

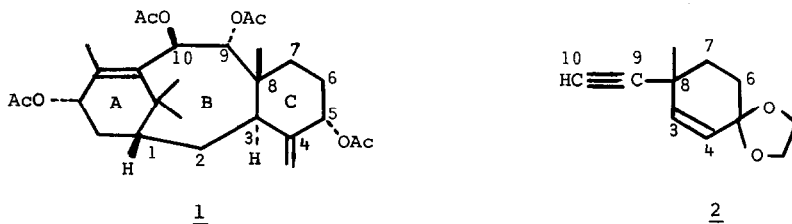
THE DICHLOROVINYLATION OF ENOLATES

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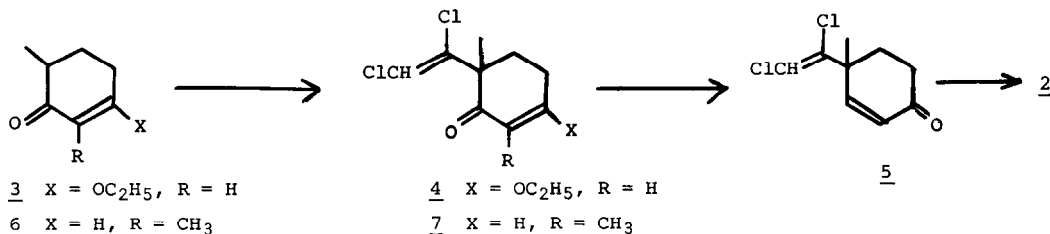
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ABSTRACT: The condensation of certain ketone and ester enolates with trichloroethylene proceeds with surprising ease to yield dichlorovinylated products. The *trans* stereochemistry for one such product is established by X-ray, and subsequent transformations of these initial products to ethynyl or ω -chloroethynyl derivatives is described.

In connection with the total synthesis of taxane diterpenes¹ (cf. taxusin, 1) we required facile access to the monocyclic acetylenic synthon 2 corresponding to the C-ring plus carbons 9 and 10 of the target skeleton. We report in this communication a novel condensation reaction, the dichlorovinylolation of enolates, and demonstrate its utility in the synthesis of certain α - and γ -acetylenic ketone derivatives not readily available by alternative syntheses.

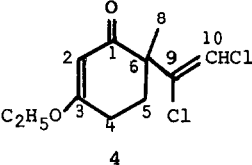
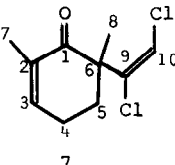
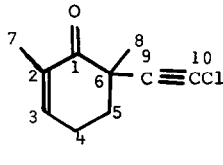
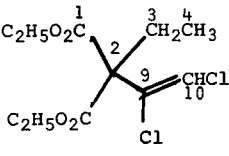


It is generally assumed that direct reactions of enolates with vinyl halides are not practical methods for carbon-carbon bond formation.² We now report an exception to this rule in that trichloroethylene appears to serve as an effective reactant in condensation with conjugated ketone enolates. When the lithium enolate³ derived (1.5 eqt LDA, THF, -78°), from 3-ethoxy-6-methylcyclohex-2-en-1-one (3) was reacted with 1.5 eqts of trichloroethylene (THF, 1.5 eqts HMPA, -78° to rt, 16 hrs) the major product was the dichlorovinyl ketone 4. The yield of 4 was 68-70% after distillation (bp 140-142°, 1 mm), with the bulk of the remainder being unreacted 3. The structure 4 was supported by ¹H nmr [δ 6.20 (1H, s), 5.28 (1H, s), 3.84 (2H, q), 2.6-1.6 (4H, m), 1.40 (3H, s), 1.32 (3H, q)], its ¹³C-nmr (Table I), mass spectrum and elemental analysis. The regiochemistry of the side chain was indicated by the δ 6.20 singlet for the -CCl=CHCl proton, in contrast to the alternative -CH=CCl₂ unit which should give a proton signal near δ 5.8-5.9.⁴



Conversion of dichlorovinyl ketone 4 to the acetylene 2 was readily achieved by reductive transposition of the carbonyl using *i*-Bu₂AlH (2 eqts, 0°, C₆H₆, 75 min) followed by acidic workup to yield the dichlorovinyl enone 5 (bp 79-83°, 0.1 mm) in 92% yield. Ketal formation (ethylene glycol, *p*-TSA, C₆H₆ reflux, 24 hrs) followed by reaction with *n*-butyllithium (2 eqts, -60°, THF, 1 hr) gave the acetylenic ketal 2 in 85% yield. The identity of 2 has been confirmed by ¹H-nmr [δ 5.68 (1H, d, *J* = 10 Hz), 5.44 (1H, d, *J* = 10 Hz), 3.92 (4H, broad s), 2.2-1.6 (4H, m), 2.10 (1H, s), 1.30 (3H, s)], by mass spectrometric and elemental analyses, and by its condensation reactions with ketonic taxane A-ring precursors.⁵

