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A HIGHLY EFFICIENT METHOD FOR ONE-CARBON RING EXPANSION. PREPARATION OF 1-ALKOXY-2-METHYLENECYCLOALKANES

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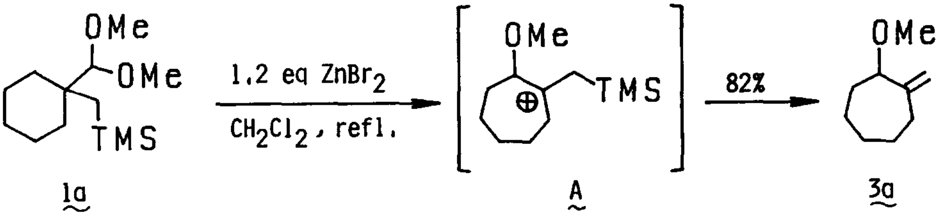
Summary: $ZnBr_2$ induces a facile one-carbon ring expansion of 1-(TMS-methyl)-cycloalkanecarbacetals to yield the corresponding 1-alkoxy-2-methylenecycloalkanes, whereas a similar transformation can be performed efficiently from the parent aldehydes under the influence of TMS-OTf (1 mol%) and TMS-OMe (2 equiv).

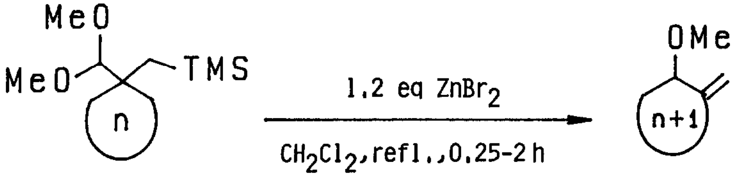
Several methodologies have been developed for one-carbon ring expansion of carbocyclic system, but there have been still remained several problems especially on generality or efficacy of the procedures.[1,2] Sometimes, difficulties are also encountered on stereo- and regio-control during rearrangement processes. We previously reported the role of a silyl group to control the direction of rearrangement[3] in the reaction of 1-(TMS-methyl)cycloalkanecarbaldehydes.[4] In the present, we describe a general and extremely efficient method for such synthetic purpose.

By utilizing cation-stabilizing effect of a silyl group,[5] we examined the reaction of acetals **1** of 1-(TMS-methyl)cycloalkanecarbaldehydes **2** in the presence of several Lewis acids. Different from the parent aldehydes **2**, use of $AlCl_3$ resulted in the formation of non-polar unidentified products, but on heating with relatively weak Lewis acid such as $ZnBr_2$ in dichloromethane, the cyclohexanecarbaldehyde dimethyl acetal **1a** can be converted to 1-methoxy-2-methylenecycloheptane **3a** in a high yield. Similarly with the aluminum-mediated rearrangement of the parent aldehydes **2**,[3] an initial carbon skeleton rearrangement occurs so as to form β-silicon stabilized cationic species **A**, but a preferential removal of the silyl group occurs from the resulting **A** to produce **3** (Scheme 1).



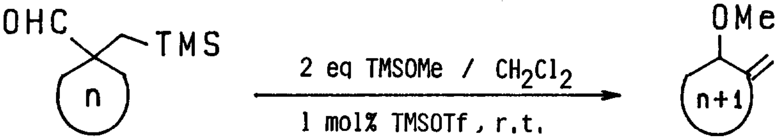
Scheme 1

The procedure is applicable equally well to various ring-sized acetals.



1	3
a: n = 6	82 %
b: n = 8	83 %
c: n = 12	100 %

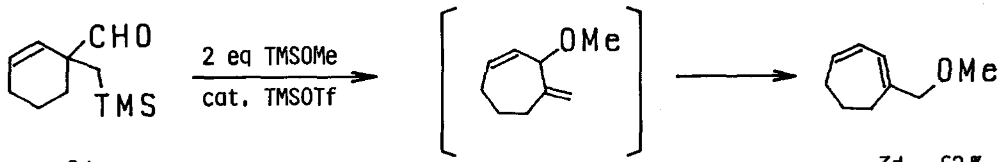
Steric crowding around an aldehyde function sometimes prevents a smooth conversion of **2** to the acetal **1**. For example, an acetalization of **2c** was too slow to achieve a complete conversion to **1c** under usual conditions (MeOH/HC(OMe)$_3$/cat.TsOH). Use of silicon-based nucleophiles such as methoxytrimethylsilane circumvented this difficulty and greatly improved the procedure: On treating with methoxytrimethylsilane (2 equiv) and trimethylsilyl triflate (1 mol%)[6] in dichloromethane at room temperature, aldehydes **2** directly undergo the same transformation to afford 3 in excellent yields.



