

COMPETITIVE AND PREFERENTIAL REACTIVITY OF LITHIUM DIMETHYLCUPRATE
WITH THE SATURATED CARBONYL OF A CARBOCYCLIC KETO-ENONE

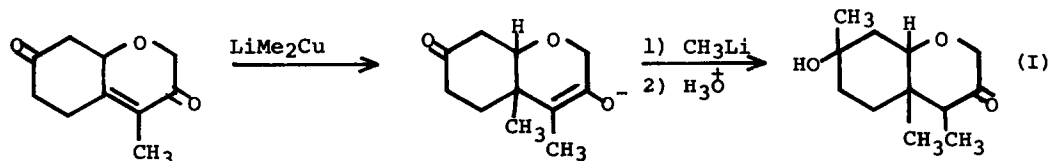
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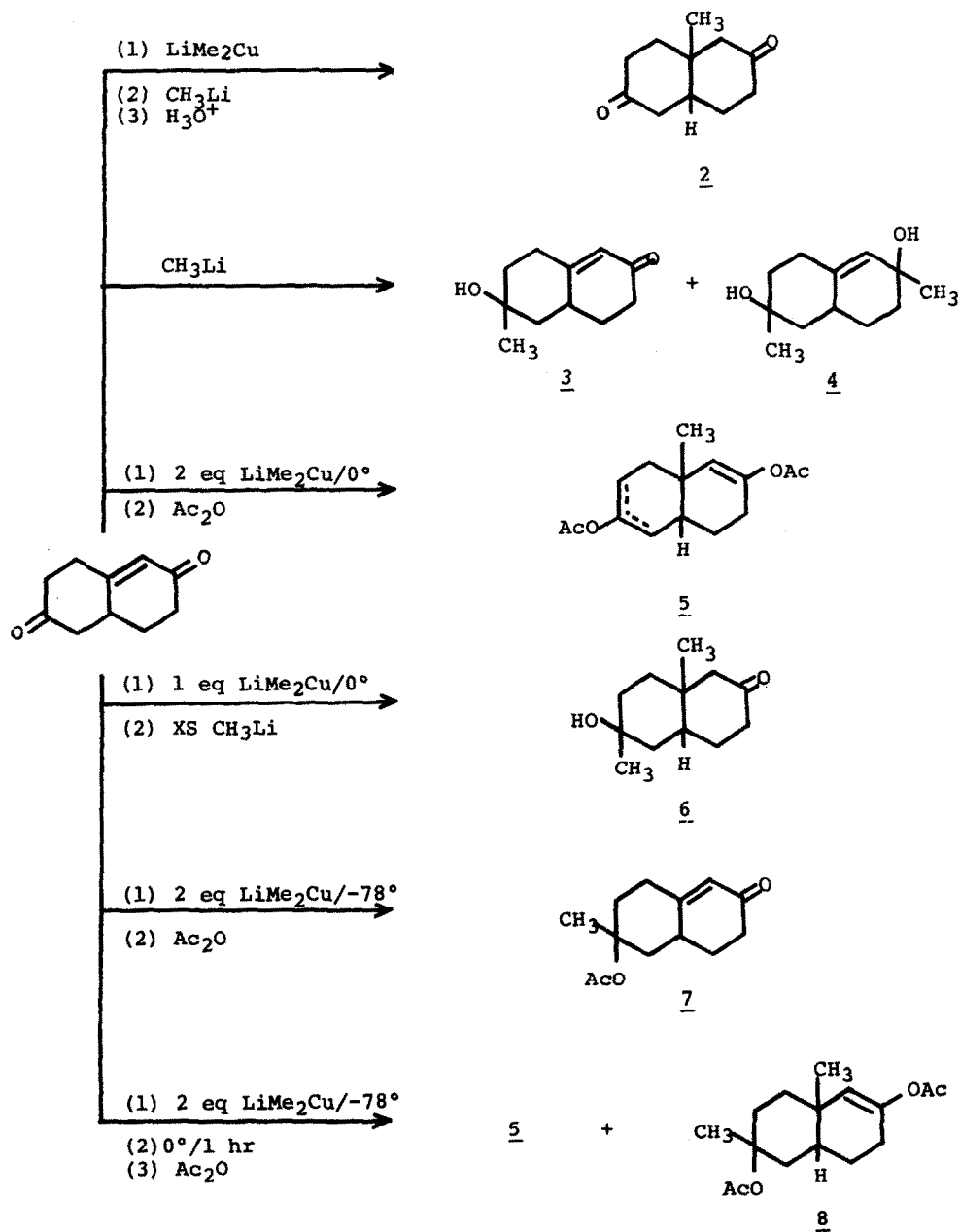
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The conjugate addition of lithium dialkylcuprates to α,β -unsaturated carbonyl compounds is a well established and synthetically valuable process¹. Numerous studies have shown that reagents like lithium dimethylcuprate react overwhelmingly, if not exclusively, at the β -position of unsaturated ketones, and products resulting from 1,2-addition to the carbonyl group are rarely observed. The addition of dialkyl cuprates to saturated ketones, as well as enolization affected by these reagents, has not been extensively investigated. These two processes are generally considered to be slow relative to conjugate addition. For example, methyl isobutyl ketone is only slowly consumed by lithium dimethylcuprate at 0° compared to an unsaturated ketone², and di-n-butyl ketone can be recovered in greater than 85% yield from solutions of dialkylcuprates at temperatures up to -10°C³. Taking advantage of this reactivity difference we recently carried out⁴ the sequential 1,4- and 1,2-organo-metallic additions shown in Equation (I). In this sequence the formation of an





