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PREPARATION OF FUNCTIONALIZED 2-VINYLCYCLOPROPYLLITHIUM AND COPPER REAGENTS

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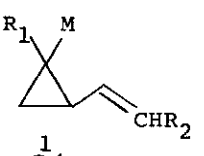
The preparation of functionalized cyclopropanes and vinylcyclopropanes has received considerable attention for mechanistic studies and to a lesser extent for synthetic methodology. The usual synthetic approach of addition of carbenoids to alkenes and dienes works adequately for some simple and symmetrical cyclopropanes, but is inadequate for highly functionalized systems. In connection with our synthetic approach to functionalized hydroazulenes,[1] we have sought more general and convenient methods for preparing functionalized vinylcyclopropanes and divinylcyclopropanes. In this report, we wish to describe convenient procedures for the regiospecific synthesis of substituted 2-vinylcyclopropyllithium[2] (M=Li) and copper (M=Cu) reagents, 1, from readily available 1,1-dibromocyclopropanes.



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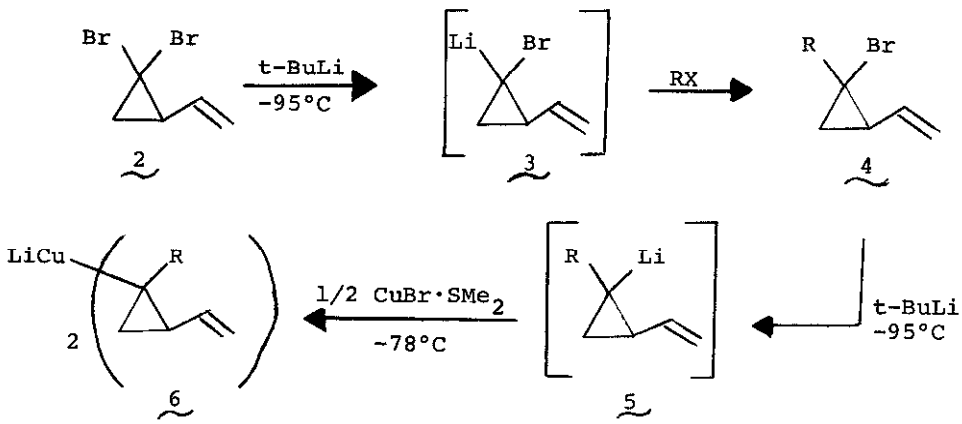
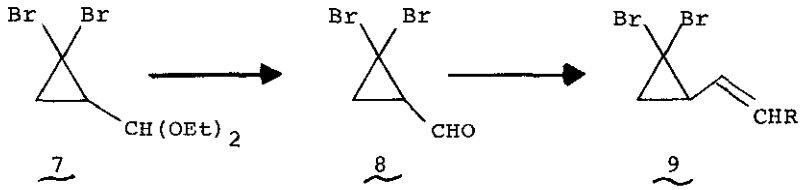
Metallation of 1,1-Dibromo-2-vinylcyclopropane (2). Since the addition of halocarbenes to unsymmetrical dienes usually results in mixtures of regioisomers,[3] we proceeded to introduce cyclopropyl substituents, as in 1 (R_1=alkyl, R_2=H), through alkylations of the 2-vinylcyclopropyllithium reagent, 1 (R_1=R_2=H; M=Li). The recent successes of Nozaki[4] and others[5] in achieving sequential metallations and alkylations in simple cyclopropane systems prompted us to utilize the readily available 1,1-dibromo-2-vinylcyclopropane[6] as a starting material. The presence of two cyclopropylbromine atoms for sequential metallation is a synthetic advantage for the desired substitution of the ring. The

first metallation of dibromide 2 was carried out at -95°C with one equivalent of t-butyllithium in a mixture of THF and ether (2:1). After ten minutes at -95°C, the lithiocyclopropane intermediate 3 could be quenched with anhydrous hydrobromic acid in ether or methyl iodide to produce in high yield[7] the 1-bromo-2-vinylcyclopropane 4 (R=H) or the 1-bromo-1-methyl-2-vinylcyclopropane 4 (R=Me). Treatment of the reaction mixture with a second equivalent of t-butyllithium at -78°C for two hours generated the new cyclopropyllithium reagents 5 (R=H or Me).



The formation of the homocuprate reagent 6 (R=H) was affected at -78°C by adding via syringe the solution of 5 to 0.5 equivalent of a cuprous bromide dimethylsulfide complex.[8] The cuprate reagent 6 appeared as a homogeneous yellow solution at -78°C, and could be used for a variety of conjugate additions to α,β-unsaturated carbonyl compounds.[11] The protonation of intermediate 3 consistently[9] gave a 4:1, trans-cis mixture of 4 (R=H), while the trans-cis mixture of 4 (R=Me) from methylation was between 50:50 and 60:40 for several experiments. Based on previous precedence[4] for the stereospecific metallations of dibromocyclopropanes and cis-1-bromo-2-vinylcyclopropane,[2] further work may yield selectivity in other vinylcyclopropyl halide systems.

