

## A Practical Synthesis of Bicyclo[3.3.1]nonan-9-one

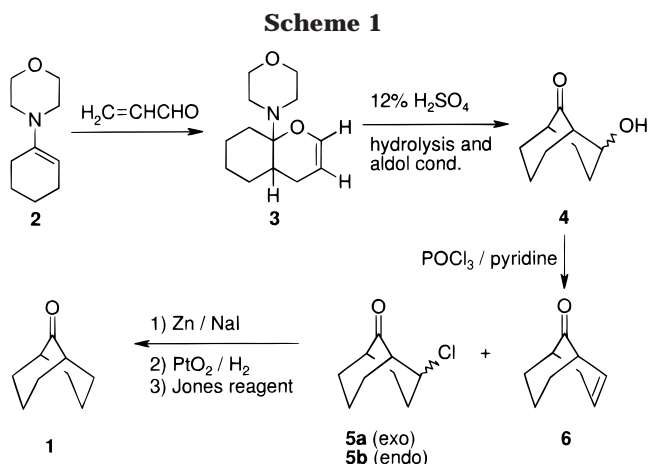
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Bicyclo[3.3.1]nonan-9-one **1** is a well-known starting material for the synthesis of [3.3.*n*]hydrocarbons, etc., and the compound is commercially available.<sup>1</sup> There are a number of reported syntheses; the most direct methods are an *Organic Synthesis* preparation<sup>2</sup> starting from 9-BBN (9-borabicyclo[3.3.1]nonane) (78–83% yield) and the reaction<sup>3</sup> of 1,5-cyclooctadiene with Ni(CO)<sub>4</sub> (60%). The 9-BBN method employs syringe techniques and is moderately costly (9-BBN, <sup>n</sup>BuLi, dichloromethyl methyl ether). The latter method is unattractive because of the toxicity of Ni(CO)<sub>4</sub>. The 1964 six-step synthesis of Foote and Woodward, starting from the cyclohexanone enamine **2** and acrolein, has been the most used route in the older literature, but the overall yield is only ca. 20%.

The route described herein uses the same starting materials as the Foote–Woodward synthesis and is shown in Scheme 1. The reaction of enamine **2** with acrolein is known<sup>5</sup> to first give **3**, but ultimately 2-*N*-morpholinobicyclo[3.3.1]nonan-9-one is formed. This latter compound was used by Foote and Woodward, but the removal of the morpholino group is troublesome. One can verify the in situ formation of **3**, from **2** and acrolein, by means of an <sup>1</sup>H NMR spectrum of a sample of the crude mixture, focusing on the alkene protons. Cope et al.<sup>6</sup> and Allan et al.<sup>7</sup> have described the mild hydrolysis of **3** to the respective keto aldehyde and the subsequent aldol condensation to give an epimeric mixture of **4**. We have modified this procedure to give **4** in a one-pot process from **2**, using a 12% aqueous H<sub>2</sub>SO<sub>4</sub> solution for the combined hydrolysis–aldol condensation step. The overall yield is much improved since isolation of the labile keto aldehyde is avoided. The crude alcohol **4** was used directly for the next step (purity > 95% by GLC and <sup>1</sup>H NMR). The replacement of the hydroxyl group in **4** by chlorine, using POCl<sub>3</sub>–pyridine, results in a mixture of **5** and **6**, as also reported by Allan et al.<sup>7</sup> Premixing the pyridine–POCl<sub>3</sub>, using an excess of pyridine, and then adding **4**, gave the best results. Various attempts to reduce the formation of **6** were unsuccessful,<sup>8</sup> so **5** and **6** were directly used in the zinc reduction step, a modification of the method of Fujimoto et al.<sup>9</sup> In the workup of this final reaction, a room temperature–atmospheric pressure PtO<sub>2</sub>/H<sub>2</sub> hydrogenation was carried out on the mixture of **1** and **6**. This reaction is rapid in methanol



but is accompanied by ca. 5% of ketone reduction, which was reversed with a small amount of Jones reagent. The crude off-white crystalline product **1** has an estimated 99.5% purity by GLC, and the <sup>1</sup>H NMR spectrum is identical to that obtained from recrystallized material, mp 152–154 °C (crude), reported<sup>3</sup> mp 155–158.5 °C. This protocol uses inexpensive amounts of readily available reagents, involves no purification of intermediates, and has been carried through on a ca. 20 g product scale in 47% yield.

### Experimental Section

All solvents were reagent grade and used without further purification. Reagents were obtained from Sigma and Aldrich and used as delivered unless otherwise specified. The morpholinone enamine of cyclohexanone was prepared as described.<sup>10</sup> Gas chromatography was conducted on a HP5890 instrument using a 10 m OV1 530 μm film column.

