Tetrahedron Letters No. 6, pp 405 - 408, 1975. Pergamon Press. Printed in Great Britain.

THE γ-METHYLTHIOCROTONIC ESTER ANION: A VERSATILE BIFUNCTIONAL MICHAEL NUCLEOPHILE

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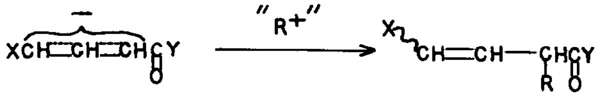
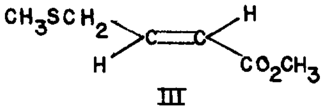
(Received in USA 1 November 1974; received in UK for publication 2 January 1975)

It is well established that the extended enolates (I) derived from α,β-unsaturated carbonyl systems normally undergo alkylation by alkyl halides and Michael acceptors on the carbon atom α- to the carbonyl group.[1] If the nucleophilic enolate contains a heteroatom X on the γ-carbon, the result of such deconjugative alkylation is to generate a new enol derivative (II) equivalent to a latent carbonyl function on the γ-carbon. This function can be unmasked at an appropriate time to participate in subsequent condensation reactions. We wish to illustrate this simple concept by employing the readily accessible methyl γ-methylthiocrotonate[2](III) to achieve facile syntheses of cyclohexenone, acylcyclopentene, γ,δ-unsaturated and triene carboxvlic acids.



I II

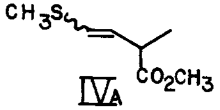
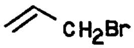
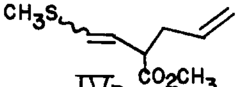
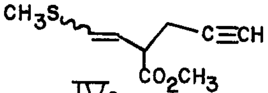
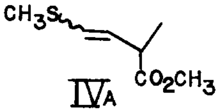
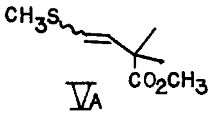
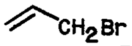
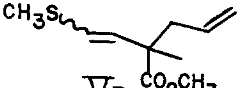
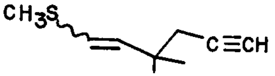


III

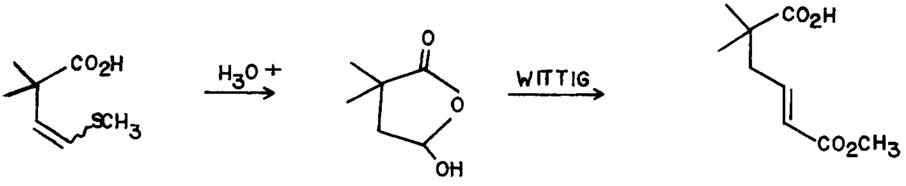
Lithium diisopropylamide (LDA) in tetrahydrofuran (-78°) for 30 minutes converts ester III into an enolate which reacts smoothly at -78° with methyl iodide in the presence of hexamethylphosphoramide (HMPA) to give 92% of the alkylation product IVa [bp 2 mm., 58°; 1:1 cis/trans;[3] nmr in $CDCl_3$, 1.23 δ (3H, d, J = 6 Hz), 2.22 δ (3H, s), 3.30 δ (1H, m), 3.64 δ (3H, s), 5.50 δ (1H, m), 6.0 δ (1H, m)]. A second methyl substituent can be introduced at the α-carbon of IVa in 96% yield. Table I lists alkylation products and yields derived from ester III.

