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Formic Acid Reduction of Enamines from D-Camphor. A Facile Route to Chiral Bornyl Amines

ROLF CARLSON and ÅSA NILSSON

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

Camphor enamines are easily reduced by formic acid. The reaction is highly stereoselective and gives predominantly the *endo*-isomer of the tertiary bornylamines.

The current trend in organic synthesis is to proceed by stereocontrolled synthesis as early as possible along the synthetic route, *i.e.* to use chiral synthons in specific transformations to ensure the correct stereochemistry of the target molecule. Easy access to chiral tools is therefore of considerable interest either to resolve racemic starting materials or to produce chiral reagents. Various derivatives of camphor have been used in this context (see Ref. 1).

The direct preparation of camphor enamines from camphor and secondary amines is possible by an improved titanium tetrachloride procedure.[2] Synthesis of camphor enamines by a multistep procedure *via* nitroimines has been reported.[3] The reduction of the dimethylamino, pyrrolidino and piperidino enamines of camphor by catalytic hydrogenation, or by sodium borohydride reduction of the corresponding iminium perchlorate, has been reported to give mixtures of *endo*- and *exo*- isomers of the bornylamines in different proportions.[4] Formic acid has been used for the reduction of enamines,[5] although it has been reported that bicyclic enamines, *e.g.* from norcamphor, are not readily reduced by formic acid.[6]

Here we report that camphor enamines can easily be reduced by formic acid in good yields and with high stereoselectivity to give the *endo* isomer as the predominant product.

RESULTS

1. *Enamine reduction.* A preliminary study showed that the addition of 98 % formic acid to the neat morpholine enamine from camphor gave rapid reduction of the enamine. See Ref. 7 for a similar procedure with enamines from aldehydes. A factorial experimental design was used to determine the influence of the reaction temperature (room temperature –100 °C) and the amount of formic acid (1.0–1.5 equivalents) on the yield. It was found that it was not necessary to use an excess of formic acid, but the reaction should be conducted at elevated temperature. The following reaction conditions were adopted for subsequent studies of the method: a reaction temperature of 100 °C and a slight excess (1.04–1.07 equiv.) of formic acid (Fig. 1).

The reduction of camphor enamines with formic acid is highly stereoselective compared to other methods of reduction, *e.g.* catalytic hydrogenation or reduction of the corresponding iminium perchlorates, which gave at best 80 % stereoselectivity.[4b] A high stereoselectiv-

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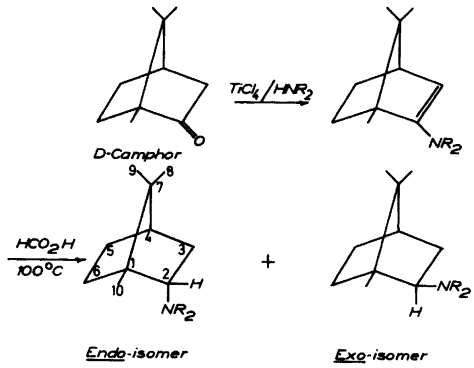

Fig. 1. Synthesis of bornylamines *via* enamines obtained from camphor and numbering of the carbon skeleton of bornylamines.

ity in reduction of enamines from 2-substituted cyclohexanones with formic acid has been reported.[5b]

The reduction might involve charged intermediates, and the possibility of further enhancing the stereoselectivity by using a suitable solvent was studied. The pyrrolidine enamine which showed the lowest stereoselectivity was used as a model, substrate and the following solvents were tested; formamide, sulfolane, 1,2-dichlorobenzene, cyclohexane, tetrahydrofuran, methoxyethanol, methanol, 2-methyl-2-butanol and diethylene glycol. The selection was based on a principal components analysis of solvent properties.[8] The reaction was studied at 100 °C, except for tetrahydrofuran (b.p 67 °C) and methanol (b.p 65 °C), which were employed at reflux temperature. In all cases the amount of *endo*- isomer was in the range 85–87 %, which is the same as without solvent, and since the selected solvents cover a large variation in solvent properties no further attempts were made to manipulate the reaction medium.

