A Viable Route to *exo*-2-Benzyliminobornan-3-ol: A Key Intermediate in the Synthesis of a Chiral Auxiliary

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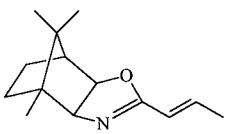
Received 6 December 1996

A new synthesis of the title compound **2** has been achieved in which benzylamine reacts with the novel hydroxy *N*-nitroimine **6** with concomitant evolution of nitrous oxide, whereas the published reaction between benzylamine and the corresponding ketone **4** does not occur reproducibly.

Effective use has been made of α-β-unsaturated oxazolines, e.g. **1**, as chiral auxiliaries for asymmetric Diels–Alder cycloadditions in which high diastereoselectivities, generally in excess of 90%, have been obtained.[1] The reported synthesis of **1** started from enantiomerically pure camphor and proceeded via Schiff's base **2** and *exo*,*exo*-2-aminobornan-3-ol **(3)**. Compound **3**, obtained by the same route, has been used for the formation of an oxazolidinone, which is also a successful chiral auxiliary.[2]

The appeal of this protocol is vitiated by the irreproducibility of the reaction of *exo*-3-hydroxycamphor **(4)** with benzylamine.[1] For an indeterminate reason compound **2** could not be obtained in either of two other laboratories[3] using the reported conditions.[1] In order that the methodology of Langlois' group can be exploited, it is desirable to have a reliable pathway to **2**. Presently we report our synthesis of this compound by an alternative route.



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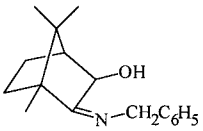

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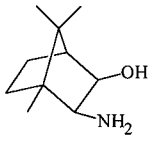

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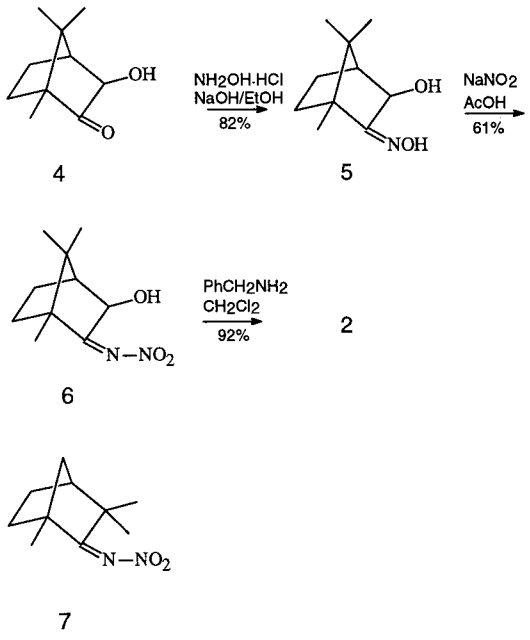
(1*R*)-(+)-Camphor was converted, as previously,[1] into *exo*-3-hydroxycamphor **(4)** in 35% overall yield after purification. Oxime **5** was obtained following reaction of **4** with hydroxylamine hydrochloride and sodium acetate. We used sodium acetate, rather than the more commonly employed sodium hydroxide, in order to minimise the chances of base-catalysed epimerisation to the more stable *endo*-3-epimer of **4** (or **5**). In the event, stereochemical integrity was maintained at C3, as shown convincingly by the presence, in the ^{1}H NMR spectrum, of a singlet absorption for *endo*-3H (since $J_{endo\text{-}3H,4H} \approx 0$ Hz) for both **4** ($\delta = 3.75$) and **5** ($\delta = 4.94$).

