Discovering an Improved Synthetic Route to [1.1.1]Propellane

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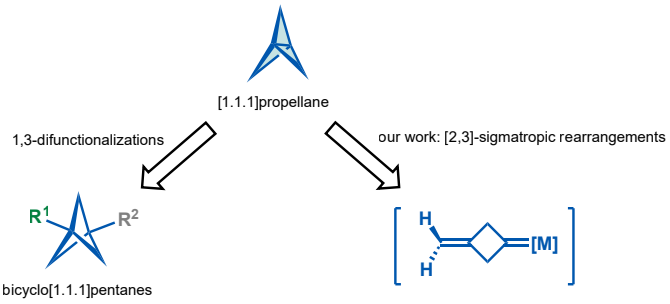
Abstract

We are interested in exploring new reactivity modes of [1.1.1]propellane. The most extensively studied aspect of the reactivity of propellanes involves the functionalization of the bridgehead carbon atoms, which allows for 1,3-difunctionalization, leading to the formation of bicyclo[1.1.1]pentanes (Scheme 1). Our group has recently utilized the carbene reactivity of [1.1.1]propellane for [2,3]-sigmatropic rearrangements.[1] A search in Science of Synthesis quickly revealed several key references detailing the preparation of [1.1.1]propellane. The conditions reported in these references allowed us to achieve a better yield than in our previous attempts.

Discussion

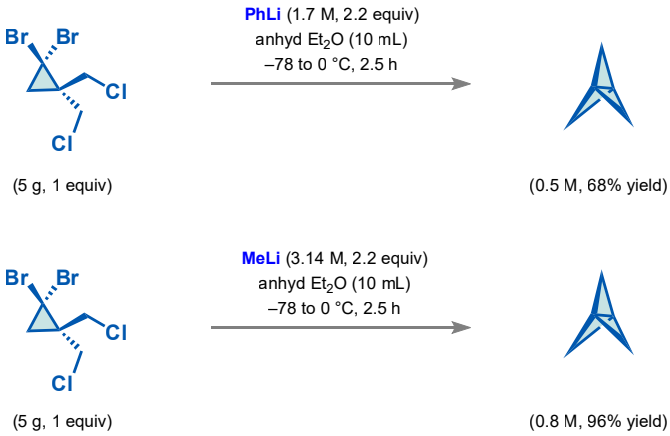
Propellanes are known for their highly strained structure, particularly [1.1.1]propellane, which is the smallest member of this family. This strain contributes to their high reactivity and can lead to the formation of three-dimensionally constrained bicyclo[1.1.1]pentane derivatives, or rearrangements into useful methylenecyclobutane motifs (Scheme 1). To further explore this area of research, we required a reliable synthetic procedure for preparing [1.1.1]propellane as a starting material.



Scheme 1 Reactivity Modes of [1.1.1]Propellane

A text search for "[1.1.1]propellane" in *Science of Synthesis* provided a short hitlist of interesting results. However, for our purposes a structure search was found to be particularly effective; a search for the [1.1.1]propellane core returned 10 hits. Applying filters for an "exact structure match" and "reaction product" guided us to relevant methods for synthesizing [1.1.1]propellane. Among the results obtained, we found a *Science of Synthesis* article on the synthesis of cyclobutanes, including the use of propellanes as precursors (Section 48.3.1.1.2).[2] This review directed us to a report by Werner, Stephenson, and Szeimies, published in 1996 on the "Synthesis of [1.1.1]Propellanes by Bridging of Bicyclo[1.1.0]butanes",[3] which includes a reported method for the synthesis of [1.1.1]propellane.

The synthesis is achieved through a one-pot reaction using methyllithium to bridge the 1,3-positions of a 1-bromo-3-(chloromethyl)bicyclobutane intermediate, which is generated from 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (Scheme 2). This article has been invaluable in refining our reaction conditions for the effective synthesis of [1.1.1]propellane. Previously, we had attempted to synthesize [1.1.1]propellane using phenyllithium; however, the molarity and yield were subpar, with a concentration of 0.5 M resulting in a yield of only 68%. After conducting a thorough review of the information gained from utilizing *Science of Synthesis*, we were able to optimize our process and this led to a significant improvement in yield. Thus, by modifying the reaction conditions to employ methyllithium instead of phenyllithium, the yield of [1.1.1]propellane was enhanced to an impressive 96% at a concentration of 0.8 M.



Scheme 2 Improvement of Yield in the Synthesis of [1.1.1]Propellane

The synthesis started with titration of MeLi against *N*-benzylbenzamide at 0 °C. Next, a suspension of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (5.0 g,

17 mmol, 1.0 equiv) was prepared in 10 mL of dry diethyl ether. A 3.1 M solution of MeLi in diethoxymethane (12 mL, 37 mmol, 2.2 equiv) was then added dropwise at –78 °C under a nitrogen atmosphere. Following the addition of MeLi, the reaction mixture was maintained at –78 °C using a dry ice/acetone bath for 30 minutes. After this period, the mixture was removed from the dry ice/acetone bath and transferred to an ice-water bath at 0 °C, where it was stirred for 2 hours. Subsequently, a bulb-to-bulb distillation apparatus was set up, with the receiving flask cooled to –78 °C. [1.1.1]Propellane was obtained as a solution in diethyl ether at a concentration of 0.8 M; yield: 96%.

Conclusion

Science of Synthesis is an invaluable resource for chemists looking for effective synthetic procedures. With its help, we discovered an alternative approach for preparing [1.1.1]propellane that resulted in a significantly increased yield. Additionally, *Science of Synthesis* offers a user-friendly interface, making it an accessible resource for anyone interested in synthetic methodology. It provides a comprehensive overview of the reported literature, allowing one to select the optimal reaction conditions in an efficient manner.

References

[1] Midya, S.; Ali, A.; Hari, D. P., *Nat. Commun.*, (2025) **16**, 6233.

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[3] Werner, M.; Stephenson, D. S.; Szeimies, G., *Liebigs Ann.*, (1996), 1705.

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