



Studies of Stoichiometric Monobenzoylation of Cross-bridged Cyclam by S_N2 Alkylation and Reductive Alkylation

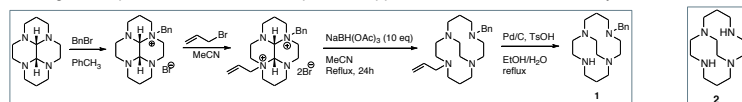
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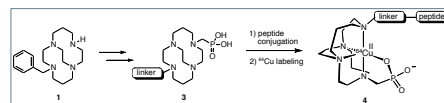
Introduction

Production of monobenzyl cross-bridged (CB) cyclam (**1**) in high yields has previously been accomplished through a four-step synthesis outlined in Scheme 1.¹ The goal of this research project was to explore whether **1** could be synthesized from CB-cyclam (**2**) through S_N2 alkylation or reductive alkylation. If successful, this direct synthesis would be more suitable for large scale production of **1**. If not, the previous approach is validated as necessary.



Scheme 1: Previous synthesis of monobenzyl CB-cyclam (**1**).¹

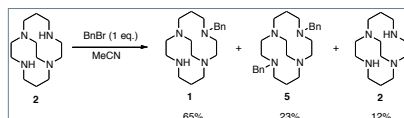
Monobenzyl CB-cyclam (**1**) is an important intermediate for synthesis of second generation ligands that are useful in radiopharmaceutical applications. Such ligands can be linked to a biologically-active target molecule and subsequently complexed with ^{64}Cu (II), as shown in Scheme 2. Bioconjugates, like **4**, are potentially useful for



Scheme 2: Formation of second generation ligands from **1**.

Positron Emission Tomography-based tumor detection (PET). The benzyl group of **1** functions to protect one of the secondary amines of CB-cyclam (**2**) so that efficient monofunctionalization of the other secondary amine can be achieved.²

Results and Discussion



Scheme 3: S_N2 alkylation of **1** with benzyl bromide

The S_N2 alkylation (Scheme 3) involved treating CB-cyclam (**2**) with 1 equivalent of benzyl bromide to form a mixture of **1**, **5**, and leftover **2** in a ratio of 0.65: 0.23: 0.12, respectively. This ratio was determined by integration of specifically-denoted resonances (green = **1**, blue = **5**, orange = **2**) in the ^1H NMR spectrum (Figure 1). $^{13}\text{C}\{^1\text{H}\}$ NMR relative peak heights (Figure 2) were consistent with the ^1H results. In Figure 1, the integrations of the resonances at δ 3.50, 4.00 and 1.15 were compared to give the ratio of **1**:**5**:**2**. The resonances representing **2** and **5** were normalized due to the ligands' C_2 symmetry.

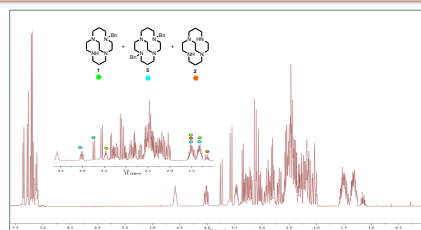


Figure 1: ^1H NMR spectrum of **1**, **2**, and **5** in C_6D_6 (400 MHz) for S_N2 alkylation

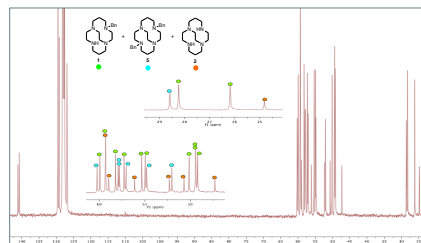
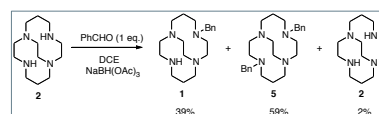


Figure 2: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **1**, **2**, and **5** in C_6D_6 (100 MHz) for S_N2 alkylation



Scheme 4: Reductive alkylation of **1** with benzaldehyde

The reductive alkylation (Scheme 4) involved treating CB-cyclam (**2**) with 1 equivalent of benzaldehyde in the presence of excess sodium triacetoxyborohydride to form a mixture of **1**, **5**, and **2** in a ratio of ~0.39: ~0.59: ~0.02, respectively. These ratios were calculated or supported by ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra (Figures 3 and 4, respectively). The ratio of **1** to **5** was determined by comparing the normalized integrations of the resonances at δ 3.53 and 4.00 in Figure 3. The ratio of **2** was determined using the multiplets from δ 1.10-1.60, which contain protons from each compound in the final mixture. Based upon total integrations and integrations of **1** and **5**, the quantity of leftover **2** was established. The $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum showed very small amounts of starting material (**2**), but was not clear enough to confirm the final ratio.

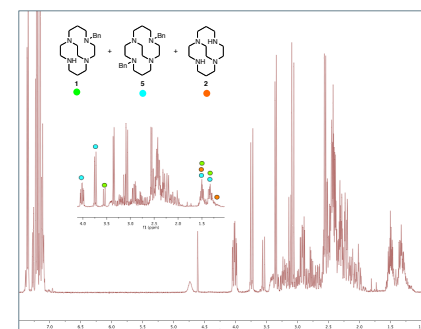


Figure 3: ^1H NMR spectrum of **1**, **2**, and **5** in C_6D_6 (400 MHz) for reductive alkylation

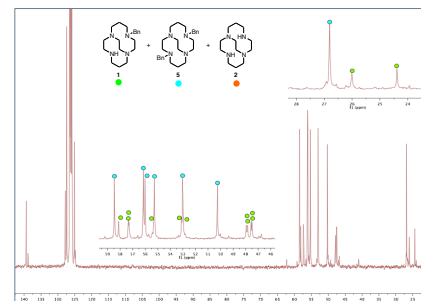


Figure 4: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **1**, **2**, and **5** in C_6D_6 (100 MHz) for reductive alkylation

These data show that S_N2 alkylation and reductive alkylation are not effective methods for producing high yields of monobenzyl CB-cyclam (**1**) when compared to previous methods of synthesis; thus, these methods would not be appropriate for large-scale synthesis of compound **1**.

The reductive alkylation will be repeated using freshly purified PhCHO and dried **2**.

Conclusions

In summary, S_N2 alkylation and reductive alkylation of CB-cyclam are not efficient methods for producing high yields of the desired product **1**. These reactions produce mixtures of **1**, **2**, and **5**, and would require intensive separation and purification. Therefore, it can be concluded that the most efficient route to date for preparation of desired synthetic intermediate **1** is the procedure previously designed and realized (Scheme 1).

Acknowledgements

This work was supported by Award Number R01CA093375 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. BJK thanks Leon Wong, Barbara Li, Amanuel Ghidye, and Justin Fleming for help and support in the lab.

References

1. G. R. Weisman, personal communication; route is the work of Shanta Bist, Matthew Young, Kaitlyn Dugan, Leon Wong, and David Wilk.
2. Wadas, T.J.; Wong, E.H.; Weisman, G.R.; Anderson, C.J. *Chem. Rev.* **2010**, *110*, 2858-2902.