Oxime **5** was then converted into the hydroxy *N*-nitroimine (nitrimine) **6** by reaction with nitrous acid in aqueous acetic acid.[4,5] Our result is thus in accord with that of Brooks et al.[4] who have shown that formation of *N*-nitroimines from certain hydroxy steroids did not compromise the hydroxy group.[4]

The *N*-nitroimine functional group has long been known but little exploited.[6] Stability of these compounds is enhanced when the carbons α to the *N*-nitroimine-bearing carbon possess a higher degree of substitution.[7,8] In the present work the *N*-nitroimine structure of **6** was confirmed by the IR and ^{13}C NMR spectra; in the latter case the absorption of C2 at $\delta = 189.64$ is in accord with those of related *N*-nitroimines.[9,10] Further, although the configuration of the imine is uncertain in **6** (and indeed in the related compounds **5** and **2**) we have no evidence for the existence of geometric isomers, unlike the more congested fenchone *N*-nitroimine **7**.[10]

A solution of *N*-nitroimine **6** in dichloromethane in the presence of molecular sieves was treated with an equimolar quantity of benzylamine at room temperature. After the almost immediate release of bubbles had subsided, the desired product **2** was isolated as a white solid with identical spectroscopic properties to those given by Langlois[1] (Scheme).



Scheme

The *N*-nitroimine group is very susceptible to nucleophilic attack in a reaction whose first step is reminiscent of a Michael addition.[11–16] That the gas evolved is nitrous oxide, an occasionally encountered leaving group, is supported by the following observations:

I) We have previously shown, by high resolution mass spectrometry, that nitrous oxide evolution accompanies the conversion of camphor *N*-nitroimine into camphene 1-carboxamide on sequential treatment with KCN and dilute HCl.[12]

II) Identification of nitrous oxide by analysis of the infrared spectrum in a less directly comparable case.[15]

Our methodology in part follows a benchmark example of Eschenmoser.[17] In order to realise our hydroxyimine **2**, we introduced the *N*-nitroimine group in **6** and then disposed of it as nitrous oxide (and also as the oxygen of water). Eschenmoser, *en route* to vinylogous amidines, introduced a sulfur atom that permitted a desired electrocyclic reaction to occur; sulfur was then removed in an extrusion process with a compound of general type R_3P to give the desired product.

Whereas two groups[1,2] have been able to obtain **2** by the route reported,[1] a further two have not.[3] Apparently unknown local circumstances determine the ability to form imine **2** directly from **1**. We find the *N*-nitroimine route to be reproducible, and note that the last two steps operate under mild conditions. Our result signifies that in certain circumstances *N*-nitroimines should be considered as a substitute for a carbonyl group when reactions of the latter are problematical.

^{1}H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ using Varian Gemini 200 and Bruker AM 200SY spectrometers at 200 MHz for ^{1}H spectra and at 50.3 MHz for ^{13}C spectra. ^{1}H chemical shifts are quoted relative to $\delta = 7.26$ for $CHCl_3$ and ^{13}C chemical shifts are quoted relative to $\delta = 77.0$. DEPT experiments were carried out on Bruker DRX 500 and AM 200SY spectrometers. IR spectra were determined with a Perkin-Elmer 983 spectrometer. High resolution mass spectra were determined with a VG-70S spectrometer using FAB with a glycerol-thioglycerol matrix. Melting points were determined with a Reichert hot stage apparatus. Optical rotations were measured with a Polaar 2000 polarimeter. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Petroleum ether refers to the fraction with bp 40–70 °C.

exo-3-Hydroxycamphor **(4)**: This was prepared from (1*R*)-(+)-camphor, $[\alpha]_D$ +44.05 (c = 2.70, EtOH), by the method of Langlois et al.[1] The keto alcohol was purified by column chromatography; elution was achieved with EtOAc/petroleum ether (30:70, v/v). Compound **4** was obtained as a white solid.

IR ($CHCl_3$): ν = 3440, 1755 cm^{-1}.

^{1}H NMR: δ = 3.76 (s, 1 H, *endo*-3H) [Lit.[18] δ = 3.76 (s, 1 H, *endo*-H)].

exo-2-Hydroxyiminobornan-3-ol (5):
To a solution of **4** (2.16 g, 12.86 mmol) in EtOH (100 mL) was added $NaOAc \cdot 3H_2O$ (2.19 g, 16.10 mmol) and $NH_2OH \cdot HCl$ (1.12 g, 16.08 mmol), each dissolved in the minimum volume of H_2O. After reflux for 5 h, most of the EtOH was removed (rotary evaporator) and the residue was partioned between Et_2O and H_2O in a separating funnel. The Et_2O layer was washed with H_2O (2 × 25 mL) and dried (Na_2SO_4). Since TLC analysis indicated a small amount of impurity, pure **5** was obtained after column chromatography and elution with EtOAc/petroleum ether (45:55, v/v); yield: 82%; $[\alpha]_D$ − 100.08 (c = 0.469, EtOH); mp 151–153 °C.