Reduction of the morpholine enamine with formic acid-d_2 yielded a mixture of mono-, di- and tri- deuterated bornylmorpholine in the following proportions: 28 % d_1, 45 % d_2 and 27 % d_3.

Chromatography of endo/exo *isomers.* The separation of *endo*- and *exo*-isomers of bornylpyrrolidine and bornylpiperidine by chromatography on alumina with light petroleum as eluent has been reported by Bondavalli *et al.*[4b] However, we were unable to reproduce these findings. Attempts at separating these isomers by HPLC on straight phase silica or reversed phase C-8 columns with various eluents also failed, as did chromatography on Sephadex LH-20.

Bornylmorpholine isomers could be separated by chromatography on silica using ethyl acetate as eluent. However, the separation by chromatography is time-consuming, and for preparative applications another separation procedure was desired.

Recrystallization of amine hydrochlorides. Repeated recrystallization from isopropanol afforded pure (>99 %) *endo*-bornylmorpholine hydrochloride and *endo*-bornylpiperidine hydrochloride. Recrystallization of the corresponding pyrrolidine hydrochloride from isopropanol/pentane gave *endo*-bornylpyrrolidine hydrochloride (purity 98.8 %) but was less satisfactory with regard to yield, see Experimental.

DISCUSSION

Assignment of configuration. the conclusion that the predominant reduction product is the *endo*-isomer is based on the following observations:

^{1}H NMR spectra of bornylpyrrolidines and bornylpiperidines are in accordance with reported spectra.[4b]

The isomer mixture of the bornylamines from morpholine, pyrrolidine and piperidine are all dextrorotatory, see Experimental. The reported rotation of *endo*-bornyl-dimethylamine is $[\alpha]_D^{23}=+50.0°$ and for *endo*-bornylamine $[\alpha]_D^{23}=+46°$.[9]

The isolated isomers of bornylmorpholines showed the following rotations: major isomer $[\alpha]_{578}^{23}=+34.2°$ (c=1.11, EtOH), minor isomer $[\alpha]_{578}^{23}=-65.9°$ (c=0.97, EtOH). The *exo*-isomers of bornylamine and bornyldimethylamine are laevorotatory, $[\alpha]_D^{23}=-33°$ and $-61°$, respectively.[9]

Further support of the proposed *endo*-configuration of the major product is obtained from the ^{13}C NMR spectra of the morpholine isomer. Partially decoupled off-resonance ^{13}C NMR spectra, and ^{13}C NMR spectra of the deuterated product obtained by formic acid-d_2 reduction, made it possible to assign the individual carbon resonance signals. A study of the carbon-13 NMR chemical shifts of bicyclic compounds[10] reports that *endo*- and *exo*- bornyl derivatives differ in the relative positions of the ^{13}C resonances from carbons 5,6 and 8,9,10 (see Fig. 1 for numbering). In accordance with this study, the ^{13}C NMR spectrum of the major isomer is assigned to *endo*-bornylmorpholine.

Reaction mechanism. The stereoselectivity of the reduction was not influenced by solvent properties. This suggested that the reaction might involve a synchronous transfer of a proton and a hydride from formic acid, and that the reaction does not involve a highly polar transition state susceptible to changes in solvent properties. The formation of mono-, di- and tri- deuterated amine by formic acid-d_2 reduction rules out this possibility and supports a two-step mechanism shown in Fig. 2. The first step is a reversible protonation of the

