2 mL) was added a solution of (-)-menthyl chloroformate (0.1 mL, 0.47 mmol) and Et_3N (100 mg, 1 mmol). The solution was stirred overnight at rt when TLC (conc aqueous NH_3/MeOH/$CHCl_3$ 2:18:80) indicated the reaction to be complete. The solvent was evaporated *in vacuo* and the residue was dissolved in EtOAc (10 mL) and washed with water (2 x 5 mL). Evaporation of the solvent afforded the enantiomeric *cis* isomer **7** (150 mg, 88%) as a colorless oil: ^1H NMR δ 0.78 (d, J=6.9Hz, 3H), 0.90 (d, J=7.2Hz, 6H), 0.96-1.12 (m, 2H), 1.32-1.68 (m complex, 17H), 1.86-2.08 (m, 4H), 2.52 (s, 3H), 2.58-2.70 (m, 1H), 2.98 (s, 2H), 4.01 (s broad, 1H), 4.57 (dt, J^1=4.2Hz, J^2=10.8Hz, 1H); HRMS (M^+ calcd for $C_{22}H_{40}N_2O_2$): 364.3090. M^+ (found): 364.3107.

1S,2R-*cis*-N-(Menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine (8). *Cis* isomer **8** was synthesized as

described for **7** from (+)-**2**[2] (18 mg, 0.1 mmol, 1.1 eq) and was obtained as a colorless oil (29 mg, 88%): ^{1}H NMR δ 0.79 (d, J=6.8Hz, 3H), 0.89 and 0.91 (2d, J=6.8Hz, 6H), 0.79-0.92 (m, 2H), 0.97-1.08 (m, 2H), 1.10-2.53 (m, 20H), 2.70-2.96 (m, 5H), 4.08 (s broad, 1H), 4.52-4.58 (m, 1H); HRMS (M^+ calcd for $C_{22}H_{40}N_2O_2$): 364.3090. M^+ (found)=364.3107.

Reference 7 and 8 (1:1 ratio). *Cis* isomers **7** and **8** (1:1) as a GC standard were synthesized as described for **7** starting with (±)-**2**•2HCl[2] (46 mg, 0.18 mmol, 1.1 eq). The product (57 mg, 98%) was obtained as a colorless oil. ^{1}H NMR indicated a 1:1 mixture of **7** and **8**.

1R,2R-*trans*-N-(Menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine (9). Enantiomeric *trans* isomer **9** was synthesized as for **7** starting with (-)-**1**[1] (270 mg, 1.48 mmol, 1.5 eq). The product (314 mg, 86%) was obtained as a colorless oil: ^{1}H NMR δ 0.78 (d, J=6.9 Hz, 3H), 0.89 (d, J=6.9Hz, 6H), 0.93-1.49 (m complex, 10H), 1.87-2.04 (s, 3H), 3.95-4.05 (m, 1H), 4.54-4.59 (m, 1H); HRMS (M^+ calcd for $C_{22}H_{40}N_2O_2$): 364.3090. M^+ (found): 364.3082.

1S,2S-*trans*-N-(Menthyloxycarbonyl)-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine (10). *Trans* isomer **10** was obtained as for **7** starting with (+)-**1**[1] (166 mg, 0.91 mmol, 1.1 eq) as a colorless oil (194 mg, 64%): ^{1}H NMR δ 0.79 (d, J=6.8Hz, 3H), 0.89 (d, J=6.7Hz, 6H), 0.93-1.49 (m complex, 8H), 1.67-1.79 (m complex, 10H), 1.85-1.93 (m, 2H), 2.04-2.08 (m, 1H), 2.46-2.56 (m, 2H), 2.62-2.74 (m, 2H), 2.71 (s, 3H), 2.78 (s, 1H), 4.05-4.12 (m, 1H), 4.57 (dt, J^1=4.5Hz, J^2=10.8Hz, 1H); HRMS (M^+ calcd for $C_{22}H_{40}N_2O_2$): 364.3090. M^+ (found): 364.3100.

Reference 9 and 10 (1:1 ratio). *Trans* isomers **9** and **10** (1:1) as a GC standard were synthesized as described for **7** starting with (±)-**1**[1] (160 mg, 0.88 mmol, 1.1 eq). The product (147 mg, 51%) was obtained

as a colorless oil. ^{1}H NMR and GC confirmed the expected 1:1 ratio of **9** and **10**.

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(Received in the USA 21 November 1993)