Unprecedented Formation of a Benzo[*d*]azepine by Acid-Catalyzed Cyclization of a Camphor-Derived *N*-Formylenamine

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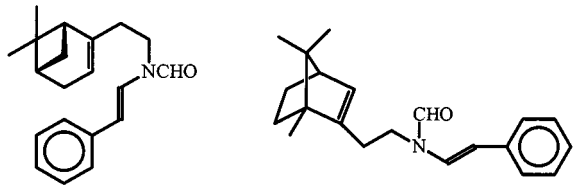
A convenient synthesis of (–)-*N*-styryl-*N*-[2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-enyl)ethyl]formamide (**2**) was developed starting from natural (+)-camphor (**3**) via (–)-2-(bornen-2-yl)ethanol (**6**). Cyclization of the *N*-formylenamine **2** with the aid of 9-borabicyclo[3.3.1]non-9-yl triflate yielded a methano-bridged octahydro-1*H*-benzo[*d*]azepine derivative.

Introduction

Recently, we have found that properly substituted *N*-formylenamines are convenient starting materials for the preparation of 1,2,3,4,5,6,7,8-octahydroisoquinolines by an acid-catalyzed cyclization reaction.[1] The enamides were synthesized either from γ,δ-unsaturated amines[2] or γ,δ-unsaturated alcohols.[3] In order to investigate the preparation of chiral octahydroisoquinolines by the cyclization of suitable enamides we synthesized (−)-*N*-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl]-*N*-styrylformamide (**1**; Scheme 1) starting from the β-pinene-derived (−)-nopol.[3] However, acid treatment of **1** resulted mainly in isomerization of the bicyclic ring system and we could not isolate any cyclic isoquinoline product.[4] Since we expected the enamide with a camphor-derived bicyclic system (−)-*N*-styryl-*N*-[2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-enyl)ethyl]-formamide (**2**; Scheme 1) to be more stable under acidic conditions, we also investigated the cyclization of this compound. We now wish to report on the preparation of **2** via (−)-2-(bornen-2-yl)ethanol. Surprisingly, its cyclization yielded a methano-bridged octahydro-1*H*-benzo[*d*]azepine derivative.



1 **2**

Scheme 1. Chiral *N*-formylenamines with a bicyclic ring system

Results and Discussion

For the synthesis of **2** we started from camphor (**3**; Scheme 2), which was converted into camphor 2,4,6-triisopropylbenzenesulfonylhydrazone (**4**) by reaction with 2,4,6-triisopropylbenzenesulfonyl hydrazide.[5][6] The hydrazone was treated with *sec*-butyllithium in accordance with a previously reported procedure.[6] This gave 2-lithiobornene (**5**) which was converted into (−)-2-(bornen-2-yl)ethanol (**6**) by reaction with ethylene oxide. It was not possible to prepare the lithium compound from camphor by reaction with PCl_5 in $POCl_3$ and subsequent lithiation with lithium powder. This method has been reported earlier for the synthesis of cyclohexenylethyl alcohol from cyclohexanone.[7] The hydroxy function in **6** was replaced by a tosylate group after treatment with tosyl chloride, preferably in pyridine. The tosylate proved to be unstable and was converted without further purification (the purity was about 90% according to TLC and ^{1}H NMR) into (−)-*N*,*N*-diformylbornen-2-ylethylamine (**8**) by a substitution reaction with sodium diformamide.[3,8] Diformamide **8** was the starting compound for a Wittig reaction with the ylide derived from benzyltriphenylphosphonium chloride in the presence of potassium *tert*-butoxide.[3] This reaction gave target enamide **2**.

Compound **2** was investigated in an acid-catalyzed cyclization reaction. On the basis of earlier studies[1] the strong Lewis acid 9-borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate (9-BBN triflate) was used as cyclization catalyst. A mixture of the enamide and one equivalent of 9-BBN triflate was heated under reflux in toluene. A complete conversion of the enamide was observed after 2 h (TLC). The major product was isolated after a first purification with column chromatography and proved to be a mixture of five isomers (GC-MS). The major isomer was present in 70%. Since it was not possible to elucidate the structure of this major product it was decided to reduce the *N*-formyl groups of the mixture of isomeric compounds. Reaction with lithium aluminium hydride gave a mixture of products which now gave separated spots on TLC. It was possible to isolate the major product by column chromatography.