**2-Hydroxybicyclo[3.3.1]nonan-9-one 4.** Enamine **2** (74.99 g, 0.448 mol) was dissolved in 400 mL of ether and cooled to 0 °C in a 2 L round-bottomed flask, and acrolein (90%, 27.9 g = 33.3 mL, 0.448 mol) was added. The resulting colorless solution was stirred for 12 h at 20 °C (<sup>1</sup>H NMR signals at 6.06 (m) and 4.58 (m) for **3**). Water (300 mL) and then 65.9 g of 98% H<sub>2</sub>SO<sub>4</sub> in 150 mL of H<sub>2</sub>O were added to the reaction mixture (ca. 12% w/w H<sub>2</sub>SO<sub>4</sub> in water). The ether was distilled off followed by about 50 mL of water, and then the mixture was refluxed for an additional 3 h. The cold reaction mixture was filtered (glass) and then extracted with 4 × 150 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to yield 59.0 g (ca. 85%) of the crude waxy solid alcohol **4** as a ca. 1:1.45 mixture of the exo and endo isomers, whose <sup>13</sup>C NMR shifts were in good agreement with the literature<sup>11</sup> values.

**2-Chlorobicyclo[3.3.1]nonan-9-one 5 and Bicyclo[3.3.1]non-2-en-9-one 6.** Crude alcohol **4** (5.00 g, 32.4 mmol) in pyridine (10 mL) was added with magnetic stirring to a premixed solution of pyridine (21 mL, 0.26 mol) and phosphorus oxychloride (5.9 mL, 0.065 mol), cooled to 0 °C in an ice bath, at a rate

(8) Chloride **5a** has been shown to undergo aqueous (NaOH) base-catalyzed elimination whereas isomer **5b** gives mainly a ring-opened cyclooctenecarboxylic acid under the same conditions. We also find that only the exo chloride **5a** is dehydrochlorinated by *tert*-butoxide. The OH → Cl replacement in our work requires temperatures of at least 20 °C and several hours of reaction time. It is possible therefore that **5a** is the source of alkene **6** via a slow reaction with the excess pyridine. Alternatively, the elimination may occur via the initially formed phosphate ester of the exo alcohol.

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such that the temperature remained between 0 and 5 °C. The mixture was allowed to warm to 20 °C and stirred an additional 3 h. Water was added cautiously at a rate such that the temperature of the reaction mixture stayed below 50 °C. A slush formed during this addition making stirring difficult, and the mixture was manually shaken while the water was added. Eventually a clear brown solution was formed. This was concentrated on the Rotovap to half the original volume. Acidification with 10% HCl followed by extraction (CH<sub>2</sub>Cl<sub>2</sub>), drying (MgSO<sub>4</sub>), and concentration gave 5.27 g of residual solid (ca. 87% **5** and 12% **6** by GLC), ca. 95% combined yield. Samples of separated **5a**, **5b**, and **6** had <sup>1</sup>H and <sup>13</sup>C NMR spectra in good agreement with published data.<sup>11,12</sup>

**Bicyclo[3.3.1]nonan-9-one 1.** The mixture of chlorides **5** and alkene **6** (29.85 g, 0.173 mol based on 87% **5** and 12% **6**), sodium iodide (51.8 g, 0.346 mol), and zinc powder (45.2 g, 0.692 mol) were mixed with 250 mL of dimethylformamide and refluxed for 14 h. After cooling, 500 mL of water was added and the mixture filtered. The filter residue was washed several times with hexane, and the aqueous filtrate was extracted with hexane (4 × 200 mL). The combined hexane solution was washed twice with water, dried (MgSO<sub>4</sub>), and concentrated to give 20.1 g of solid product containing alkene **6** and ketone **1**

(ca. 8% **6**, 89% **1** by GLC). This material was placed in a 250 mL round-bottomed flask, methanol (100 mL) and PtO<sub>2</sub> (20 mg) were added, and the flask was fitted with a septum and a syringe needle inlet. The flask was evacuated through the needle until the methanol began to boil and hydrogen was introduced from a cylinder using a very low back pressure; this process was repeated two times. The solution was then stirred at ambient temperature for 2 h. The platinum was filtered off, and the methanol evaporated. The residue was taken up in 100 mL of acetone, and 5 mL of Jones reagent was added. After 10 min of stirring, a 10% aqueous sodium bisulfite solution was added until the solution color became green, the precipitate was filtered and washed with acetone, and the acetone was evaporated. The residue was taken up in ether, washed with water and a 5% bicarbonate solution, dried (MgSO<sub>4</sub>), and concentrated to give 17.96 g of an off-white crystalline residue (ca. 75% from **5-6**), mp 152–154 °C, lit. mp 155–158.5 °C. The <sup>1</sup>H NMR spectrum of the crude product is identical to that of the recrystallized material, and GLC analysis on several different columns gives a single peak.

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