Synthesis and Reactions of 2,2-Dibromocyclopropylcarbaldehyde (8). In order to synthesize metallocyclopropanes containing functionalized vinyl groups, we sought a simple precursor which would allow for the introduction of the substituted vinyl unit regiospecifically. The previously unknown 2,2-dibromocyclopropylcarbaldehyde (8) appeared to be such a precursor, if one could affect alkene formation without interfering with the gem-dibromocyclopropane unit. Addition of dibromocarbene to acrolein diethyl acetal yielded the dibromocyclopropane 7, which was smoothly hydrolyzed to the required aldehyde 8 with 10% hydrochloric acid. The reactions of 8 with ethylidene triphenylphosphorane and the lithio carbanion of diethylphenylthiomethyl phosphonate produced the substituted vinylcyclopropanes 9 (a, R=Me, 70% yield) and (b, R=SPh, 70% yield) respectively.[10] Thus, it is possible to regiospecifically construct the dibromovinylcyclopropane system.



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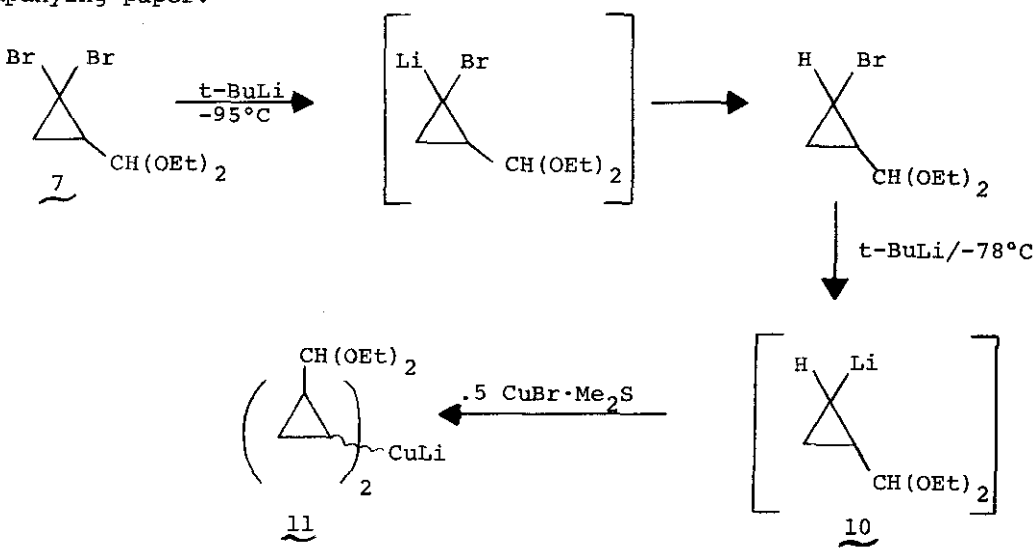
The functionalized vinylcyclopropanes 9a and 9b were efficiently converted to their respective lithio (1, R_1=H, R_2=Me or SPh, M=Li) and cuprate (1, R_1=H, R_2=Me or SPh, M=Cu^I) reagents via the aforementioned experimental sequence. Conjugate addition reactions of the copper reagents and 1,2-carbonyl addition reactions of the lithio reagents are reported in the accompanying paper.[11]

Cyclopropane 7 is also a novel precursor for incorporating a protected cyclopropane carbaldehyde unit. Following a procedure analogous to that for the formation of reagent 3, we were able to sequentially metallate 7, protonate and metallate the monobromocyclopropane to generate the 2-lithiocyclopropane acetal 10 at -78°C. Further, treatment of a solution of 10 with 0.5 equivalents of the cuprous bromide-dimethyl sulfide complex yielded the homocuprate 11. Quenching reactions of 10 and 11 with acid confirmed that the efficiency of generation of these two metallocyclopropanes (>90% yield based on v.p.c. analysis). Several examples of the conjugate additions of 11 will be reported in the accompanying paper.[11]



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References and Footnotes

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2. J. A. Landgrebe and L. W. Becker, J. Org. Chem., 33, 1173 (1968). These workers have prepared the 2-vinylcyclopropyllithium species from the metallation of 1-bromo-2-vinylcyclopropane with i-propyllithium.
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7. All of the experiments described herein were monitored by quenching aliquots of the reaction mixtures with ammonium chloride solutions and subjecting the hydrolysates to v.p.c. analysis. Yields (90-95%) were based on weights of isolated material which was then analyzed by v.p.c. All new compounds gave satisfactory elemental analyses and had spectral data consistent with the assigned structures.
8. The generation of and conjugate addition reactions of lithium dicyclopropylcuprate will be described shortly. J. P. Marino and L. J. Browne, J. Org. Chem., in press.
9. In ten runs, the isomer distribution for 4 (R=H) was found to be 4:1, trans:cis.
10. These are isolated yields (column chromatography) and no attempt was made to maximize the yields. After v.p.c. separation on a 5% SE30, 5' x 1/4", 60/80 Chrom W column of the isomers of 9a, n.m.r. analysis indicated a cis/trans ratio of 4:1. N.m.r. analysis of the 9b vinylcyclopropanes indicated a cis/trans ratio of 3:5.
11. J. P. Marino and L. J. Browne, Tetrahedron Lett., 0000 (1976).