

METHYLATION OF KINETICALLY GENERATED DIENOLATE ANIONS
DERIVED FROM α,β -UNSATURATED KETONES

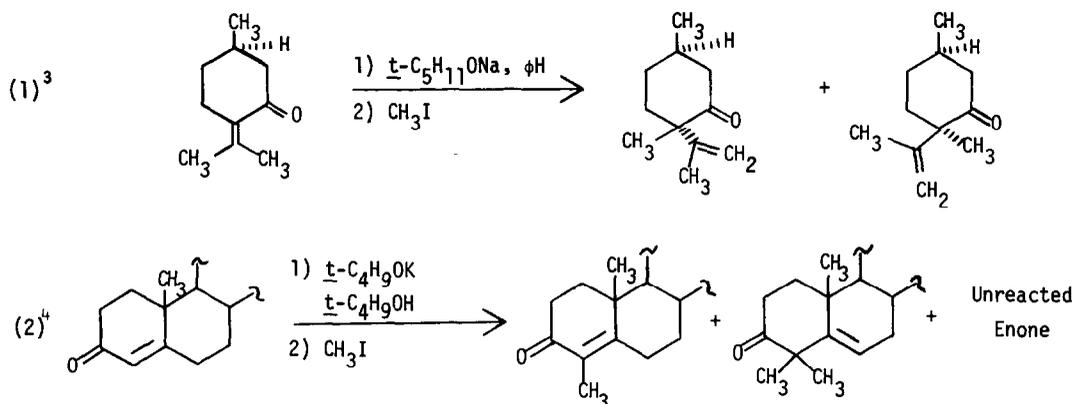
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Alkylation reactions of ketone enolate anions constitute an important, well-established and synthetically useful method of elaborating complex molecules.^{1,2} Selectivity in the alkylation of unsymmetrically substituted ketones may be achieved by the use of activating or blocking groups, or by taking advantage of the fact that kinetic controlled enolate formation generally favors creation of the less substituted enolate anion, while under equilibrating conditions the more highly substituted anion usually predominates.

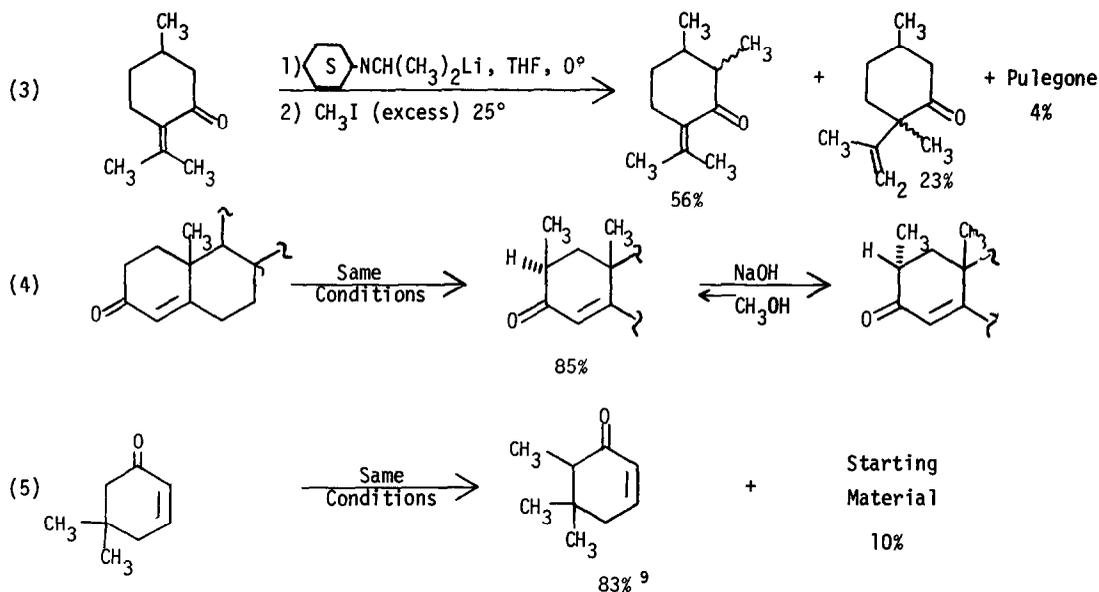
Alkylations of α,β -unsaturated ketones having enolizable gamma-hydrogen atoms proceed almost exclusively at the alpha position, giving α -alkyl- β,γ -unsaturated ketones (eg. equation 1). In many cases this initial product may undergo further alkylation or isomerization to the corresponding α,β -unsaturated ketone (eg. equation 2).



