1-Bromobicyclo[1.1.0]butane as an Easily Obtainable C4-Building Block: A Novel Route to Cyclobutanone†

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Introduction

Carbocyclic four-membered ring compounds have emerged from the provenance of pure academic fascination to important building blocks in organic synthesis. Although a number of cyclobutane derivatives are readily available through a variety of ring formation reactions, many synthetic routes still rely on the transformation of existing cyclobutane rings.[1] The formation of cyclobutane derivatives from substituted bicyclo[1.1.0]butanes have been previously observed and the corresponding reaction mechanisms were investigated.[2] However, this route was seldom considered as a major strategy in synthesis.

The high strain energies of bicyclobutanes[3] are responsible for the enormous reactivity of this class of compounds. The central bond, which is akin to an olefinic double bond, undergoes addition reactions with a large variety of electrophilic reagents.[4] Acid-catalyzed electrophilic additions of methanol or water usually occur without major skeletal rearrangements during the formation of cyclobutane derivatives.[5]

Results and Discussion

The preparation of 1-bromobicyclo[1.1.0]butane (**2**) (Figure 1) was performed according to Skattebøl and Baird et al.[6] The first step of the synthesis, dibromocarbene addition to allyl chloride, was carried out under phase transfer conditions applying ultrasound.[7] The addition product, 1,1-dibromo-2-chloromethylcyclopropane (**1**), was isolated in 86% yield. 1,3-Ring-closure of **1** to bicyclobutane **2**[8] was accomplished through reaction with methyllithium at −78 °C. A subsequent metal−halogen exchange reaction with *tert*-butyllithium results in the corresponding lithiobicyclobutane **3**, which was previously prepared by deprotonation of the highly volatile parent bicyclobutane with alkyllithiums.[8] Lithium compound **3** (Figure 1) is valuable for introducing a variety of substituents in the bridgehead position of bicyclobutane.[9] For example, trapping of **3** with ethyl chloroformate gives 1-carboethoxybicyclobutane **4**[5a] in an overall yield of 23% in a simple three-step, one-pot reaction starting from cyclopropane **1**.

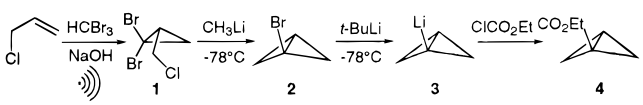

Figure 1. Preparation of 1-carboethoxybicyclo[1.1.0]butane (**4**).

Preliminary study and a similar example in the literature[5c] show that when a leaving group such as bromine is located at the bridgehead position of bicyclobutane **2**, a halohydrin intermediate **6** (Figure 2) is formed during the addition of water. The loss of the bromide ion generates carbocation **7** and consequently cyclobutanone (**9**).

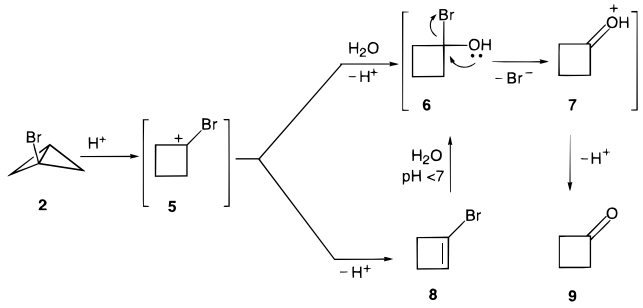

Figure 2. Acid-catalyzed rearrangements of 1-bromobicyclo-[1.1.0]butane (**2**).

It is known that vinyl halides can be transformed into ketones with acids such as sulfuric acid.[10] Therefore, when cation-exchange resin DOWEX 50 WX4 and water were added to 1-bromobicyclo[1.1.0]butane (**2**) at −78 °C, it was no surprise that small amounts of cyclobutanone (**9**) were formed in addition to 1-bromocyclobutene (**8**), the major product. Moreover, some 1,1-dibromocyclobutane was also detected and probably results from addition of HBr to **8**. Monitoring of the reaction by GC-MS showed that after the reaction warmed up to room temperature within 2 h, around two-thirds of **8** was hydrolyzed to **9**.