TABLE I - ¹³C-NMR SIGNALS (ppm from TMS) OF REACTION PRODUCTS (in CDCl₃)

	Carbon Atoms									
	1	2	3	4	5	6	7	8	9	10
 <p><u>4</u></p>	197.7	101.8	175.3	32.0	26.2	50.7	-	22.2	137.9	115.0
 <p><u>7</u></p>	198.3	134.7	142.5	34.5	22.9	51.4	16.6	21.8	137.4	114.5
 <p><u>8</u></p>	195.8	133.1	144.8	34.3	21.5 ^a	41.8	16.3	21.3 ^a	60.1 ^b	69.6 ^b
 <p><u>12</u></p>	167.2	63.4	27.8	9.3					131.2	118.1

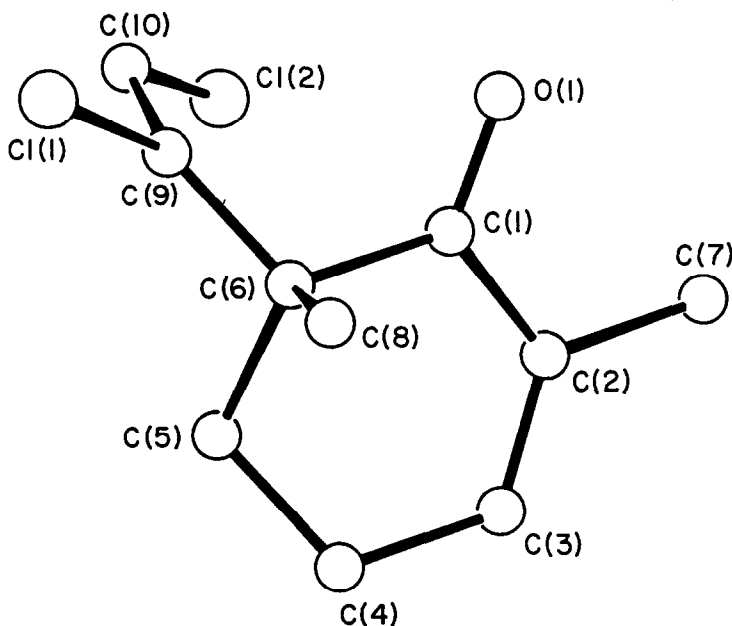
^aThese signal assignments may be inverted. ^bCf. D. D. Traficante and G. E. Maciel, *J. Phys. Chem.*, 69, 1348 (1965).

The scope of our dichlorovinylation reaction has been extended to other conjugated ketones. Thus 2,6-dimethylcyclohex-2-en-1-one (6) can be converted to its C-6 enolate (1.0 eqt of LDA, THF, -78°) which on reaction with trichloroethylene (1.0 eqt, THF, 1.0 eqt HMPA, -78° to rt, 4 hrs) gave in addition to ca. 40% starting material an approximately 50% yield of a crystalline dichlorovinyl enone (7), mp 44-45°. Longer reaction times led to greater conversions of 6 but were accompanied by formation of a secondary product identified by ir, ms, ¹H-nmr and ¹³C-nmr (Table I) as the chloroacetylene 8.

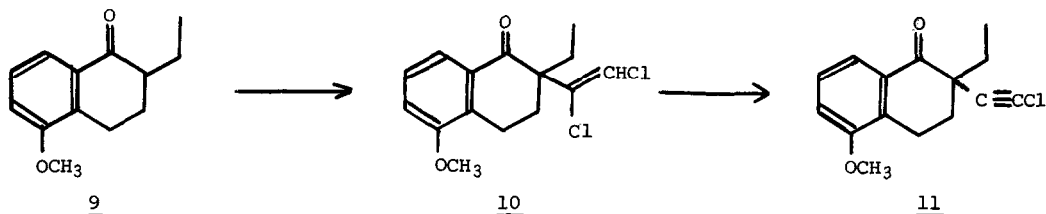
A crystal of the dichloroolefin 7 was placed in a thin-walled capillary to prevent sublimation. Preliminary X-ray photographs revealed orthorhombic symmetry and accurate cell constants, obtained by a least-squares fitting of 15 reflections, were $a = 12.215(4)$, $b = 7.337(2)$ and $c = 11.845(4)$ Å. Systematic extinctions were consistent with space groups $Pca2_1$ or $Pcam$ but since the density (1.37g/cc) required four molecules of $C_{10}H_{12}Cl_2O$ per unit cell and none of the proposed structures could have mirror symmetry, the former space group was chosen. All unique diffraction maxima with $2\theta \leq 114^\circ$ were recorded on a fully automated four circle diffractometer using 1° ω -scans. A total of 927 reflections were measured and after correction for Lorentz, polarization and background effects, 746 (82%) were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$).