^{1}H-NMR spectroscopy in $CDCl_3$ revealed that only one vinylic proton was left and that a complete rearrangement of the bicyclic system had occurred. Signals of only two remaining methyl groups were visible, together with those of the *N*-methyl group and five aromatic protons. We also performed 2D ^{1}H-^{1}H correlation spectroscopy (COSY) and 2D ^{13}C-^{1}H correlation spectroscopy (HETCOR). Analysis of the COSY spectrum indicated the presence of a

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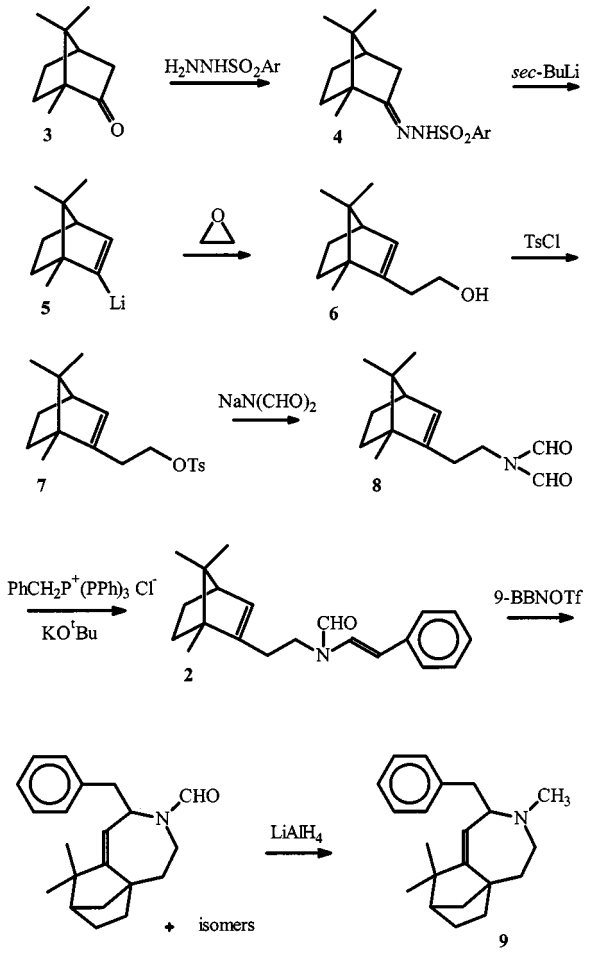

Scheme 2. The synthesis of benzo[*d*]azepine **9** from (+)-camphor (**3**)

>C=CH−CH−CH_2 moiety and a CH_2−CH_2 moiety. In addition, the HETCOR spectrum showed the presence of a >CH−CH_2−CH_2 moiety and one remaining CH_2 group. From these data, combined with the data from MS and ^{13}C NMR (including APT) we concluded that the new compound is 4-benzyl-7,9a-methano-3,6,6-trimethyl-2,3,4,6,7,8,9,9a-octahydro-1*H*-benzo[*d*]azepine (**9**; Scheme 2).

The position of the double bond and the disappearance of one of the methyl groups indicate a 9-BBN triflate catalyzed isomerization of enamide **2** prior to the cyclization reaction in which the enamide double bond is involved. A possible mechanism starts with the addition of the boron atom to the bornylene double bond which gives a tertiary carbenium ion. After rearrangement, another carbenium ion is formed from which only the product with an exocyclic double bond can be formed after proton elimination. Subsequently, the trialkylborane moiety is cleaved by protonolysis.[9] The exocyclic double bond reacts with the *N*-acyliminium ion which can be formed after addition of the Lewis acid to the enamide double bond. In this process the seven-membered ring is formed. However, it is also possible that these reactions are exclusively proton-catalyzed after formation of a superacid from the Lewis acid 9-BBN triflate with traces of water or triflic acid.[10]

We have made various efforts to improve the synthesis of **9**. Firstly, we investigated strong protic acids such as triflic acid and tungstophosphoric acid ($H_3PW_{12}O_{40}$) supported on silica gel.[1] However, these acids were found to be less active than 9-BBN triflate. They also gave no improvement of the isolated yield of the mixture of *N*-formyl isomers. Secondly, we carried out the 9-BBN triflate catalyzed reaction at different temperatures with varying amounts of 9-BBN triflate, however, the isolated yield of the *N*-formyl isomers did not exceed 40%.