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†Carbene Rearrangements, part 50. For part 49, see: Xu, L.; Brinker, U. H. In *Sonochemical Organic Synthesis*; Luche, J. L., Ed.; Plenum: New York, 1998; p 354.

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Cyclobutanone (**9**) was separated from the remaining 1-bromocyclobutene (**8**) and 1,1-dibromocyclobutane by exhaustive extraction with ice water. The aqueous phase was then extracted with dichloromethane. Isolation of **9** was accomplished by exhaustive distillation through a Spaltrohr column. The isolated yield of cyclobutanone (**9**) over two steps after distillation was 28%. Cyclobutanone-*p*-tosylhydrazone could be formed in 31% overall yield starting from cyclopropane **1** by the reaction of crude cyclobutanone (**9**) with *p*-toluenesulfonylhydrazide.

Despite the large number of published syntheses, cyclobutanone (**9**) had still not been simply and cheaply made.[1a] The novel route to cyclobutanone (**9**), described here, represents an inexpensive and short three-step synthesis starting from allyl chloride.

Experimental Section

Preparation of 1,1-Dibromo-2-chloromethylcyclopropane (1) Using the Ultrasonic Method.[7] The following reagents were added to a 250-mL flask in the given order: (1) 32 g (0.8 mol), a 10-fold excess, of powdered sodium hydroxide, (2) 50 mL of methylene chloride, (3) 9.2 g (120 mmol) of allyl chloride, (4) 20.2 g (80 mmol) of bromoform, and (5) about 30 mg of triethylbenzylammonium chloride (TEBA). The flask was fitted with a reflux condenser and a bubbler. The setup was immersed in the bath of an ultrasonic cleaner (35 kHz), and the mixture was sonicated for 40 min. The initiation of the reaction, as indicated by the evolution of gas or discoloration of the mixture, could be observed immediately. The crude yield was 25 g, and a GC analysis showed a small amount of leftover bromoform. The inorganic solids were removed by suction filtration through a filter agent (Celite 545). The solvents were removed with a rotary evaporator. An optional purification procedure entails the addition of pentane and silica gel to the residue, followed by filtration and evaporation of the solvent. Distillation of the mixture was performed in vacuo: bp 68−72 °C (10 mmHg). Further purification was accomplished through column chromatography (pentane/ether 98:2): yield 17.0 g (86%).

Preparation of 1-Bromobicyclo[1.1.0]butane (2).[6,8] At −78 °C and under an inert gas atmosphere, 11.2 g (45 mmol) of dibromocyclopropane **1** in 20 mL of dry diethyl ether were treated with 33 mL of a 1.4 M solution of methyllithium in diethyl ether. The mixture was allowed to warm to −60 °C over a period of 4 h. The cold bath was then removed, and all volatile compounds were condensed into a trap. The condensation was completed under slight heating with a water bath (35 °C). Under basic conditions (NaOH, diethyl ether), **2** can be stored in a freezer for several days without significant decomposition.

Preparation of Cyclobutanone (9) from 1-Bromo[1.1.0]-bicyclobutane (2). The etheral solution of bromobicyclobutane **2**, was cooled to −78 °C, and 5 g of DOWEX 50 WX4 and 5 mL of water were added. The mixture was allowed to warm to room temperature overnight and was analyzed on the analytical gas chromatograph HP6890 with MSD HP5973: column HP-5 M, phenyl methyl siloxane, 30 m × 250 μm capillary; flow 0.8 mL/min; temperature program injection temperature 150 °C, oven temperature initial 40 °C for 5 min and then ramp 30 °C/min up to 200 °C, 2 min at 200 °C; ratio of **8**: **9** = ca. 1:2. The reaction mixture was filtered and extracted 10 times with 45-mL portions of ice water until no cyclobutanone (**9**) could be detected in the ether phase by GC. The aqueous phase was saturated with sodium chloride and extracted 15 times with 15-mL portions of dichloromethane until no cyclobutanone (**9**) could be detected in the aqueous phase. The organic phase was dried over magnesium sulfate. The dichloromethane was carefully distilled off through a 20-cm Spaltrohr column: yield 0.89 g (28%, purity: 99%) of cyclobutanone (**9**) over two steps starting from cyclopropane **1**.

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