A phasing model was achieved by standard heavy atom methods although some difficulty was encountered. Both Cl atoms had $y \sim 1/4$ which was first revealed in the approximately C-centered nature of the diffraction data. This false centering complicated the early electron density syntheses. Eventually all atoms were located and after full-matrix least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens the conventional crystallographic residual is 0.063 for the observed data.^{6,7} Figure 1 is a computer-generated perspective drawing of the final X-ray structure less hydrogens. The regiochemistry proposed has thus been confirmed and the trans dichlorovinyl stereochemistry demonstrated.

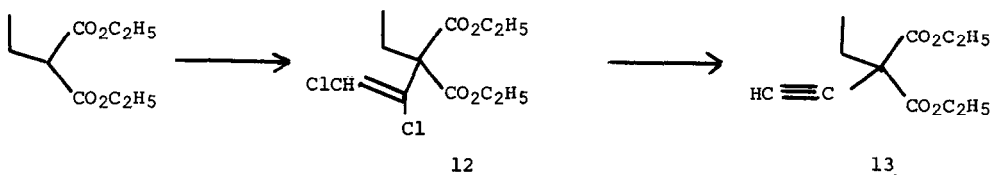
FIGURE 1



The lithium enolate of methoxytetralone⁸ 9 condensed with trichloroethylene to give the expected dichlorovinylation product 10 accompanied by the chloroacetylene by-product 11. Complete conversion of 9 to 11 (44% yield, ir 2210, 1695 cm^{-1} , m/e 262) could be achieved by retreatment of the crude product mixture with LDA (THF, -78 to rt, 9 hrs).



Preliminary studies with the lithium enolates of 2,6-dimethylcyclohexanone, dibenzyl ketone and ethyl isobutyrate have not given the desired dichlorovinylation products. However, the active methylene compound diethyl ethylmalonate has been condensed with trichloroethylene under more vigorous conditions (NaH, THF, HMPA, reflux, 17 hrs) to yield 64% of analytically pure dichlorovinyl derivative 12, (bp 120-122°, 2.5 mm) which could be directly dechlorinated with *t*-butyllithium (2 eqts *t*-BuLi, -78°, THF 90 min) to the ethynyl malonate 13 in 63% yield.⁹ The dichlorovinylation of the sodium derivative of ethyl 2-acetylpropionate has been similarly achieved.



The scope, mechanism and further synthetic utility of related enolate condensations with polyhaloolefins are under investigation in our laboratories.¹⁰

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3. G. Stork and R. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).
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5. C.-F. Yan, unpublished results from these laboratories.
6. All crystallographic calculations were done on a Prime 400 CPU operated by the Materials Science Center and Department of Chemistry, Cornell University. The program package has been described previously (*J. Am. Chem. Soc.*, **100**, 7079, 1978).
7. Tables of fractional coordinates, thermal parameters, bond angles and their errors have been deposited with the Cambridge Crystallographic Data Centre and are also available from JC.
8. Prepared from 5-methoxy-1-tetralone by reaction of its Li enolate with EtI in the presence of triethanolamineborane using the method of M. W. Rathke and A. Lindert, *Synthet. Commun.*, **8**, 9 (1978). (J. A. Rizzi, unpublished observations from these laboratories.)
9. Compound 13 gave the correct mass spectrum and showed ¹H-nmr signals at δ 4.40 (4H, q), 2.56 (1H, s), 2.20 (2H, q), 1.36 (6H, t), 1.08 (3H, t).
10. Partial support of this work through NCI grants CA-18846 and CA-24487 to ASK and JC is gratefully acknowledged. MB acknowledges with thanks a fellowship from CNRS for a research leave from the Inst. de Chim. des Produits Naturelles, Gif-sur-Yvette, France. ASK thanks the Guggenheim Foundation for a Fellowship.

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