In conclusion, we have shown that (+)-camphor can be converted easily into (−)-*N*-styryl-*N*-[2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-enyl)ethyl]formamide via the alcohol (−)-2-(bornen-2-yl)ethanol. The cyclization of the *N*-formylenamine yielded finally a methano-bridged benzo[*d*]azepine derivative in the presence of the strong Lewis acid 9-BBN triflate.

Experimental Section

General: *sec*-Butyllithium (1.29 M in hexanes) and 9-BBN triflate (0.5 M in hexanes) were purchased from Aldrich. The reactions with these compounds were performed under nitrogen. 2,4,6-Triisopropylbenzenesulfonyl hydrazide[5] and camphor 2,4,6-triisopropylbenzenesulfonylhydrazone[6] were prepared according to known procedures. − Mass spectra were determined using a VG70-SE spectrometer. − ^{1}H- (400 MHz) and ^{13}C-NMR (101 MHz) spectra were recorded using a Varian VXR-400S spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal reference. − Infrared spectra were recorded using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. − Gas chromatography was performed using a Packard 427 gas chromatograph with a CP Sil 5 GB (10 m × 0.53 mm) column. − Optical rotations were measured using a Perkin Elmer 241 polarimeter at the sodium D line (λ = 589 nm). − Column chromatography was performed on silica (Merck kieselgel 60, particle size 63−200 μm) and TLC on deactivated silica (0.25 mm, Merck F_{254}).

(−)-2-(Bornen-2-yl)ethanol (6): Camphor 2,4,6-triisopropylbenzenesulfonylhydrazone[6] (**4**; 60.0 g, 138 mmol) was suspended in a mixture of hexane (freshly distilled, 250 mL) and tetramethylethylenediamine (freshly distilled, 250 mL) and the mixture was cooled to −70°C in a CO_2/acetone bath. *sec*-Butyllithium (1.29 M in hexanes, 200 mL, 258 mmol) was added dropwise by syringe over a period of 30 min. The orange solution was stirred for 2 h, and the cold bath was removed. After 20 min, the flask was placed in an ice bath. After 30 min, ethylene oxide (14.0 g, 318 mmol) was bubbled through the stirred solution at 0°C. The ice bath was removed and the reaction mixture was stirred overnight. Ethanol (35 mL) and aqueous ammonium chloride (6 M, 20 mL) were added and the solution was stirred for 15 min. The mixture was added to water (300 mL) and the layers were separated. The aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were washed with water (4 × 200 mL), a saturated solution of NaCl (200 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure. Distillation of the residue at 0.6 Torr gave **6** (11.5 g, 64 mmol, 47%) boiling at 80−85°C as a slightly yellow liquid which solidified on standing at −6°C. − $[\alpha]^{20} = -13$ (*c* = 1.80 in $CHCl_3$/ethanol 9:1). − ^{1}H NMR: δ = 0.76 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 0.92 (m_c, 2 H, CH_2), 0.97 (s, 3 H, CH_3), 1.49 (m_c, 1 H), 1.84 (m_c, 1 H), 1.96 (bs, 1 H, OH), 2.25 (m_c, 3 H, CH_2CH_2OH

and bridge-head proton), 3.72 (t, 2 H, CH_2OH), 5.65 (m_c, 1 H, C=CH). − ^{13}C NMR: δ = 145.79, 128.60, 60.62, 56.34, 54.25, 51.37, 31.44, 31.23, 25.81, 19.74, 19.66, 11.43. − MS; *m/z* (%): 180 (63) [M^+], 165 (35), 149 (50), 121 (100), 105 (48), 91 (59), 77 (38). − HR MS; *m/z*: 180.1517; calcd. for $C_{12}H_{20}O$: 180.1514. − IR (neat): $\tilde{\nu}$ = 3333 cm^{-1} (OH).

