

SYNTHESIS OF β,γ -UNSATURATED KETONES. A NOVEL REACTION OF METHYL LITHIUM
WITH β,γ -UNSATURATED CARBOXYLIC ACIDS

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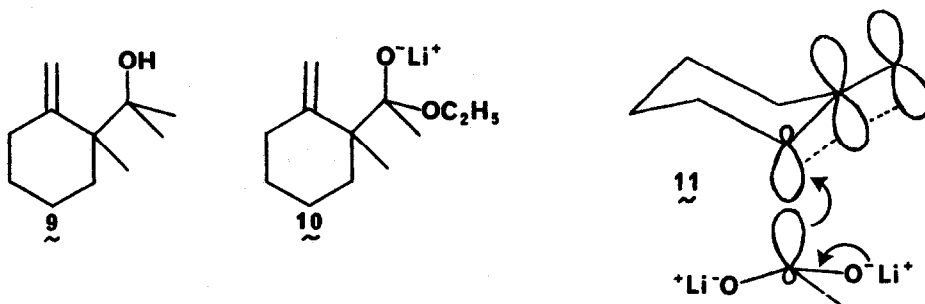
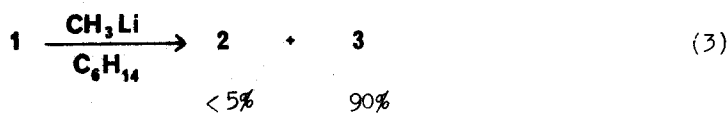
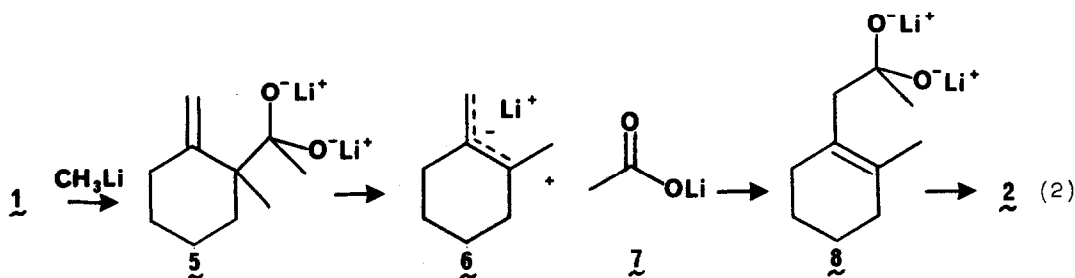
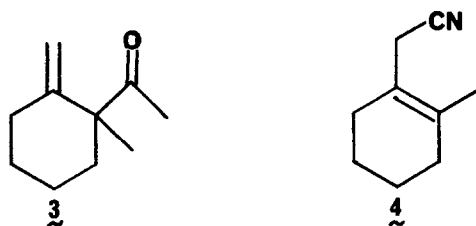
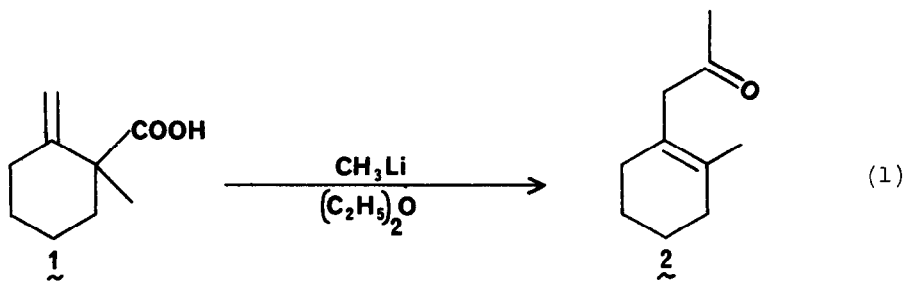
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The reaction of organolithium reagents and carboxylic acids is a popular method for the synthesis of ketones.¹ To date, β,γ -unsaturated acids have led to the expected product.^{2,3} We report the first example of a reaction of an organolithium compound with a β,γ -unsaturated carboxylic acid which leads to a rearranged ketone, and note that this novel rearrangement, if undesired, can be suppressed by proper choice of solvent.

Dropwise addition of two equivalents of methyl lithium to an ethereal solution of 2-methyl-2-carboxymethylenecyclohexane,^{4,5} **1**, at 0°C under nitrogen followed by reflux overnight and workup with either 10% hydrochloric acid or saturated ammonium chloride solution gave a crude reaction mixture shown by glpc to consist of only one product (eqn. 1). The spectral properties of the product,⁵ isolated by glpc,⁶ are in accord with 2-methylcyclohexenylacetone, **2**, rather than the expected product 2-methyl-2-acetylmethylenecyclohexane, **3**. For example, the nmr of **2** has singlets at δ 1.6 and 2.0, but shows no absorption in the region characteristic for exocyclic methylene protons around δ 5.0.⁷ The assigned structure for **2** is further verified by an independent synthesis from the reaction of methyl lithium with 2-methyl-1-cyclohexenyl acetonitrile,⁸ **4**.