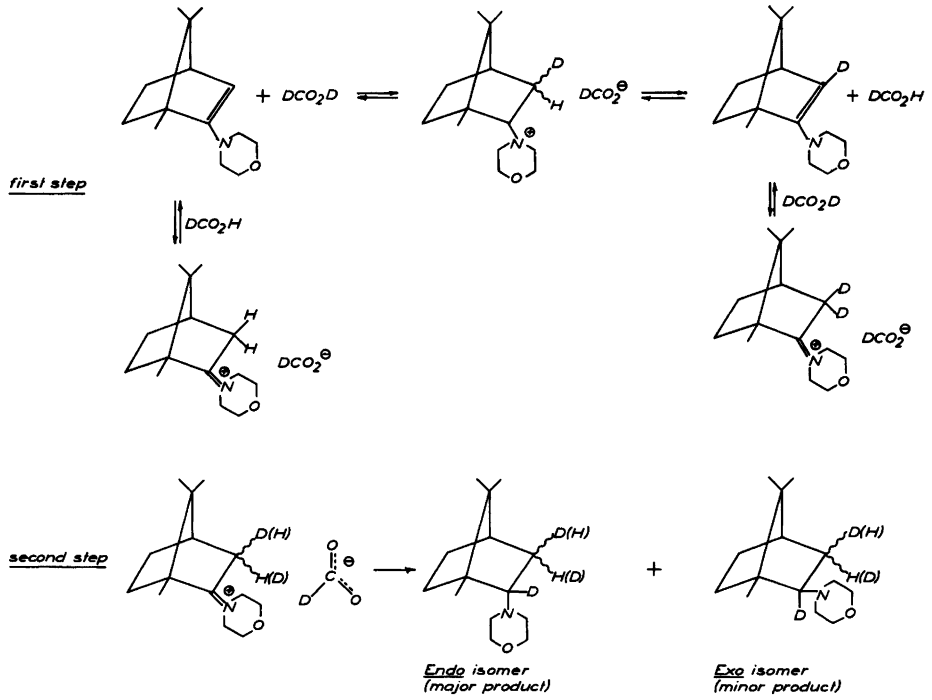

Fig. 2. Mechanism of formic acid reduction of bornylamines.

enamine to give the corresponding iminium formate, and the second step is an irreversible transfer of hydride from the formate ion. A similar result was obtained in the reduction of $\Delta^{1(10)}$-dehydroquinolizidine with labelled formic acid.[11]

Dreiding models of the *exo*-isomer show steric congestion between the geminal *syn*-methyl groups and the six-membered morpholine and piperidine rings; the steric interaction is less pronounced with the five-membered pyrrolidine ring. The *endo*-isomers show no such steric congestion. This may contribute to the observed high stereoselectivity in the reduction, and may also explain the somewhat lower stereoselectivity in the reduction of the pyrrolidine enamine of camphor than in the reduction of the enamines from morpholine and piperidine.

Conclusions. Chiral *endo*-bornylamines are available by the two-step reductive amination of camphor outlined above. The facile separation of bornylmorpholine and bornylpiperidine offers a means of producing chiral tertiary amines at low costs using readily available chemicals.

EXPERIMENTAL

General techniques. ^1H and ^{13}C NMR. Spectra were recorded on a Bruker WM-250 instrument. *Mass spectra:* A Finnigan 4021 mass spectrometer with an INCOS data system was used. *Optical rotations:* A Perkin Elmer 141 polarimeter was used to determine optical rotations. *GC analyses: endo-* and *exo-* isomer distribution was analysed on a Carlo-Erba Fractovap series 4160 high resolution gas chromatograph (FID detector) with a HP 3388A integrator for measuring the peak areas. Operating conditions: SE-54 capillary column (0.30 m m ID, 25 m), split injection (1/50), column temperature 250 °C and flow rate 1.7 ml/min. The *endo-* and *exo*-isomers were assumed to have the same FID response.

Chemicals and solvents. Amines and solvents were commercial *puriss* or *p.a* products and titanium tetrachloride was of technical grade. D(+)-Camphor, $[\alpha]_D^{23}=+44.1$ (c 10, EtOH) was purchased from EGA, and formic acid (*puriss* 98 %) from Riedel de Haen was used. Formic acid-d_2 (99 %), *Uvasol*^{R} from Merck was used in the deuteration experiments.