Tosyl Ester of (−)-2-(Bornen-2-yl)ethanol (7): (−)-2-(Bornen-2-yl)ethanol (**6**; 11.0 g, 61.2 mmol) was added to a solution of tosyl chloride in pyridine (200 mL) and the mixture was stirred at room temperature. After 3 h, TLC showed a complete conversion of the alcohol, and water and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with a solution of hydrochloric acid (3 M, 3 × 300 mL) and a saturated solution of NaCl (300 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure, and 19 g (55 mmol, 89%) of **7** was obtained. The purity was approximately 90%. − Selected NMR data: ^1H NMR: δ = 0.71 (s, 3 H, CH_3), 0.73 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 2.19 (t, 1 H, bridge-head proton), 2.31 (m_c, 2 H, CH_2CH_2OTs), 2.45 (s, 3 H, CH_3 of tosyl group), 4.12 (t, 2 H, CH_2OTs), 5.50 (m_c, 1 H, C=CH), 7.60 [dd, 4 H, aromatic protons, *J* = 8.2 Hz]. − ^{13}C NMR: δ = 144.67, 143.69, 133.34, 129.81, 128.89, 127.88, 68.75, 56.37, 54.17, 51.38, 31.24, 27.33, 25.57, 21.63, 19.64, 19.52, 11.32.

(−)-*N,N*-Diformylbornen-2-ylethylamine (8): (−)-*N,N*-Diformylbornen-2-ylethylamine (**8**) was prepared from tosylate **7** according to a procedure described in ref.[3] Tosylate **7** (crude product, 19 g, 55 mmol) yielded 6.2 g (26 mmol, 41% based on alcohol **6**) of **8** as an oil. − $[\alpha]^{20}$ = −14 (*c* = 1.70 in $CHCl_3$/ethanol, 9:1). − ^1H NMR: δ = 0.75 (s, 3 H, CH_3), 0.76 (s, 3 H, CH_3), 0.92 (m_c, 2 H), 0.97 (s, 3 H, CH_3), 1.50 (m_c, 1 H), 1.80 (m_c, 1 H), 2.22 (m_c, 3 H, $CH_2CH_2N(CHO)_2$ and bridge-head proton), 3.75 [t, 2 H, $CH_2N(CHO)_2$, *J* = 7.9 Hz], 5.65 (m_c, 1 H, C=CH), 8.82 (s, 2 H, 2 × CHO). − ^{13}C NMR: δ = 164.08, 145.38, 128.38, 56.35, 54.27, 51.41, 37.53, 31.36, 25.70, 19.69, 19.60, 11.33. − MS; *m/z*: 235 (52) [M^+], 162 (47), 147 (54), 134 (82), 119 (100), 105 (33), 91 (44). − HR MS; *m/z*: 235.1576; calcd. for $C_{14}H_{21}NO_2$: 235.1572. − IR (neat): $\tilde{\nu}$ = 1674 cm^{-1} (C=O).

(−)-*N*-Styryl-*N*-[2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-enyl)ethyl]-formamide (2): (−)-*N*-Styryl-*N*-[2-(1,7,7-trimethylbicyclo[2.2.1]-hept-2-enyl)ethyl]formamide (**2**) was prepared from diformamide **8** according to a procedure described in ref.[3] Compound **8** (1.74 g, 7.40 mmol) yielded 1.83 g (5.92 mmol, 80%) of enamide **2** as a yellow oil which solidified on standing. − M.p. 70−73°C. − $[\alpha]^{20}$ = −11 (*c* = 1.45 in $CHCl_3$/ethanol, 9:1). − ^1H NMR (rotamer ratio 65:35, value for the minor rotamer in parentheses): δ = 0.77 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 0.96 (m_c, 2 H), 1.00 (0.98) (s, 3 H, CH_3), 1.52 (m_c, 1 H), 1.84 (m_c, 1 H), 2.27 (2.35) (s, 1 H, bridge-head proton), 2.28 (2.38) [m_c, 2 H, CH_2CH_2N, *J* = 3.4 Hz, *J* = 6.6 Hz], 3.78 (3.68) [m_c, 2 H, CH_2N, *J* = 8.2 Hz], 5.70 (m_c, 1 H, C=CH in ring), 6.05 (6.08) [d, 1 H, N*CH*=CH, *J* = 14.7 Hz], 7.03 (7.72) [d, 1 H, NCH=*CH*, *J* = 14.4 Hz], 7.28 (m_c, 5 H, aromatic protons), 8.41 (8.21) (s, 1 H, CHO). − ^{13}C NMR (both rotamers): δ = 162.25, 161.24, 146.05, 145.56, 136.21, 136.00, 128.81, 128.72, 128.08, 127.44, 126.86, 126.77, 125.79, 125.47, 122.98, 112.53, 111.23, 56.36, 54.34, 51.45, 44.74, 39.77, 31.43, 26.33, 25.77, 24.68, 19.65, 11.54, 11.46. − MS; *m/z*: 309 (35) [M^+], 162 (35), 147 (100), 134 (55), 119 (50), 91 (35). − HR MS; *m/z*: 309.2085; calcd. for $C_{21}H_{27}NO$: 309.2093. − IR (neat): $\tilde{\nu}$ = 1640 cm^{-1} (C=C) and 1689 (C=O).

