Cyclizations of ω -Allenyl Organometallic Reagents

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Abstract: Allenyl organometallic reagents of type $R_2C=C=CH(CH_2)_nCH_2M$ undergo cyclization at the central allenic carbon for n = 2 (M = Li) and at the near allenic carbon for n = 3 (M = CuCNLi) to provide cyclopentane systems; little cyclization was observed for the n = 4 systems (M = Li, CuCNLi).

Technical advances that permit facile, efficient lithium-iodide exchange¹ without the intervention of radical processes have stimulated the development of methodology for carbocycle construction involving intramolecular additions of organolithium centers to pendant alkene² and alkyne³ functions. In connection with our long-standing interest in the utilization of the allene unit as a site for intramolecular reactions in free-radical and organometallic processes,⁴ we have recently examined the chemistry of β -allenyl organolithium reagents 1, generated from the corresponding iodides 2.⁵ Appropriately substituted examples of 1 undergo efficient cyclization upon warming briefly to room temperature to give the cyclobutenylmethyllithium reagents 3 in a transformation remarkable for its unexpected regiochemistry.^{6,7} In this report we extend our studies to related systems in which the reactive functions are separated by longer carbon chains.⁸

$$\xrightarrow{R}_{2} \xrightarrow{R}_{I} \xrightarrow{A \text{ Bull}}_{-78 \text{ °C}} \xrightarrow{-1}_{1} \xrightarrow{R}_{Li} \xrightarrow{\text{room}}_{\text{temp}} \xrightarrow{Li}_{3}$$

The smooth generation⁹ of acyclic γ -allenyl alkyllithium 4a was effected by treatment of iodide 5a with *t*-BuLi at -100 °C as shown by the subsequent introduction of CH₃OD to give allene 6a (E=D) in 97% GC yield with >98% incorporation of deuterium. Alternatively, the addition of benzaldehyde to 4a at -100 °C resulted in a 75% isolated yield of allenic alcohol 6a (E = CHOHPh). Performing the exchange reaction at -100 °C is critical if trapping of acyclic 4a is desired, since treatment of 5a with *t*-BuLi at -78 °C gave an 85% GC yield of a mixture of cyclic hydrocarbons 7a and 8a (E = H) after protonolysis. This result indicates the formation of cyclic organolithium 9a under these conditions.¹⁰ The facility of this cyclization was confirmed by warming a solution of acyclic 4a from -100 °C to -78 °C for 10 min before protonation to produce a 1:1 mixture of acyclic



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and cyclic products. This cyclization is particularly rapid compared to those of the β -allenyl reagents 1 and most related olefinic and acetylenic derivatives.^{2,3}

The availability of cyclic organolithium 9a from a simple acyclic precursor prompted a sampling of its synthetic potential. Thus, reaction of 9a with 5-nonanone occurred with reasonable allylic regioselectivity¹¹ to provide an 88:12 mixture of 7a and 8a (E = COHBu₂) from which 7a was isolated in 56% yield by flash chromatography. Lower regioselectivity was observed for the addition of 9a to benzaldehyde (7a:8a = 2.3:1) and cyclohexanone (7a:8a = 2.6:1). Conversion of 9a to an "ate" complex by reaction with Ti(O-*i*-Pr)4¹² greatly improved this situation, since this modified organometallic reagent gave only regioisomer 7a with both benzaldehyde (70% yield; 3:1 mixture of diastereomers) and cyclohexanone (64% yield).

The dimethyl-substituted allenic iodide 5b was similarly converted by t-BuLi at -78 °C into the acyclic organolithium 4b, which was trapped with benzaldehyde to generate allenic alcohol 6b in 89% yield. Evidently, substituted lithium reagent 4b does not cyclize nearly as readily as the parent 4a. However, warming the solution to room temperature for 30 min before hydrolysis provided a 63:21:16 mixture of cyclic hydrocarbons 7b and 8b and allene 6b (E = H). This indicates that 4b cyclizes in an analogous manner to give allylic organolithium 9b, which is the precursor of 7b and 8b. It is noteworthy that terminal disubstitution in 4b does not prevent cyclization, given that such substitution stops cyclization in the 5-hexenyl and β -allenyl organolithiums. Addition of benzaldehyde to 9b proceeded without regioselectivity to provide a 1:1 mixture of 7b and 8b (E = CHOHPh). The prior conversion of 9b to an organotitanium reagent with Ti(O-i-Pr)4 once again resulted in high regioselectivity, in this case producing 8b (E = CHOHPh) in 82% yield. This mode of reaction is contrary to that found for parent 9a, but it is consistent with the usual attack of carbonyl compounds at the more-substituted end of an allylic organotitanium reagent.¹²