Synthesis of enamines. A previously described modified titanium tetrachloride procedure was used.[2] Use of high boiling light petroleum (b.p. 100–110 °C) shortened the reaction time for the synthesis of the morpholine enamine from 44 to 10 h, (yield 79–81 %). The piperidine enamine of camphor, not previously described, was obtained in 63 % yield after 21 h reflux in hexane, b.p. 65.5–67 °C/0.001 mmHg. ^1H NMR (250 MHz, $CDCl_3$): δ methyl resonances, 0.72 (3H, s), 0.83 (3H, s), 1.04 (3H, s) and vinylic proton, 4.80 (1H, d, J=3.5 Hz). *MS* (EI, 70 eV): *m/z* (relative abundance), 219 (23.1) M^+, 191 (88.4)$M^+-C_2H_4$ (retro Diels-Alder fragmentation), 176 (100.0) $M^+-C_3H_7$.

Reduction of enamines. A 100 ml Erlenmeyer flask equipped with a Liebig condenser was charged with 50 mmol of enamine. The enamine was magnetically stirred and heated to 100 °C.[a] Formic acid (98 %)[b], 2.0 ml (52 mmol) was added dropwise through the condenser at such a rate that the resulting foaming could be kept under control. When the carbon dioxide evolution ceased (*ca.* 2 min), 50 ml of water and 5 ml of concentrated hydrochloric acid were added to the reaction mixture and stirring was continued for 0.5 h to hydrolyse the unreacted enamine. The mixture was cooled and washed twice with 20 ml of ether to remove camphor. The aqueous layer was made alkaline by the careful addition of 5 M NaOH (*ca.* 15 ml). The amine layer was separated and the aqueous layer extracted with ether (3×25 ml). The combined organic layers were dried overnight (KOH). The crude product, after removal of solvent, was distilled (20 cm Vigreux column) under reduced pressure.

Bornylmorpholine: b.p. 84–88 °C/0.005 mmHg, yield 10.0 g (90 %), $[\alpha]_{578}^{23}=+25.1°$ (c 1.84, EtOH), *endo/exo*=93/7.

Bornylpiperidine. b.p. 64–66 °C/0.005 mmHg, yield 9.05 g (82 %), $[\alpha]_{578}^{23}=+24.8°$ (c 1.68, EtOH), *endo/exo*=92/8.

Bornylpyrrolidine. b.p. 66–68 °C/0.005 mmHg, yield 9.04 g (87 %), $[\alpha]_{578}^{23}$=+16.6° (c 1.53, EtOH), *endo/exo*=85/15.

Notes.[a] Reduction with formic acid-d_2 was carried out in a similar fashion.[b] If formic acid is added to cold enamine, the reaction is slow and formic acid accumulates. The reaction can then become too vigorous when the temperature rises.

Preparation of amine hydrochlorides. The amine was dissolved in ether to give *ca* 15 % (w/v) solution. The solution was cooled (0 °C) and gaseous hydrogen chloride was bubbled through it. The yields of amine hydrochlorides were quantitative.

Crude hydrochlorides of *bornylmorpholine,* $[\alpha]_{578}^{23}$=+15.6° (c 1.00, EtOH), *bornylpiperidine,* $[\alpha]_{578}^{23}$=+14.3° (c 1.03, EtOH), *bornylpyrrolidine,* $[\alpha]_{578}^{23}$=+7.8° (c 1.00, EtOH).

Purification of amine-hydrochlorides. The crude amine hydrochloride was dissolved in the minimum volume of boiling solvent, and allowed to crystallize for at least two days to give a first crop of partially purified *endo*-amine hydrochloride. Repeated recrystallization affords the pure *endo*-amine hydrochlorides.

Bornylmorpholine hydrochloride was purified by repeated crystallizations from isopropyl alcohol (*no of recrystallizations,* amount of *endo*-isomer/%, $[\alpha]_{578}^{23}$, yield/%): *1,* 97, +18.4°, 67; *2,* 99, +19.4°, 69; *3,* 99.6, +20.4°, 62.

