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VINYLOGOUS THIOESTER CHEMISTRY: THE TOTAL SYNTHESIS OF DESMETHYL-β-CYPERONE

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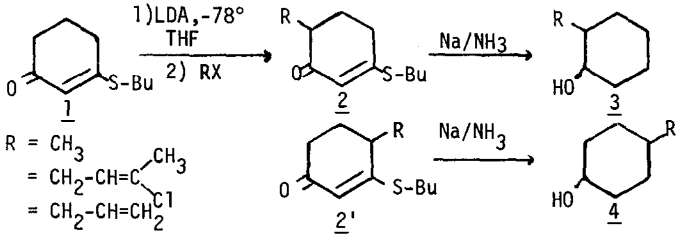
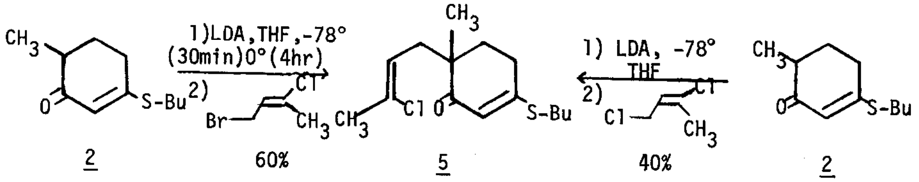
Recent interest in this lab and others concerning the direction and mode of alkylation using complex carbanions derived from enaminoketones[1] and enol ethers of β-diketones[2] has lead us to study the chemistry of vinylogous thioester 1.

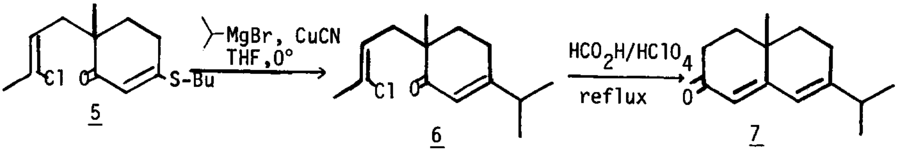


We have found that treatment of 1 with lithium diisopropylamide (LDA, 1.1 eq. in THF, -78°, for 0.5 hr and -20° for 2 hr) followed by addition of various alkyl halides (RX) results in α'-alkylation affording 6-alkyl-3-thiobutyl-2-cyclohexene-1-ones (2 and not 2') in good yield. Attempts to substitute NaH for LDA in a variety of solvents (DMF, DME, Et_2O) lead to lower and inconsistent yields.

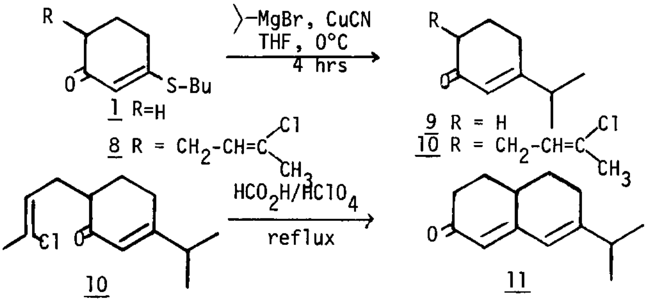
The site of alkylation in 1 was apparent from (a) the presence of the α-vinyl proton in 2 (R, variable), (b) the fact that unsymmetrical alcohols 3 (and not alcohols 4) were formed from the Na/NH_3-reduction of 2, $R=CH_3$ and from (c) comparison of reduction product 3 (^1H, ^{13}C, and glc) with authentic alcohols 3 and 4. Similarly alkylation of 2 ($R=CH_3$) with 1,3-dichloro-2-butene (LDA, THF, -78°) yielded 5 from a second α'-alkylation but in only 40% yield.[2] However, the enolate of 2 ($R=CH_3$) [2 eq LDA, in THF, -78° for 0.5 hrs. and 0° for 4 hrs.] with 1-bromo-3-chloro-2-butene afforded 5 in 60% isolated yield [ir ($CHCl_3$) 1660, 1580 cm^{-1}; $\delta^{TMS}_{CDCl_3}$ 5.78, (s, 1H, vinyl), 5.45 (t, 1H, J = 6Hz, vinyl), 2.78 (t, 2H, J = 6Hz, γ - CH_2-), 2.47 (m, 2H, -S-CH_2-), 2.08 (s, 3H, vinyl methyl), 1.20-2.00 (m, 6H, aliphatic), 1.12 (s, 3H, α'-methyl), 0.95 (t, 3H, J = 6Hz, -CH_2-$\underline{CH_3}$); m/e 286].