The formation of **2** from reaction of **1** with methyl lithium can be rationalized by the mechanism shown in equation 2. Presumably the first equivalent of methyl lithium forms the lithium salt of the acid and the second equivalent adds across the carbonyl to give the dilithio compound,⁹ **5**. Breakdown of **5** then generates the resonance stabilized allyl anion **6** and lithium acetate, **7**. Reaction of the primary end of the allylic anion (or allyl lithium), **6**, with lithium acetate gives the rearranged dilithio compound, **8**, which on workup yields the rearranged ketone, **2**. The following evidence provides support for the proposed mechanism. First, when the reaction is worked up after only three



hours in refluxing ether, 1,2-dimethylcyclohexene,¹⁰ ketone 2 and unreacted acid 1 are the isolated products. This indicates that the allyl anion (or allyl lithium), 6, is an intermediate in the rearrangement of 5 to 8 and argues against a concerted rearrangement. Secondly, treatment of 1 with ethereal methyl lithium (0.6 ml) in n-hexane (5 ml) at 35°C for three hours, gives the normal ketone,⁵ 3, in about 90% yield and less than 5% of the rearranged ketone, 2 (eqn. 3). Thus by simply changing the solvent, the rearrangement can be almost completely suppressed, allowing either the rearranged or the normal ketone to be obtained by the proper choice of solvent. Presumably, the fragmentation of 5 occurs more readily in solvents like ether which are better at solvating the lithium cation.¹¹ Finally, treatment of the ethyl ester of 1 with methyl lithium in ether yields 3 in addition to the tertiary alcohol, 9, indicating that the monolithium salt, 10, does not fragment. Thus the dilithio salt is required for the rearrangement to occur, perhaps because its dianionic character provides an electrostatic driving force for the elimination. There are literature precedents for elimination occurring from dilithio salts when the elimination results in formation of a particularly stable anion.¹²

We are left with the intriguing question of why 1 in ether undergoes rearrangement on treatment with organolithium reagents while other β,γ -unsaturated acids in ether are reported to yield unrearranged ketones.^{2,3} We suggest that the rearrangement is particularly favorable in this case because of two factors. First, the relief of steric crowding in the dilithio salt, 5, should provide some driving force for the fragmentation. Second, and perhaps most important, the dilithio group in 5 will sometimes be axial where it can gain full advantage of the stabilizing effect of the allyl anion resonance as the elimination takes place (see 11). This could lower the transition state energy for the elimination considerably.

In summary, we observe a novel rearrangement upon reaction of 1 with methyl lithium in ether, suggesting that this solvent should be used with caution for reactions of β,γ -unsaturated acids with organolithium reagents. Non polar solvents like hexane, with a small amount of ether added to enhance solubility, may be a better choice of solvent.

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4. Prepared by hydrolysis of the analogous ester which was obtained by reaction of 2-methyl-2-carbethoxycyclohexanone with methylenetriphenylphosphorane.
5. Spectral data: acid 1, nmr (CCl₄) δ0.9-2.5 (11H, complex multiplet with singlet at 1.35), 4.74 (2H, d, J = 4Hz), 13.0 (1H, s); ir (CCl₄) 3100-3300, 1700 and 1645 cm⁻¹; m/e 154 (M⁺), 109 (base). Ketone 2, nmr (CCl₄), δ1.4-2.2 (14H, complex multiplet with singlets at 1.6 and 2.0), 2.98 (2H, s); ir (CCl₄) 1705 and 1670 cm⁻¹; m/e 152 (M⁺), 109 (base). Ketone 3, nmr (CCl₄) δ0.8-2.6 (14H, complex multiplet with singlets at 1.16 and 1.95), 4.92 (2H, d, J = 4Hz); ir (CCl₄) 1700 and 1645 cm⁻¹; m/e 152 (M⁺), 109 (base).
6. A 9' x 1/4" 5% Carbowax 20M on chromosorb W 45/60 column was used.
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8. M-C. Chiang, J. Chinese Chem. Soc., 18, 65 (1951) [C. A. 46, 4471 (1952)].
9. Reference 1, p. 3-5.
10. Identified by comparison with an authentic sample. G. S. Hammond and T. D. Nevitt, J. Amer. Chem. Soc., 76, 4121 (1954).
11. T. E. Hogen-Esch and J. Smid, ibid., 88, 307 (1966).
12. See reference 1, p. 26-28 and references therein.