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CYCLIZATIONS OF ALKENYLLITHIUM REAGENTS

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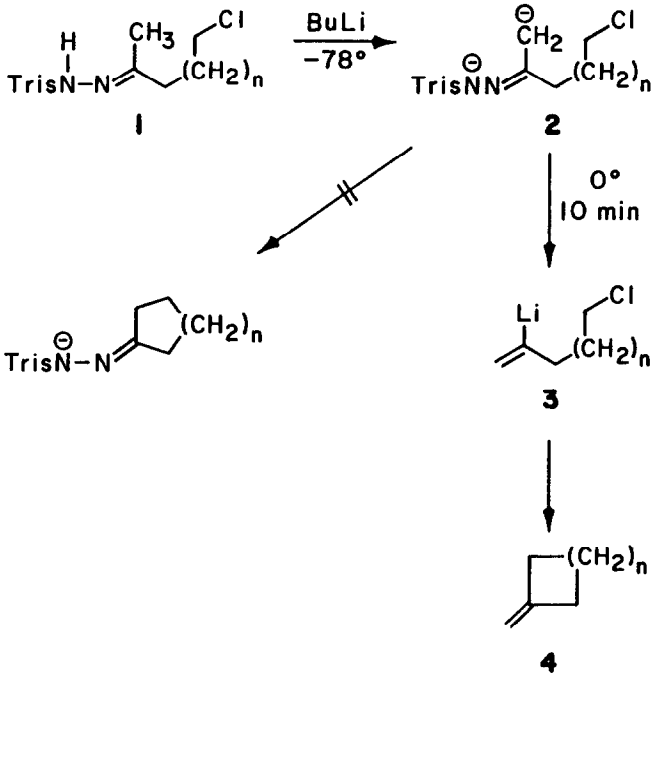
Abstract: Alkenyllithium species containing a primary chloride group can be generated efficiently. They undergo subsequent cyclization to alkylidene cycloalkanes of various ring sizes.

The cyclization of cationic,[1] radical,[2] and stabilized anionic[3] species all are common methods of forming carbocyclic rings. On the other hand, examples of controlled, synthetically useful cyclizations of relatively reactive organometallic nucleophiles are much rarer, in part because of the difficulty of generating such species selectively in the presence of the necessary internal electrophile. There are several long-established exceptions to this generalization, including the intramolecular Barbier[4] and Wurtz[5] reactions, which unfortunately can suffer from a lack of generality and other drawbacks. Several other more recent examples involving various organometallic species[6-9] have, however, illustrated the potential of this general type of cyclization as a useful method of forming carbocyclic rings. In this communication we report our preliminary results on the cyclization of alkenyllithium reagents generated from ketone arenesulfonylhydrazones.

We set out initially to attempt one of the simplest possible organolithium cyclizations; that of an internal SN_2 displacement of a primary chloride by a vinyllithium nucleophile. A ketone triisopropylbenzenesulfonylhydrazone (trisyl hydrazone) was selected as the precursor because of easy accessibility and because this group offers an especially mild and regioselective means of generating vinyllithium reagents,[10] one that we hoped would be compatible with the internal primary chloride electrophile. This choice proved to be a good one, as illustrated by the successful cyclizations shown below. In most cases the crystalline trisyl hydrazone, prepared[10] from the corresponding ω-chloro ketone, was dissolved in 10% TMEDA hexane at -78°C and treated with 2.1 equiv of sec-BuLi. Warming of the resulting dianion solution to 0°C resulted in the rapid evolution of nitrogen, signalling formation of the vinyl anion. The ice bath was then removed, and after 3 h the reaction mixture was quenched with aqueous bicarbonate solution. These conditions were satisfactory for all but the seven-membered ring; in that case the relatively low rate of cyclization was competitive with protonation of the vinyllithium nucleophile (presumably

by TMEDA), as shown by the isolation of the acyclic protio-chloroalkene when the reaction was quenched with D_2O after 24 hours. The problem was easily circumvented, however, by conducting the reaction in THF and adding Kochi's catalyst[11] (Li_2CuCl_4) after vinyl anion formation was complete (i.e., when N_2 evolution had ceased). This modification increased the yield of methylene



n =	% Yield[a]
2	40[b]
3	59[b], 66[c]
4	30[b], 72[c]
5	0%[c]

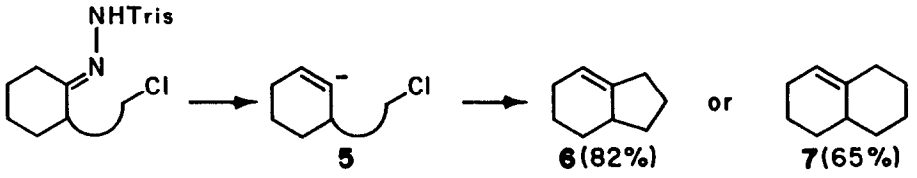
a: internal standard gc
b: s-BuLi, TMEDA-hexane
c: t-BuLi, THF; Li_2CuCl_4

cycloheptane from 30% to 72%, and also marginally increased the yield in 6-membered ring formation as well. The yield of methylene cyclopentane was low due to volatility problems (see below for another example of efficient cyclopentane formation), but the 8-membered ring yield not unexpectedly was essentially nil, even with copper catalysis.