IR (KBr): ν = 3416 (br s), 1636 cm^{-1} (m).

^{1}H NMR: δ = 0.90 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 3.52 (br s, 1 H, OH), (4.94, s, 1 H, *endo*-3H), 9.12 (br s, 1 H, C=NOH).

^{13}C NMR: δ = 10.72 (C-10), 19.56, 20.85 (C-8, C-9), 24.69, 31.98 (C-5, C-6), 48.62, 51.83 (C-1, C-7), 49.81 (C-4), 74.65 (C-3), 171.85 (C-2).

Oxime **5** has been reported once before in recent times[19] as an oily mixture of C-3 epimers. Our ^{13}C chemical shift data show some differences from those reported.

exo-2-(*N*-Nitroimino)bornan-3-ol (6):
To a solution of oxime **5** (1.51 g, 8.25 mmol) in HOAc (20 mL) was added portionwise $NaNO_2$ (0.86 g, 12.4 mmol) over 20 min. The solution was stirred at r.t. for 4.5 h, and neutralised cautiously with aq $NaHCO_3$ solution and extracted with Et_2O. The Et_2O solution was dried (Na_2SO_4); after filtration and removal of the solvent a white solid was obtained. This showed a major spot on TLC, accompanied by a smaller spot with a lower R_f. Pure **6** was isolated in 61% yield after column chromatography and elution with EtOAc/petroleum ether (35:65, v/v), followed by recrystallisation from 1-chlorobutane; mp 77–78 °C; $[\alpha]_D$ −176.08 (c = 0.471, EtOAc).

IR (KBr): ν = 3520, 3460, 1648, 1560, 1310 cm^{-1}.

^{1}H NMR: δ = 0.97 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 2.55 (br s, 1 H, OH), 4.62 (s, 1 H, *endo*-3H).

^{13}C NMR: δ = 10.43 (C-10), 19.50, 20.80 (C-8, C-9), 24.51, 30.53 (C-5, C-6), 48.62, 53.90 (C-1, C-7), 51.21 (C-4), 74.98 (C-3), 189.64 (C-2).

HRMS-FAB: m/z obs: 213.1224. Calc for $C_{10}H_{17}N_2O_3$ $(M+H)^+$: 213.1239.

exo-2-Benzyliminobornan-3-ol (2):
To a solution of *N*-nitroimine **6** (212 mg, 1 mmol) in anhyd CH_2Cl_2 (3 mL), containing activated molecular sieves (4 Å), was added a solution of benzylamine (107 mg, 1 mmol) in CH_2Cl_2 (2 mL). Evolution of N_2O usually commenced within 2 min, and was complete shortly thereafter. After 30 min, the solution was filtered and the solvent was evaporated to give an off-white solid. This was purified by chromatography; elution with EtOAc/CH_2Cl_2 (1:4, v/v) gave pure **2** as a white solid; yield: 92%; mp 106–108 °C. Spectral properties (IR, ^{1}H NMR) were in accord with those described.[1]

^{13}C NMR: δ = 11.32 (C-10), 19.8, 21.35 (C-8, C-9), 24.38, 31.85 (C-5, C-6), 46.58, 54.09 (C-1, C-7), 51.90 (C-4), 55.94 (CH_2 benzylic), 74.21 (C-3), 126.26, 127.33, 128.11, (CH, arom), 140.42 (C, arom), 183.78 (C-2).

We thank Professor Günther Helmchen (University of Heidelberg), for informing us of his inability to synthesise **2** *and for further discussions. Part of this work was carried out at the Max Planck Institut für Polymerforschung, Mainz. D.G.M. would like to thank the Royal Society and Professor Klaus Müllen for support, and Professor Müllen also for use of facilities. We are grateful to Dr J.W. Thomson, Astra Charnwood, Loughborough for the high resolution mass spectrum.*

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