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An efficient route to 3-substituted cyclobutanone derivatives

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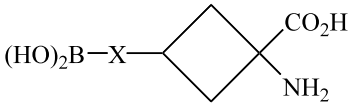
Abstract—An efficient route to 3-(hydroxymethyl)cyclobutanone acetals via a [2+2] cycloaddition reaction is reported. The dramatic effect of different diol acetals on benzyl deprotection is discussed. Efficient synthesis of two synthetically useful intermediates, 3-methylenecyclobutanone acetal and 3-(bromomethyl)cyclobutanone, are provided.

Boron neutron capture therapy (BNCT) is a binary cancer therapy in which a compound containing boron-10 is selectively delivered to tumor tissues prior to irradiation by neutrons.[1] It is believed that amino acids are preferentially taken up by growing tumor cells[2] and recent positron emission tomography (PET) investigations carried out at the University of Tennessee confirm that carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) selectively localizes in tumors.[3] For this reason, we have focused our efforts on the synthesis of boronated ACBC derivatives as potential BNCT agents.[4,5] In a continuation of these studies, we have been developing the syntheses of ACBC derivatives such as **1** in which alkylboronic acids serve the boron source (Fig. 1).



X = CH_2; $CH_2O(CH_2)_3$

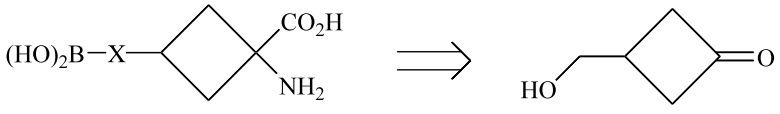
1

Figure 1.

The retro synthetic analyses (Scheme 1) for **1** led to the key intermediate 3-(hydroxymethyl)cyclobutanone **2** or its corresponding acetal. Among the reported methods[6] for preparing 3-(hydroxymethyl)cyclobutanone acetal, the most straightforward route involves the cyclocondensation of 1,3-dibromo-2,2-dimethoxypropane and diisopropyl malonate.[6c] However, this reaction proceeds in low overall yield (14%) after four steps.

Lacking an efficient method to generate **2** led us to explore alternate synthetic strategies. Our approach is outlined in Scheme 2.

The [2+2] cycloaddition reaction of allyl benzyl ether and dichloroketene[7] was utilized to generate **3** which was converted to cyclobutanone **4** in 56% isolated yield in two steps on a 30 mmol scale. We then discovered that the direct benzyl deprotection by hydrogenation was inefficient and led to a mixture of compounds. It is worth noting that this problem had been reported earlier.[8]



X = CH_2; $CH_2O(CH_2)_3$

1 **2**

Scheme 1.

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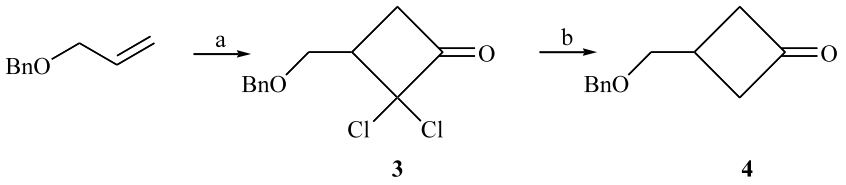


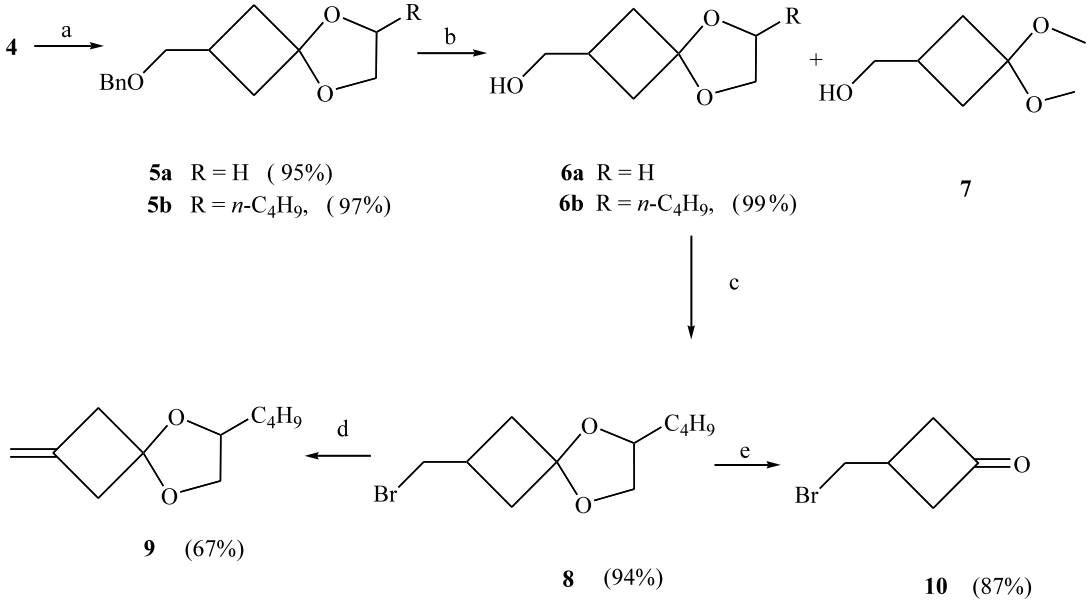
Scheme 2. *Reaction conditions*: (a) Cl_3CCOCl, $POCl_3$, Zn–Cu, Et_2O; (b) Zn, HOAc.