Direct hydrolysis of the enol thioether function in esters of type IV or V proved unexpectedly refractory using a variety of reagents.[4] However, saponification of Va ($Ba(OH)_2$ soln, r.t., 24 hrs) gives the free acid Vd (85% yd) which now can be hydrolyzed in 1:1 HCl-acetic acid (90 , 1 hr) to yield 67% of the hemiacylal VI[5] (mp 60°, 2,4-DNP, mp 107°; ir, 3400 and 1765 cm^{-1}). The masked

TABLE I. ALKYLATION PRODUCTS FROM ESTERS III AND IVa

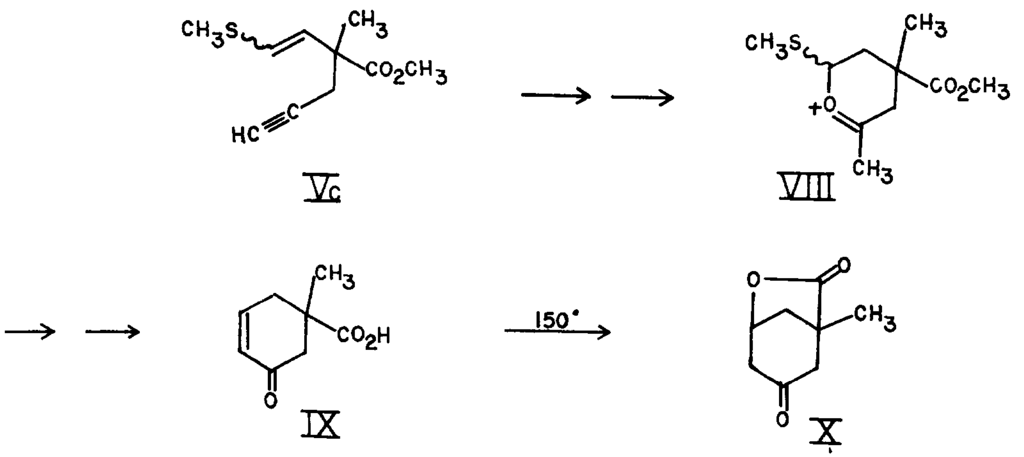
Starting Ester	R-X	Conditions	Product	Yield
 III	CH_3I	-78°, 12hrs.	 IVA	92%
"		"	 IVB	63%
"	$HC\equiv CCH_2Br$	"	 IVC	65%
 IVA	CH_3I	-78°, 12 hrs.	 VA	95%
"		-35°, 9 hrs.	 VB	80%
"	$HC\equiv CCH_2Br$	-78°, 12 hrs.	 VC	49%

aldehyde of VI undergoes normal Wittig condensation with carbethoxymethylenetriphenylphosphorane to produce the unsaturated ester acid VII in 62% yield [nmr, δ 1.25 (6H, s), δ 1.30 (3H, t, J = 8 Hz), δ 2.50 (2H, d, J = 8 Hz), δ 4.23 (2H, q, J = 8 Hz), δ 5.90 (1H, d, J = 18 Hz) δ 6.90 (1H, m), δ 10.8 (1H, exch.)].



VD VI VII

A synthetically valuable consequence of these alkylations is suggested by the reaction of ester Vc with 1:1 HCl-acetic acid which leads in 1 hr at reflux to 93% of a single $C_8H_{10}O_3$ keto acid identified as cyclohexenone IX based on spectra [nmr δ 1.30 (3H, s), δ 2.0-3.0 (4H, m), δ 5.98 (1H, m), δ 6.90 (1H, m), δ 10.8 (1H, exch.); ir, 3010, 1710 and 1670 cm; uv, λ_{max} 224 nm, ε = 9400 (MeOH)] and its quantitative conversion to lactone X (mp 110°, ir 1780, 1720 cm^{-1}) on sublimation at 150°. Since the alkyne bond of propargylmalonic ester is completely hydrated under these conditions[6] an intermediate such as VIII may be involved in the generation of IX.