The synthetic potential of this alkylation should be viewed in relation to the reactions that the vinylogous thioester functional group undergoes[3,4,5] and the convenient high yield synthesis of desmethyl-β-cyperone 7 completed as follows:

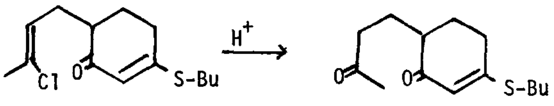


Thioester 5, prepared from 1 in two steps [1 to 2, R-CH$_3$, 60%, then 2 to 5, 60%] was converted to unsaturated ketone 6 by the copper cyanide catalyzed 1,4-addition of isopropylmagnesium bromide [97%, λ_{max}^{EtOH} 235 nm; ir (CHCl$_3$) 1680, 1640 cm^{-1}; $\delta_{CDCl_3}^{TMS}$ 5.80 (s, 1H, vinyl) 5.45 (t, 1H, J = 6Hz, vinyl), 1.11 (d, 6H, J = 6Hz, $-\!\!<^{CH_3}_{CH_3}$), 1.09 (s, 3H, α-methyl); m/e 240]. We had previously found that CuCN-catalyzed additions (>-MgBr) to 1 and 8 afforded 9 [86%, λ_{max}^{EtOH} 235 nm; ir (CHCl$_3$) 1680, 1620, cm^{-1}; $\delta_{CDCl_3}^{TMS}$ 5.92 (s, 1H, vinyl), 1.17 (d, 6H, J = 6Hz, $-\!\!<^{CH_3}_{CH_3}$)] and 10 [85%, λ_{max}^{EtOH} 235 nm; ir (CHCl$_3$) 1680, 1640 cm^{-1}; $\delta_{CDCl_3}^{TMS}$ 5.89 (s, 1H, vinyl), 1.15 (d, 6H, $-\!\!<^{CH_3}_{CH_3}$); m/e 226] respectively, complimenting the work of Posner and Mukaiyama.[5] Clearly copper-1,4-Grignard additions are compatible with the vinyl chloride group which is not always the case with lithium dialkyl cuprates.[6]



The eudesmane or desmethyl-β-cyperone (7) skeleton becomes accessible by ring closure of 6. Both 6 and the analogous model system 10 when treated with $HCO_2H/HClO_4$[7] (9:1, v/v, reflux two hours) undergo concommitant vinyl chloride hydrolysis and cyclodehydration to 7 [78%, λ_{max}^{EtOH} 295 nm; ir ($CHCl_3$) 1660, 1610, 1590 cm^{-1}; $\delta_{CDCl_3}^{TMS}$ 6.00 (s, 1H, vinyl), 5.70 (s, 1H, vinyl), 1.19-1.27 (m, 9H, α'-methyl and $-\!\!<^{CH_3}_{CH_3}$); m/e 204; Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.80; found C, 82.10; H, 9.70] and 11, respectively [71%, λ_{max}^{EtOH} 295 nm; ir ($CHCl_3$) 1660, 1610, 1590 cm^{-1}; $\delta_{CDCl_3}^{TMS}$ 6.05 (s, 1H, vinyl) 5.78 (s, 1H, vinyl), 1.11 (d, 6H, J = 6Hz, $-\!\!<^{CH_3}_{CH_3}$); m/e 190].

It is interesting to note that treating 8 with concentrated H_2SO_4 or $HCO_2H/HClO_4$ (9:1, v/v) yielded 12 as the only product, thus the conjugated thioenol ether is resistant to not only simple acid hydrolysis but also acid catalyzed cyclodehydration in the direction of 13.



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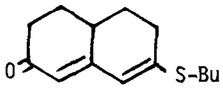

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The cyperone system has been a key feature of several synthetic investigations.[8] Therefore, the conversion of thioester 1 to analytically pure desmethyl-β-cyperone (7) in slightly less than 30% yield illustrates the utility of vinylogous thioesters for (1) regiospecific α'-alkylations, (2) ring annelations and (3) the introduction of variety of substituents[3,4,5] when pursuing carbocyclic synthesis. Other aspects of this sulfur chemistry and its applications to more complex natural product will be forthcoming.

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