Since deprotection of **4** by hydrogenation failed to produce ketone **2** in good yield, we decided to protect the ketone group prior to hydrogenation (Scheme 3). Ethylene acetal **5a** was prepared in 95% yield from **4** using standard procedures. Unfortunately, the hydrogenation of **5a** in methanol led to significant quantities of **7** in addition to the desired product **6a**. The methanol–acetal exchange is attributed to the ready cleavage of the ethylene acetal in **5a** which was confirmed by carrying out the exchange in the absence of the catalyst (Pd/C). The ratio of **6a**:**7** was variable but, generally, **7** accounted for more than 20% of the reaction mixture. This led us to consider the use of more stable diol acetals. Utilizing 1,2-hexanediol proved quite effective. The hydrogenation reaction proceeded smoothly in methanol at room temperature and produced pure **6b**[9] after simple filtration and solvent removal. The method was used to efficiently construct 3-(hydroxymethyl)cyclobutanone acetal **6b** starting from allyl benzyl ether in 54% overall isolated yield. Since **5b**, **6b**, and **8** contain two chiral centers, diastereomers are formed (in essentially equal quantities.) They are readily detectable in the ^{13}C NMR and are the source of the extra resonances reported for **6b**.[9]

The subsequent transformation of **6b** to other valuable synthetic intermediates was then investigated. Bromination of **6b** using CBr_4/PPh_3 in dichloromethane[10] at room temperature produced 3-(bromomethyl)cyclobutanone acetal, **8**, in 94% isolated yield. Dehydroboromination of **8** using NaOH in PEG-600[11] generated 3-methylenecyclobutanone acetal, **9**, in 67% yield.[12] Alkene **9** is a useful intermediate in the total synthesis of biological active hydantoin- and isoxazoline-substituted dispirocyclobutanoids.[13] The deprotection of acetal **8** using 2 M HCl in refluxing ethanol produced 3-(bromomethyl)cyclobutanone,[14] **10**, which is an important intermediate in the total synthesis of antifeedant compounds such as 2,4-methanoproline.[6c,15] The low yields of **10** (10–30%) produced by existing methods[6c,8a] are readily surpassed by the 44% isolated yield based on allyl benzyl ether using the synthetic route developed here.

Conclusion

In conclusion, a practical and efficient route to 3-(hydroxymethyl)cyclobutanone acetal **6b** starting from commercial available allyl benzyl ether has been developed. The choice of diol to protect the ketone intermediate is critical to the synthetic strategy. The successful conversions of **6b** to the 3-methylenecyclobutanone acetal **9** and 3-(bromomethyl)cyclobutanone, **10**, are also provided.



Scheme 3. *Reaction conditions*: (a) diol, PTSA, benzene; (b) H_2, Pd/C (10%); (c) CBr_4, Ph_3P, CH_2Cl_2, rt.; (d) NaOH (5 M), PEG 600, 90°C; (e) HCl (2 M), EtOH, reflux.

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9. Spectrum of acetal **6b**: ^{1}H NMR (250 MHz, $CDCl_3$ with TMS as internal standard): 3.93–4.05 (m, 2H); 3.63 (d, $J=6.18$ Hz, 2H); 3.45 (dd, $J=12.4$ Hz and 6.7 Hz, 1H); 3.68 (s, 1H); 2.23–2.47 (m, 3H); 2.00–2.17 (m, 2H); 1.16–1.64 (m, 6H); 0.91 (t, $J=6.48$ Hz, 3H). ^{13}C NMR: 106.7, 106.5, 75.9, 75.7, 69.0, 68.8, 66.7, 66.6, 38.6, 38.5, 38.3, 33.3, 33.1, 27.8, 26.8, 26.6, 22.6, 13.9. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.44; H. 10.09. HRMS; calcd for M+1 201.1491. Found: 201.1490.
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12. Spectrum of 3-methylenecyclobutanone acetal **9**: ^{1}H NMR (250 MHz, $CDCl_3$ with TMS as internal standard): 4.94–4.98 (m, 2H); 3.98–4.06 (m, 2H); 3.47–3.52 (m, 1H); 3.03–3.04 (m, 2H); 2.95–2.97 (m, 2H); 1.12–1.61 (m, 6H); 0.91 (t, $J=6.33$ Hz, 3H). ^{13}C NMR: 138.5; 107.9, 105.7, 76.2, 69.2, 45.7, 45.5, 33.1, 27.2, 22.6, 14.0. Anal. calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.60; H, 9.78.
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14. Spectrum of **10**: ^{1}H NMR (250 MHz, $CDCl_3$ with TMS as internal standard): 3.62 (d, $J=5.90$ Hz, 2H); 3.14–3.27 (m, 2H); 2.68–2.98 (m, 3H). ^{13}C NMR: 204.8, 51.9, 37.2, 26.2. Anal. calcd for C_5H_7OBr: C, 36.84; H, 4.33. Found: C, 36.63; H, 4.33.
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