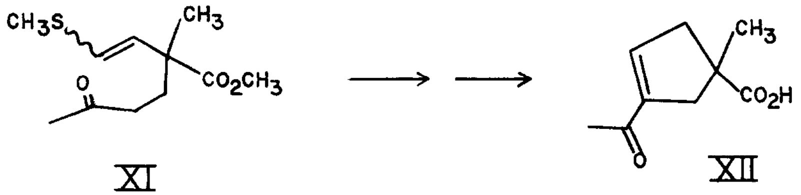
Vc

VIII

IX

X

Ester IVa undergoes Michael addition to methyl vinyl ketone (LDA, -78° in THF, 0.2 eqts. HMPA) to produce adduct XI (1:1 cis and trans). Mild hydrolysis with concomitant cyclization yields the acylcyclopentene acid XII in 55% yield [ir, 1655 and 1630 cm^{-1}; uv λ234 nm, ε = 7500 (MeOH); nmr, δ 1.4 (3H, 3), δ 2.3 (3H, s), δ 6.6 (1H, s); 2,4-DNP, mp 207-210° dec.].

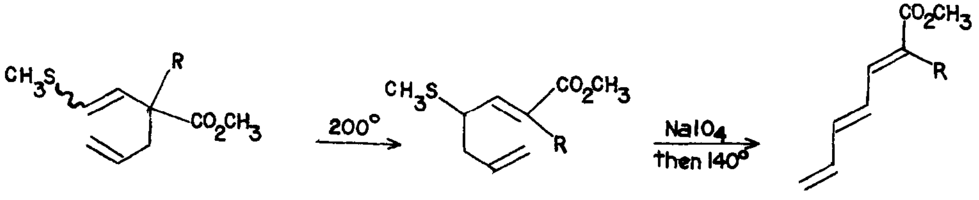


XI

XII

Of further synthetic utility is the stereoselective conversion of the allyl derivatives IVb and Vb into the sensitive linear trienes XIV. Thermolysis of the ester at 200° for 8 hrs produced in 42 and 70% yields, respectively, the

Cope products XIIIa and XIIIb having exclusively the E-configuration shown. The corresponding sulfoxides (from $NaIO_4$, H_2O, 0°, 6 hrs) underwent smooth elimination of CH_3SOH at 140° to give as major products the corresponding trienes XIVa and XIVb.



IVb R=H

Vb R=CH_3

XIIIa R=H

XIIIb R=CH_3

XIVa R=H

XIVb R=CH_3

The scope of these versatile transformations remains under investigation.

Acknowledgment. A.S.K. is grateful to Professors W. Oppolzer and K. Schaffner for valuable discussions and kind hospitality during his stay at the Univ. de Genève (1974). Partial support of this research by grant CA-11326 of the National Cancer Institute, USPHS, is acknowledged with thanks.

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2. L. Birkofer and I. Hartwig, Chem. Ber., 87, 1189 (1954).

3. All new compounds gave satisfactory combustion or mass spectrometric analyses and ir spectra consistent with the assigned structures. The stereochemistry of the double bond in the alkylation products was clearly indicated by the trans and cis couplings in the nmr. For cis IVa δ_{H-4} 6.01, d (J = 10 Hz), δ_{H-3} 5.56, t (J = 8, 10 Hz) trans IVa δ_{H-4} 6.09, d (J = 16 Hz) δ_{H-3} 5.38, q (J = 16, 8 Hz). The pure stereoisomers are separable by glc on 8' x 1/4" column (SE 30 on Chromosorb W) at 100°.

4. E.g., J. Weiland and J. Arens, Rec. Trav. Chim., 79, 1293 (1960); B. Kapin and A. Petrov, Zh. Org. Khim., 3, 975 (1957); T. Mukaiyama, S. Fukuyama and T. Kamamoto, Tetrahedron Lett., 3787 (1968); E. J. Corey and J. Shulman J. Org. Chem., 35, 777 (1970); E. J. Corey and D. Crouse, ibid., 33, 298 (1968).

5. H. des Abbayes, Bull. Soc. Chim. France, 3667 (1970).

6. Unpublished observations by S. J. Lee.

7. The chemical shifts of C-3 hydrogen in XIIIa and XIIIb, δ6.71 and δ6.50, respectively, demonstrate a cis relation between the hydrogen and the de-shielding CO_2R group (C. Pascual, J. Meier and W. Simon, Helv. Chim. Acta, 49, 164 (1966).