These results, and many others of similar nature, suggest that the dienolate anion formed by abstraction of a γ -proton from an α,β -unsaturated ketone is more stable than its cross-conjugated isomer generated by abstraction of an α' -proton. Surprisingly little work, however,

has been directed to elucidating the nature of the kinetically favored conjugate bases of α,β -unsaturated ketones. Conia and LeCraz describe⁵ an exceptional α' -allylation of 2-allylcyclohex-2-ene-1-one, but the base employed in this work (sodium *tert*-amylate) is not strong enough to effect an irreversible proton transfer. A patent issued to Schering A. B.⁶ reports the 2α -methylation of testosterone using sodium amide in liquid ammonia - the abstract gives no yields. This report contrasts, however, with the work of Newman et al.,⁷ wherein the same base effects cyclobisalkylation of 3-methylcyclohex-2-en-1-one at C-2. An early report of α' -methylation of pulegone,⁸ using sodium amide as a base, appears to be erroneous based on our observation that the major isomer from our synthesis of 2-methylpulegone (see below) is dextrotatory.

We find that lithium 2° -amide bases provide an effective means of generating irreversibly the conjugate bases of α,β -unsaturated ketones. Methylation of the conjugate bases thus derived from pulegone (equation 3), cholest-4-ene-3-one (equation 4) and 5,5-dimethylcyclohex-2-ene-1-one (equation 5) gives the α' -methyl derivatives as the predominate products.



Since tetrahydrofuran (THF) solutions of lithium 2° -amide bases are easily prepared by reacting the corresponding amine with *n*-butyllithium, the procedure described above should have great potential as a synthetic tool.¹⁰

The unsaturated ketone substrates described in the three previous equations differ from one another significantly in several respects, suggesting that the predominate α' -enolate formation observed with this amide base may well be a general rule. Thus, the degree of alkyl substitution at the α' -carbon atom is greater than that of the γ -carbon atoms in pulegone, whereas these positions are equivalently substituted (both are 2°) in cholest-4-ene-3-one. Steric hindrance effects at the α' - and γ -positions in these two cases are clearly different, but should be very similar in 5,5-dimethylcyclohex-2-ene-1-one. The latter compound, unlike pulegone or cholestenone, can only give homoannular dienolate bases.

Our conclusion that the rate of conjugate base formation is greater for α' -proton abstraction than for γ -proton abstraction is supported in the case of pulegone by a study of base catalyzed deuterium exchange at the α' - and γ -positions. Treatment of pulegone with a heavy water solution of sodium deuterioxide gave, after 15 minutes at room temperature, a sample of partially deuterated ketone, which proved to be 5.5% d_1 , 54% d_2 , 28% d_3 , 8% d_4 and 3% d_5 by mass spectrometric analysis. A shift of the base peak from m/e 81 to m/e 82 (identical to the shift observed for a $d_7 + d_8$ pulegone sample prepared by exhaustive isotopic exchange) together with the absence of M-16, M-17 or M-18 fragment ions (the $d_7 + d_8$ sample shows only M-17 and M-18 ions) indicated that the α' -methylene group had experienced rapid and complete proton exchange while the γ -methyl groups were largely unaffected.

Of the substrates studied here pulegone appears to have the most easily equilibrated conjugate bases, since it gave a higher proportion of α -methylation than the other two ketones. Furthermore, the 2-methylpulegone produced by α' -methylation proved to be the equilibrium mixture of diastereoisomers, whereas cholestenone gave exclusively the unstable 2β -methyl isomer, m.p. 110-111°, $[\alpha]_D^{25}$ 33.76° (2.14 g per 100 ml chloroform).

Finally, we wish to report an unexpected and important fact. Although the strong base trityllithium has traditionally served to generate kinetically controlled enolate bases from saturated ketones,¹ it gives predominately the γ -dienolate anions from pulegone and cholestenone. Methylation of the lithium enolates generated by slowly adding these ketones to an excess of trityllithium in THF gave 60-75% α -methylation (or dimethylation in the steroid case) and 5-15% α' -methylation. Addition of isopropylcyclohexylamine prior to the methylation step had no effect. A similar reaction with 5,5-dimethylcyclohex-2-ene-1-one took quite a different course, as described in the accompanying communication.

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