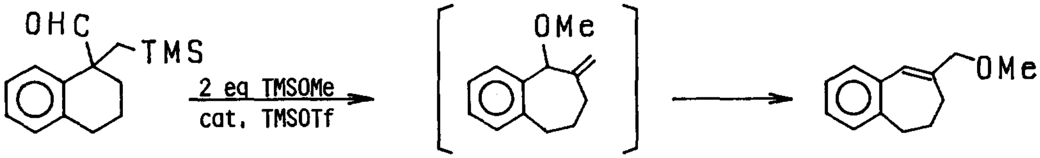
2	3
a: n = 5	(96 %)*
b: n = 8	86 %
c: n = 12	96 %

* NMR yield

In addition to general applicability to various ring-sized substrates, the present procedure has also provided several synthetically useful features. First, even on using α,α'-unsymmetrically substituted ring system, the rearrangement direction can be controlled with essentially complete regioselectivity. In competition of sp^2 with sp^3 carbons, a preferential migration of the former has been observed as exemplified by the reaction of **2d** and **2e**. The resulting allylic or benzylic ethers isomerize under the reaction conditions to give **3d** or **3e** as final products. Considering that the aluminum-mediated method[3] failed to induce a ring enlargement reaction of **2d** or **2e**, the scope for ring enlargement has been broaden by the present method.[7]



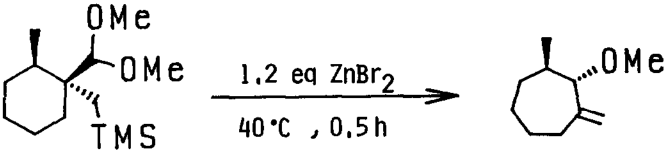
2d 3d 62%



2e 3e 88%

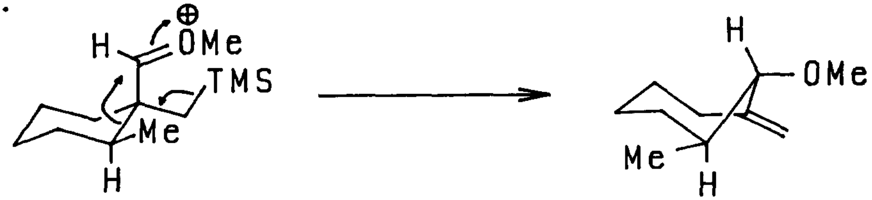
Concerning on the regioselectivity between two sp^3-carbons, a more substituted group rearranges exclusively in a similar manner with that of the aluminum-mediated rearrangement of the aldehydes **2**.

Second, it has been proved that rearrangement of an alkyl group proceeds with retention of the configuration; the cis-acetal **1f** (97:3)[8] afforded trans-2-methoxy-1-methyl-3-methylenecycloheptane **3f**[9] (>99% pure).



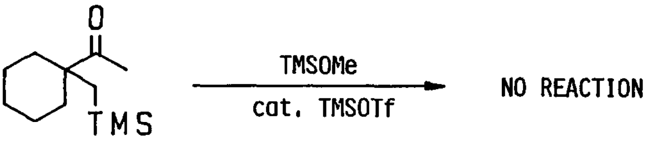
1f 3f 100%

These results may support a concerted reaction mechanism as depicted in Scheme 2.

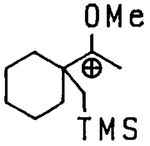


Scheme 2

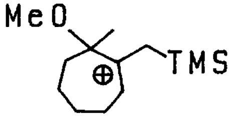
In contrast to a facile ring expansion of aldehydes, a ketone usually does not undergo such rearrangement to give back the starting material under similar reaction conditions.



Such different behavior may be attributable to the higher stability of the cationic intermediate initially generated from the ketone, which should require a formation of more stable cationic species for the reaction to proceed.



More Stable



Less Stable

Thus, in addition to an accelerating and directing effects of a silyl group, the rearrangement can be induced in a predictable way by choosing substrates bearing appropriate substituents, which may further lead to the development of synthetically useful carbon skeleton construction.

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References

1) Due to an extreme stability of six-membered ring, it has been known that conversion of cyclohexane ring to cyclopentane or cycloheptane is energetically much disfavored, while reverse reactions are greatly favorable. See; B. P. Mundy, "Concept of Organic Synthesis", Marcel Dekker, New York (1979), chapter 2.
2) On one-carbon ring expansion: B. M. Trost and G. K. Mikhail, J. Am. Chem. Soc., **109**, 4124 (1987), and references cited therein.
3) K. Tanino, T. Katoh, and I. Kuwajima, Tetrahedron Lett., the previous paper.
4) See also; K. Tanino, Y. Hatanaka, and I. Kuwajima, Chem. Lett., **1987**, 385.
5) E. W. Colvin, "Silicon in Organic Synthesis", Butterworths, London (1981), chapters 3 and 9. W. P. Weber, "Silicon Reagents for Organic Synthesis", Springer-Verlag, Berlin (1983), chapter 11. H. Sakurai, Pure Appl. Chem., **54**, 1 (1982).
6) T. Tsunoda, M. Suzuki, and R. Noyori, Tetrahedron Lett., **21**, 1357 (1980).
7) The different migration modes between acetals and their parent aldehydes are attributable to the difference of stability of the initially formed cationic species. Such feature will be discussed in a full paper.
8) See the reference 8 of the previous paper.[3]
9) The stereochemistry of the product **3f** was confirmed by coupling constant between two vicinal methyne protons (J = 7.1 Hz).

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