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AN IMPROVED SYNTHESIS OF BICYCLO[3.3.3]UNDECANE

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Abstract: A shorter and significantly higher-yield procedure for the preparation of bicyclo[3.3.3]undecane (manxane) is reported.

In the course of our measurements of the strain energies of bridgehead imines by photoacoustic calorimetry[1a], we required 1-azidobicyclo[3.3.3]-undecane, which we made from the title hydrocarbon, bicyclo[3.3.3]undecane (manxane, **1**).[1b] In the process of preparing **1**, we developed a procedure that simplifies the literature synthesis[2] and increases the overall yield from 4% to 20 - 25%.

As shown in the scheme, the synthesis involves two ring expansions of the bicyclo[3.3.1] skeleton of the starting material, ketone **2**. In contrast to the first ring expansion (**2** → **3**), the second (**3** → **5a** + **5b**) cannot be accomplished with diazomethane.[2] While this conversion can be carried out by a diazonium ion route via **4** (Demjanov-Tiffeneau ring expansion), the literature conversion of **3** to **4** required four steps with an overall yield of only 19%.

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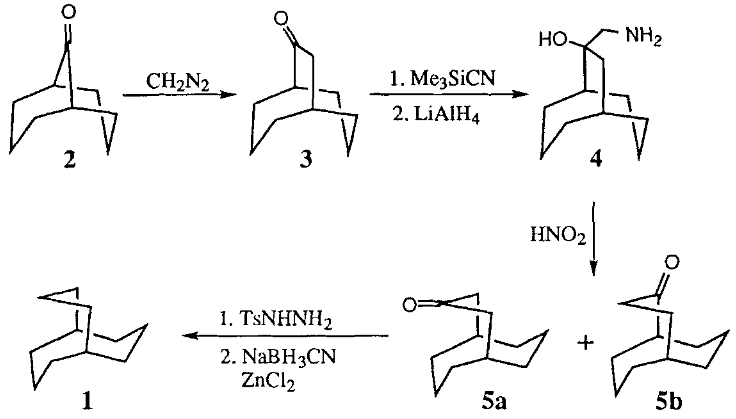

Scheme

We found that this conversion can be carried out much more efficiently and in just two steps. Trimethylsilyl cyanide reacts virtually quantitatively with **3** to give the cyanohydrin TMS-ether, which can be reduced with lithium aluminum hydride to give **4** in 60% yield.[3]

Our second improvement was made in the last step, the reduction of ketones **5a** and **5b**. The literature procedure used a modified Wolff-Kishner reduction, which went in only 40% yield.[2] We used a one-pot procedure that involved forming the tosylhydrazones of **5a** and **5b** and reducing these with sodium cyanoborohydride-zinc chloride.[4] This procedure gave moderately pure material in yields of 65-87%. Not only were higher yields obtained, but the procedure is much simpler to carry out.

In conclusion, our route reduces the number of steps in the synthesis of **1** and increases the overall yield five- to six-fold. Gram quantities of manxane (**1**) can now be made easily in a few days.

Experimental

9-cyano-9-(trimethylsiloxy)bicyclo[3.3.2]decane. To ketone **3**[2c] (699 mg; 4.60

mmol), contained in a dry reaction flask, under argon atmosphere, was added trimethylsilyl cyanide (0.67 mL; 5.06 mmol) containing a catalytic amount of anhydrous zinc chloride (5 mg) via syringe, with stirring.[3] The reaction mixture was heated to 100 °C for 2 hours. The reaction turned from yellow to dark brown in color. The excess trimethylsilyl cyanide was removed under high vacuum (0.3 mm) to yield a brown liquid (1.210 g). Purification was achieved by column chromatography on silica (CCl_4; $R_f = 0.3$). The product was a colorless oil (1.10 g; 95%). ^1H NMR ($CDCl_3$) δ 0.22 (9H, s), 1.50-1.86 (10H, complex), 2.03 (2H, complex), 2.09 (1H, dd, J = 16, 4 Hz), 2.20 (1H, quintet), 2.35 (1H, quintet), 2.59 (1H, ddd, J = 16, 4, 1 Hz). IR (neat) 2226 cm^{-1} (weak). MS *m/z* 251 (m^+). Anal. Calc'd for $C_{14}H_{25}NOSi$: C, 66.87; H, 10.02; N, 5.57. Found: C, 66.86; H, 10.10; N, 5.67.

9-(Aminomethyl)bicyclo[3.3.2]decan-9-ol hydrochloride (4•HCl). A dry flask equipped with a stirrer, reflux condenser, and addition funnel, was charged with a suspension of lithium aluminum hydride (430 mg; 11.3 mmol) in diethyl ether (15 mL). To this suspension was added a solution of the cyanohydrin TMS-ether (2.6 g; 10.0 mmol) in diethyl ether (5 mL), drop-wise, at a rate which maintained a gentle reflux.[3] Stirring was continued for one hour. The excess lithium aluminum hydride was then quenched with water and 15% sodium hydroxide. The precipitate was removed by filtration, and the solution was dried over $MgSO_4$. Hydrogen chloride gas was then bubbled through the solution, producing the HCl salt of **4** as a white solid, which was separated by filtration (1.414 g; 63%). ^1H NMR (D_2O) δ 1.50 - 1.90 (12H, complex), 1.94 - 2.10 (3H, complex), 2.27 (1H, complex), 3.03 (1H, dd, J = 13, 1 Hz), 3.23 (1H, dd, J = 13, 1 Hz) (lit:[2c] δ 3.04, 3.22, J=13 Hz).

Bicyclo[3.3.3]undecane (1). To a solution of **5a** and **5b**[2c] (1.0 g; 6.02 mmol) and p-toluenesulfonyl hydrazine (1.19 g; 3.39 mmol) in methanol (15 mL), was slowly added a solution of sodium cyanoborohydride (402 mg; 6.39 mmol) and zinc chloride (410 mg; 3.01 mmol) in methanol (12 mL).[4] After being stirred for 10 minutes, the mixture was refluxed for two hours. The reaction mixture was then treated with 0.1 M sodium hydroxide solution and extracted with petroleum ether. This solution was then washed with brine and dried over $MgSO_4$. Removal of the solvent provided **1** as a white solid (637 mg; 76%). ^1H NMR ($CDCl_3$) δ 1.43 - 1.57 (18H, complex), 2.36 (2H, complex) (lit:[2a] δ 1.5, 2.37). ^{13}C NMR ($CDCl_3$) δ 20.6, 29.5, 31.2. MS *m/z* 152 (m^+).

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