## REACTION OF METHYLENECYCLOPROPYLLITHIUM WITH ELECTROPHILES

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Abstract: Metalation of methylenecyclopropane with n-butyllithium in tetrahydrofuran affords methylenecyclopropyllithium, which reacts with carbonyl electrophiles to produce alcohols in high yields.

Methylenecyclopropane (1), due to its inherent ring strain, has been the subject of many mechanistic investigations.<sup>1</sup> More recently, methylenecyclopropane derivatives have served as key intermediates in synthetic sequences.<sup>2</sup> The preparation of these compounds is often complex and proceeds in low yield, so we felt that an easy and general method for introducing methylenecyclopropane into molecules was warranted. We have shown that the formation of methylenecyclopropyl anion 2 and its addition to carbonyl groups, which are ubiquitous in organic molecules, provides a facile synthesis of methylenecyclopropylcarbinols 3, which have been synthesized by other routes.<sup>3</sup> i)

$$\begin{array}{c} \underset{1}{\overset{}{\overset{}}{\underset{1}}} \xrightarrow{B:-} & \underset{2}{\overset{}{\overset{}}{\underset{2}}} \xrightarrow{P} & + & \underset{R}{\overset{0}{\overset{}}{\underset{R}}} \xrightarrow{R^{1}} \xrightarrow{HO} & \underset{R}{\overset{0}{\underset{R}}} \xrightarrow{R^{1}} \\ \xrightarrow{3} \end{array}$$

For example: R = H;  $R^1 = nC_3H_7$ 

Deprotonation of methylenecyclopropane (1) by strong base may be feasible, as the olefin may stabilize the anion. Russian workers have deprotonated a methylenecyclopropane derivative 4 with n-butyllithium and alkylated the anion with trimethylsilyl chloride in 20% yield.<sup>4</sup> French workers have metalated a substituted methylenecyclopropane molecule 5 by metal halogen exchange and found alkylation occurs solely on the ring.<sup>5</sup> These two examples bode well for the direct metalation of methylenecyclopropane with strong base, followed by alkylation on the ring.



However, in the direct deprotonation of methylenecyclopropane, acidic vinyl protons that are not available in compound  $\underline{4}$  may be extracted. In the experiments of the French workers, substitution on the ring of  $\underline{5}$  may have played an important role as to whether exo or endo alkylation occurs. In the metalation of methylenecyclobutane with tetramethylethylenediamine (TMEDA) and n-butyllithium (nBuLi), which was followed by reaction with an electrophile, Wilson observed exo and endo reaction products.<sup>6</sup>

Methylenecyclopropane was synthesized on a multigram scale according to the method of Köster.<sup>7</sup> Since its boiling point is 10°C, it was convenient to calculate its density (0.85g mL<sup>-1</sup>) and use a precooled syringe to measure the desired amount for reaction.

Initially, metalation of methylenecyclopropane was accomplished by employing conditions similar to those used by Wilson to deprotonate methylenecyclobutane (nBuLi, TMEDA). Other bases such as potassium t-butoxide and potassium hydride were not effective in deprotonating <u>1</u>. In later experiments, we found TMEDA was not necessary for reaction and that nBuLi in THF was sufficient. When ethyl ether was substituted for THF, the rate of deprotonation was significantly reduced.

Experimental conditions for the most favorable method of deprotonation of methylenecyclopropane were as follows: methylenecyclopropane (1.6 eq) was added to a cooled (-10°C) hexane solution of nBuLi (1.0 eq) in THF. The reaction was warmed to 10°C over a one hour period and was kept at 10°C for an additional hour to ensure complete formation of methylenecyclopropyllithium.

In reactions with various electrophiles, the anion was cooled to -10°C and 1.0 eq of the corresponding carbonyl compound, dissolved in THF, was added in one portion. Between 2 and 10 minutes after the carbonyl compound was added, the reaction was quenched with water. Extractive isolation and chromatography on silica gel afforded the alcohol adducts illustrated in Table 1.8

From Table 1 we see that the anion reacts with ketones and a lactone in good to excellent yields. The alcohol in entry 5 is a mixture of endo alcohols, which is expected from steric approach considerations, and the <sup>13</sup>C-NMRs are consistent with the <sup>13</sup>C-NMRs of endo norbornane alcohols.<sup>9</sup> Even cyclopentanone substrates, which are known to enolize easily, afford alcohols in good yields (entries 1 and 6). The steroidal products consisted of two diastereomers, which we assigned as  $\beta$ -alcohols from consideration of the anion attack from the least hindered side. Aldehydes, in contrast to ketones, react with methylenecyclopropyl-lithium in lower yields. This may be due to increased aldol side products with aldehydes. Adducts from benzaldehyde (entry 10) were formed in the same yields as other aldehydes, but were unstable. This instability is most certainly related to the benzylcyclopropylcarbinol.

The remaining adducts are quite stable. For example, the alcohol in entry 2 is stable at room temperature and in the following solvents at room temperature: ethyl acetate, chloroform, and 10% aqueous sodium hydroxide. The compound is also stable after 17 hours in THF at 70°C but is unstable after a few hours in 10% aqueous hydrochloric acid. We hope to exploit this reactivity in forming new compounds.

## Table 1

Reaction of Methylenecyclopropyllithium with Electrophiles



aThe diastereomers could not be separated and characterized separately.  ${}^{\rm b}{
m R}$  atio of isolated diastereomers.

At no time during this research did we isolate or see evidence for reaction of methylenecyclopropyllithium in the exo position with electrophiles. If the exo product was formed, it may have been unstable to the reaction or to isolation conditions. The spectral data for compounds in Table 1 are consistent with endo products (alkylation on the ring)<sup>8</sup> and consistent with spectral data for similar compounds which were prepared by reacting allenic alcohols with Simmons-Smith Reagent.<sup>3</sup> The most characteristic spectral data for this class of compounds is contained in its <sup>13</sup>C-NMR. All compounds in Table 1 exhibit <sup>13</sup>C-NMR spectra similar to the example illustrated below.



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## References and Notes

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