enolate by 1,4-addition protects one carbonyl site against subsequent 1,2-addition. The relative unreactivity of the saturated carbonyl in the first step preserves this keto-group for reaction with methyl lithium.

In an attempt to extend this method to the carbocyclic endione 1⁵ we were surprised to find almost the opposite result. The saturated carbonyl group of 1 reacts either preferentially or competitively with lithium dimethylcuprate compared with the enone group. Compound 1 was treated with two molar equivalents of LiMe_2Cu in ether at 0° for 30 minutes followed by the addition of 8.6 molar equivalents of methyl lithium. Hydrolysis of the reaction mixture led to the isolation of diketone 2 in 42% yield. Repetition of this sequence employing variations in the amount of added methyl lithium did not substantially change the course of the reaction. The lack of 1,2-addition to the saturated carbonyl group of 1 could not be ascribed, however, to some inherent lack of reactivity. Exposure of 1 to methyl lithium alone, at either room temperature or at -78° afforded a complex reaction mixture from which could be isolated, *inter alia*, both 3 and 4: the simple products of addition of methyl lithium to either the saturated keto group or to both ketone functions.

The course of the reaction between LiMe_2Cu and keto-enone 1 became apparent when the following sequence was performed. Exposure of 1 in ether solution first to two molar equivalents of LiMe_2Cu for one hour at 0°C and then to acetic anhydride afforded the bisenol acetate 5 in 84% yield (based on glpc measurement employing dodecane as internal standard). The simple 1,4-addition product, 2 (m.p. $74-75^\circ$), was obtained by treatment of 5 with methyl lithium. Thus enolization of the saturated keto group of 1 occurs with LiMe_2Cu under these conditions. The conjugate addition reaction, however, still appears to be the faster of the two processes. When 1 was treated with only 1 equivalent of LiMe_2Cu followed by excess methyl lithium at 0° ketol 6 could be isolated in 11% yield.

In the hope that the enolization reaction could be largely suppressed at lower temperature we investigated the reactivity of 1 with LiMe_2Cu at -78°C , followed by trapping of the products again with acetic anhydride. Under these

conditions (LiMe_2Cu prepared at 0°C in ether, then cooled to -78°C) the greater part of 1 was recovered unchanged. The principal reaction product, however, was the tertiary acetate 7 (25%, glpc, m.p. $82-82.5^\circ\text{C}$) not the enol acetate of 2. Finally when 1 was allowed to react with a five-fold excess of LiMe_2Cu for 1 hr. at -78°C and then for 1 hr. at 0°C , followed by the addition of acetic anhydride, 8 was obtained in 27% (glpc). The major product, however, was again the bisenol acetate 5.

Recently Posner³ has alluded to the reactivity of cuprate reagents with saturated carbonyl compounds. With the exception of aldehydes, however, this reactivity is considerably less than that of enones. Diketone 1 appears to be the first reported example with which 1,2-addition to a saturated ketone occurs in preference to conjugate addition.

The preference for enolization over 1,2-addition as a function of temperature has been observed with other organometallic reagents^{6,3}.

References

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