Bornylpiperidine hydrochloride was purified by repeated crystallizations from isopropyl alcohol (*no of recrystallizations,* amount of *endo*-isomer/%, $[\alpha]_{578}^{23}$, yield/%), *1,* 96, +15.8°, 52; *2,* 98, +18.6°, 77; *3,* 99.1, +19.0°, 60.

Bornylpyrrolidine hydrochloride was purified by repeated crystallizations from isopropyl alcohol/pentane (*no of recrystallizations,* amount of *endo*-isomer/%, $[\alpha]_{578}^{23}$, yield/%): *1,* 90, +12.4°, 53; *2,* 94, +15.7°, 50, *3,* 97, +18.6°, 62; *4,* 98.9, +19.4°, 41.

endo-*Bornylamines.* The purified amine hydrochloride was dissolved in water and a slight excess of NaOH was added to liberate the amine. Extraction with pentane and drying over solid KOH affords the pure amine after removal of the solvent.

endo-*Bornylmorpholine.* $[\alpha]_{578}^{23}$=+34.2° (c 1.12, EtOH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 17.1, 18.7 and 20.1 (methyl carbons), 27.3 (C-6), 28.9 (C-5), 36.7, 44.2, 48.2, 50.3, 53.9, 67.1 and 71.2 (see Fig. 1). ^{1}H NMR (250 MHz, $CDCl_3$): Methyl protons δ 0.83 (3H, s), 0.87 (3H, s), 0.96 (3H, s) and CH–N proton 2.23 (1H, dd, J=9 Hz, J=3 Hz). *MS* (EI, 70 eV): *m/z* (relative abundance), 223 (26.6) M^+, 152 (100.0) $m^+-C_5H_{11}$, 100 (73.7) $M^+-C_9H_{15}$ and 95 (96.7) $M^+-C_7H_{14}NO$. Purity, 99.6 % *endo*-isomer.

endo-*Bornylpiperidine:* $[\alpha]_{578}^{23}$=+34.5° (c 0.90, EtOH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 17.1, 18.7 and 20.1 (methyl carbons), 27.2 (C-6), 28.8 (C-5), 24.6, 26.0, 37.4, 44.2, 48.2, 50.2, 54.4, and 71.3 (see Fig. 1) *MS* (EI, 70 eV): *m/z* (relative abundance), 221(19.7) M^+, 150 (100.0) $M^+-C_5H_{11}$ and 95 (69.4) $M^+-C_8H_{16}N$. Purity, 99.1 % *endo*-isomer.

endo-*Bornylpyrrolidine.* $[\alpha]_{578}^{23}$=+36.8° (c 0.59, EtOH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 16.1, 18.7 and 20.1 (methyl carbons), 27.6 (C-6), 28.7 (C-5), 23.1, 37.5, 44.5, 48.7, 49.5, 54.4 and 71.6. *MS* (EI, 70 eV): *m/z* (relative abundance), 207 (22.1) M^+, 136 (100.0) $M^+-C_5H_{11}$, 95 (71.1) $M^+-C_7H_{14}N$. Purity, 98.9 % *endo*-isomer.

exo-*Bornylmorpholine.* Obtained by chromatography (Silica 60, ethyl acetate). $[\alpha]_{578}^{23}$=−65.9° (c 0.97, EtOH). ^{13}*C NMR* (69.2 MHz, $CDCl_3$): δ 14.5, 19.6 and 20.7 (methyl carbons), 27.3 (C-6), 33.0 (C-5), 37.2, 44.9, 47.0, 49.6, 53.4, 67.6, and 73.1 (see Fig. 1). ^{1}*H NMR* (250 MHz, $CDCl_3$): Methyl protons δ 0.79 (3H, s), 0.92 (3H, s), 0.97 (3H, s) and CH–N-proton δ 2.28 (1H, dd, J=10 Hz, J=5 Hz). *MS*: See *endo*-isomer above; both isomers show identical mass spectra.

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