It was gratifying that several potential side reactions did not predominate: deprotonation of the monoanion derived from 1 is faster than reaction of the primary chloride group with sec-BuLi at -78°C, and "premature" cyclization of the dianion 2 is slower than its decomposition to the desired vinyllithium species 3.[12] The high regioselectivity observed in the formation of the ter-

minal alkenyllithium isomers[13] is well-precedented[10] and it results in nearly exclusive production of the exocyclic alkene products shown.

It is also possible to take advantage of the analoguous regioselectivity reported for cyclic ketone trisylhydrazones to prepare several bicyclic systems from 5.



5 6(82%) 7(65%)

The starting ω-chloroketones were prepared by standard methods,[14] and the products were analyzed by 250 MHz proton NMR, MS, and capillary gas chromatography (coinjection with authentic samples[15]). While the products formed in the carbocyclization described in this paper obviously can be prepared by other methods, this general procedure promises to be useful in the construction of more complex products that are considerably less readily available. We currently are exploring some of these possibilities by examining a variety of internal electrophiles and other stereo- and regiochemical aspects of vinyllithium generation.

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References and Notes

1. (a) Johnson, W.S. Bioorganic Chem. 1976, 5, 1. (b) Sutherland, J.K. Chem. Soc. Rev. 1980, 265. (c) van Tamelen, E.E. Accts. Chem. Res. 1975, 8, 152. (d) Speckamp, N. Recueil, 1981, 100, 345.

2. (a) Julia, M. Rec. Chem. Prog. 1964, 25, 3. (b) Nonhebel, D.C.; Walton, J.C. "Free-radical Chemistry", Cambridge Univ. Press, 1974, Ch. 14.

3. For example, intramolecular aldol, Dieckmann, and related enolate cyclizations.

4. Crandall, J.K.; Magaha, H.S. J. Org. Chem. 1982, 47, 5368 and references therein.

5. Bailey, W.F.; Gagnier, R.P. Tetrahedron Lett. 1982, 23, 5123 and references therein.

6. Organolithium: (a) Smith, M.J.; Wilson, S.E. Tetrahedron Lett. 1981, 22, 4615. (b) Parham, W.E.; Bradsher, C.K. Accts. Chem. Res. 1982, 15, 300. (c) Cooke, M.P. J. Org. Chem. 1984, 49, 1144. (d) see also reference 5.

7. Organomagnesium: (a) Oppolzer, W.; Begley, T.; Ashcroft, A. Tetrahedron Lett. 1984, 25, 825 (magnesium ene reaction) (b) see also reference 4.

8. Organocopper: (a) Corey, E.J.; Kuwajima, I. J. Am. Chem. Soc. 1970, 92, 395. (b) Scott, F.; Mafunda, B.G.; Normant, J.F.; Alexakis, A. Tetrahedron Lett. 1983, 24, 5767. (c) Erdik, E. Chim. Acta Turc. 1981, 9, 353.

9. Organozirconium: Negishi, E.; Miller, J.A. J. Am. Chem. Soc. 1983, 105, 6761.

10. (a) Chamberlin, A.R.; Stemke, J.E.; Bond, F.T. J. Org. Chem. 1978, 43, 147. (b) Adlington, R.M.; Barrett, A.G.M. Accts. Chem. Res. 1983, 16, 55.

11. Tamura, M.; Kochi, J. Synthesis, 1971, 303.

12. Although closure of the dianion obviously is not desired for this vinyllithium cyclization, it would be useful (if controllable) for the production of endocyclic alkenes. We are currently testing this idea.

13. Capillary gas chromatography (12.5 m column) shows < 2% of contamination by the possible endo cyclic alkene isomer.

14. a) Greene, F.D.; Savitz, M.L.; Osterholtz, F.D.; Lau, H.H.; Smith, W.N.; Zanet, P.M.; J. Org. Chem. 1963, 28, 55. b) Stork, G.; Dowd, S.R. J. Am. Chem. Soc. 1963, 85, 2178.

15. The bicyclic products were hydrogenated for G.C. comparison with the respective authentic saturated alkane mixtures.

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