4-Benzyl-3,6,6-trimethyl-2,3,4,6,7,8,9,9a-octahydro-7,9a-methano-1*H*-benzo[*d*]azepine (9): Enamide **2** (1.60 g, 5.18 mmol) was dissolved in toluene (65 mL) and a solution of 9-BBN triflate in hexanes (0.5 M, 10.4 mL, 5.20 mmol) was added by syringe. The mixture was heated under reflux and after 2 h the conversion was complete (TLC). The solution was washed with a saturated solution of $NaHCO_3$ (75 mL). The aqueous layer was extracted with toluene (25 mL) and the combined organic layers were washed with a saturated solution of NaCl (100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure. The main product was isolated by column chromatography (dichloromethane/methanol, 97:3) to give 0.72 g (2.33 mmol, 45%) of a TLC-pure product as a yellow oil. Analysis by GC and 400-MHz ^1H NMR showed that this product was a mixture of isomers. The major isomer was present for 70%. The mixture of *N*-formyl isomers (0.370 g, 1.197 mmol), dissolved in 20 mL of anhydrous diethyl ether, was added dropwise to a suspension of lithium aluminium hydride (0.100 g, 2.632 mmol) in 15 mL of diethyl ether. After 1 h of stirring at room temperature, complete conversion of the starting material was observed on TLC. A 15% NaOH solution (50 mL) was added cautiously and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic layers were washed with a saturated solution of NaCl (100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure. The major product was isolated by column chromatography (CH_2Cl_2/MeOH/NH_4OH, 93:7:0.5). This gave 0.094 g (0.319 mmol, 27%) of TLC-pure **9** as an oil. A second experiment, performed at the same conditions, gave compound **9** in 25% yield. − ^1H NMR: δ = 0.94 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.22 [dd, 1 H, proton of bridge CH_2, *J* = 1.4 Hz, *J* = 9.6 Hz], 1.40 [m_c, 1 H, proton of CH_2, *J* = 2.0 Hz, *J* = 12.3 Hz], 1.53 [ddd, 1 H, NCH_2CH_2, *J* = 1.5 Hz, *J* = 4.5 Hz, *J* = 9.9 Hz], 1.60 (m_c, 1 H, proton of CH_2), 1.60 (m_c, 1 H, proton of CH_2), 1.69 [m_c, 1 H, proton of CH_2, *J* = 2.2 Hz, *J* = 4.2 Hz, *J* = 9.7 Hz], 1.79 (m_c, 1 H, bridge-head proton), 1.83 (m_c, 1 H, proton of CH_2), 2.28 [m_c, 1 H, NCH_2CH_2, *J* = 1.6 Hz, *J* = 2.7 Hz], 2.73 [m_c, 1 H, benzylic proton, *J* = 10.0 Hz, *J* = 12.4 Hz], 2.78 [m_c, 1 H, NCH_2, *J* = 2.7 Hz], 3.02 [dd, 1 H, benzylic proton, *J* = 4.8 Hz, *J* = 12.3 Hz], 3.22 [m_c, 1 H, NCH_2, *J* = 1.5 Hz, *J* = 1.5 Hz, *J* = 12.9 Hz], 3.42 [m_c, 1 H, NCH, *J* = 10.3 Hz], 4.84 [d, 1 H, C=CH, *J* = 6.0 Hz], 7.20 (m_c, 5 H, aromatic protons). − ^{13}C NMR: δ = 156.87, 140.20, 129.35, 128.07, 125.84, 117.31, 65.43, 54.20, 47.49, 46.92, 45.37, 45.15, 42.45, 39.43, 35.41, 32.01, 29.45, 26.54, 25.53. − MS; *m/z*: 295 (1) [M^+], 204 (100) [M^+ − benzyl], 161 (21), 91 (18). − HR MS for M^+ − H; *m/z*: 294.2218; calcd. for $C_{21}H_{28}N$ (M^+ − H): 294.2222.

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