The homologous δ -allenyl iodide 10a was transformed by *t*-BuLi at -78 °C to the corresponding organolithium 11a and the addition of benzaldehyde gave allenic alcohol 12a (E = CHOHPh; 54% yield). Warming 11a to room temperature for 1 hour prior to hydrolysis gave a 27:50:20:3 mixture of allene 13a, vinylcyclopentane 14a, acetylene 15a, and cyclohexene 16a (E = H) in 86% GC yield. In this instance, the portion of the reaction involving cyclization proceeds by formation of the new C-C bond to the near allenic carbon to generate cyclopentylvinyllithium 14a (E = Li) as the major cyclic intermediate, although the small amount of 16a (E = H) observed may well derive from the alternate mode of cyclization. This result is in accord



with the generally established facility for five- over six-ring formation.⁷ Interestingly, the ratio of hydrolysis products from allenic lithium 11a did not change appreciably upon standing at room temperature. This suggests

that all of the 11a had reacted after 1 hour to generate a mixture of vinylcyclopentyllithium 14a (E = Li) and rearranged allenyllithium 17a. Alkyllithiums are well-known to metallate allenes¹³ and intramolecular 1,5proton transfer conveniently forms the internally lithiated allene 17a.¹⁴ Hydrolysis of 17a provides a mixture of 13a and 15a (E = H) thereby accounting for the large amount of allenic hydrocarbon isolated from 11a.

Additional insight into the reactivity of δ -allenyllithium reagents was provided by a study of dimethylsubstituted 11b. Lithium reagent 11b was cleanly generated at -78 °C as usual from iodide 10b as shown by benzaldehyde trapping to give 12b (E = CHOHPh) in 96% yield. Warming a solution of 11b to room temperature for 1 hour before reaction with benzaldehyde resulted in a mixture of allenic alcohol 12b (E = CHOHPh, 58% yield) and acetylenic alcohol 15b (27% yield).¹⁵ The latter obviously comes from rearranged organolithium 17b, which is expected to react in this manner.¹³ The lack of cyclic products suggests that alkyl substitution retards cyclization.

The problem of proton-transfer with 11 could be circumvented by transmetallation to a less reactive organocopper species.¹⁶ Thus, formation of lithium reagent 11a at -78 °C, followed by the addition of 1 equiv of CuCN, and warming to -40 °C formed cuprate 18a. Warming of this solution to 0 °C prior to hydrolysis gave a 96% GC yield of 14a and 12a (E = H) in a 4:1 ratio without observable 15a and 16a. Evidently, organocopper 18a showed suppressed basicity as expected, without curtailing cyclization to 19a. Furthermore, subsequent chemistry can take advantage of the special organocopper reactivity as illustrated by 1,4-addition to cyclohexenone to give ketone 20. The dimethyl-substituted lithium 11b behaves analogously, since formation of the cuprate and warming to 0 °C for 30 min, followed by hydrolysis, produced a 7:1 mixture of vinylcyclopentane 14b and allene 12b (E = H). Cyclic cuprate 19b was trapped by iodine to give vinyl iodide 14b (E = I) in 68% yield. These results bode well for synthetic applications of the cyclization process.



Finally, a brief examination of the ε -allenyl iodide 21 delineated the limits of the cyclization processes. Conversion of 21 to the related organolithium 22, followed by warming to room temperature for 1 h gave a 93:7 mixture of allene 23 and vinylcyclohexane 24. Longer reaction times are not feasible owing to decomposition of the lithium reagent. In this case, reaction of 22 with CuCN to give the simple cuprate or with (CH₃)₂CuCNLi₂¹⁷ to generate a higher-order cuprate was ineffective, since appreciable cyclization ($\leq 1\%$) did not occur at room temperature for 1 hour. Thus, the formation of carbocycles with larger than five-membered rings is not facile with the present methodology.



In conclusion, procedures for the generation of cyclic organometallic reagents from allenic precursors have been developed. Both acyclic allenic and cyclic organometallic intermediates can be reacted with electrophiles to provide derivatized products. This methodology should find useful applications in organic synthesis.

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- 9. A typical cyclization procedure involved the addition of 2.05 equiv of t-BuLi in pentane to an etheral solution of ω-allenyl iodide at -78 °C followed by warming to room temperature for 30 min prior to the addition of an electrophile at -78 °C.¹ In experiments using the initially formed ω-allenyl organolithium reagents, 1.6 equiv of t-BuLi was sufficient for complete conversion of ω-allenyl iodides at -78 °C and contamination with t-BuLi adducts to added electrophiles was minimized.
- 10. Professor J. Normant has kindly informed us of a similar observation in his laboratory by C. Meyer and I. Marek.
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- Deprotonation of monosubstituted allenes occurs at the unsubstituted end in >80%;¹³ thus, the amount of acetylene 14b (E = H) necessarily resulting from lithium reagent 17b is inconsistent with intermolecular deprotonation.
- 15. Compound 15b showed: ¹H NMR δ 7.39-7.30 (m, 5), 4.45 (s, 1), 2.48 (s, 1), 2.22 (t, 2, J = 7 Hz), 1.58-1.34 (m, 4), 1.24 (s, 3), 1.05 (s, 3), 0.93 (t, 3, J = 7 Hz); ¹³C NMR δ 140.2, 127.7 (2), 127.6, 127.5 (2), 84.7 (s), 83.3 (s), 80.5 (d, J = 150 Hz), 38.0 (s), 31.1 (t, J = 130 Hz), 26.8 (q, J = 130 Hz), 24.6 (q, J = 125 Hz), 21.9 (t, J = 130 Hz), 18.4 (t, J = 130 Hz), 13.6 (q, J = 125 Hz); IR 3435 cm⁻¹.
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