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THE PREPARATION AND REACTIONS OF DIENOL ETHER AND DIENOL ESTER DERIVATIVES OF HAGEMANN'S ESTER AND ITS t-BUTYL ANALOGUE

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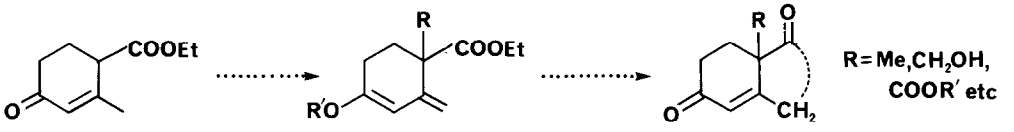
Summary: The efficient conversion of Hagemann's ester and its t-butyl analogue into dienol ethers and dienol esters, and reactions of the derived dienolates with electrophiles is described.

Hagemann's ester-ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate $\underset{\sim}{1}$[1,2] - undergoes alkylation under equilibrating conditions at C-1 and C-3.[3,4] The products of alkylation at C-3 upon hydrolysis and decarboxylation are converted into 3-methyl-2-alkylcyclohex-2-en-1-ones, which are otherwise not readily available.[4,5] It has been largely in the rôle of a convenient, although not necessarily efficient source of such compounds that Hagemann's ester has been widely used in the synthesis of natural products.[6] The ester has also been used in several syntheses wherein the ethoxycarbonyl group has been incorporated either as such,[7] or in modified form[8-10] into the final products. Our own interest in this compound stems from the realization that, by suitable protection of the carbonyl group coupled with the placement of a double bond between the ester and C-2 methyl groups, functionalization of the latter group is, in principle, a relatively simple transformation. Most obviously, this would be effected by means of its deprotonation with a strong base followed by treatment of the resulting ester dienolate with an electrophile. The transformation would then enable Hagemann's ester to serve as a precursor of bicyclic enones bearing angular substituents at a variety of oxidation levels, as indicated schematically below:-



The well-known acetal $\underset{\sim}{3}$,[7-9] however, is unsuitable, as it undergoes both endocyclic and exocyclic deprotonation.[11] Furthermore, the use of the acetal group cannot permit the effective utilization of the carbonyl group in terms of a latent enolate, once the initial transformation involving the ester and methyl groups has been carried out. We have, therefore, turned to the preparation and reactions of dienol ether and dienol ester derivatives of Hagemann's ester $\underset{\sim}{1}$ and its t-butyl analogue $\underset{\sim}{2}$.[2]

These were very easily and efficiently prepared. Thus, the ethyl dienol ether $\underset{\sim}{4}$ was obtained, routinely, in 90% yield by treatment of the ester $\underset{\sim}{1}$ with two equivalents each of diethylsulfate and sodium hydride in DMSO at room temperature.[12,13] With diisopropyl sulfate, the isopropyl ethers $\underset{\sim}{5}$ (81%) and $\underset{\sim}{6}$[14] (86%) were obtained. Treatment of the esters $\underset{\sim}{1}$ and $\underset{\sim}{2}$ with two equivalents of pivaloyl chloride and 2.5 equivalents of 4-(N,N-dimethylamino)pyridine, or more economically,

N,N,N',N'-tetramethylethylenediamine (TMEDA) in THF at room temperature gave the corresponding dienol pivalates 7 (92%) and 8 (95%).[15,16] A dienol benzoate (72%) was also prepared in similar fashion from the ester 1 and benzoyl chloride.

The orange-red ester dienolates derived from the dienol ethers 4 and 6, and dienol esters 7 and 8, and lithium diisopropylamide in THF at -78° are highly nucleophilic. They reacted rapidly with a variety of electrophiles to give products resulting from attack at C-1, α- to the ethoxycarbonyl and t-butoxycarbonyl groups, as set out in the Table.[17] With the exception of those reactions involving formaldehyde and methyl chloroformate, crude reaction products were obtained in excellent yields, and have in general been used as such for subsequent transformations.[17] Reaction of the dienolate from 4 with sulfur electrophiles provided a simple means of introducing a heteroatom into the C-2 methyl group. Thus, treatment of the dienolate in diethyl ether with either N-(phenylthio)succinimide or diphenyl disulfide at -78° followed by quenching and workup of reaction mixtures in the dark at 0° gave the α-(phenylsulfenyl) ester 9 (70-90%). This, upon exposure to laboratory lighting was quantitatively converted by virtue of a [1,3] shift of the phenylthio group[18] into the γ-product 10. On the other hand, we were unable to intercept products of α-attack in reactions of this dienolate with each of tetramethylthiuram disulfide and benzenesulfonyl fluoride,[19] which gave the γ-dithiocarbamate 11 (75%) and γ-sulfone 12 (20%).[20]

Thus, functionalization of the C-2 methyl is easily achieved. As well as providing access, by virtue of mild acid hydrolysis, to a variety of Hagemann's ester derivatives substituted exclusively at C-1, these products, in certain cases, are able to be converted into bicyclic compounds, as shall be described in due course.[21]

References and Notes

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(4) Amupitan, J.A.; Huq, E.; Mellor, M.; Scovell, E.G.; Sutherland, J.K. J. Chem. Soc., Perkin Trans.1 1983, 747.

(5) For alternative preparations, see ref. 4, and Hook, J.M.; Mander, L.N.; Woolias, M. Tetrahedron Lett. 1982, 23, 1095.

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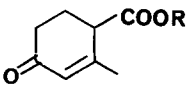
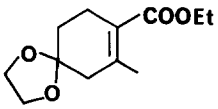
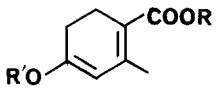


1 R=Et
2 R=*t*-Bu

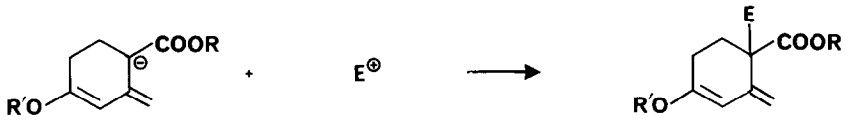


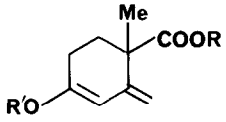
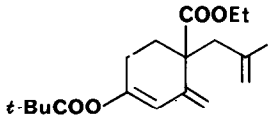
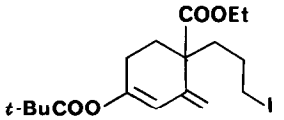
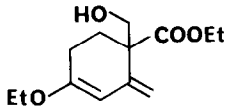
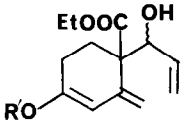
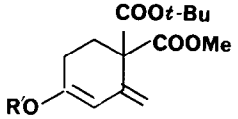
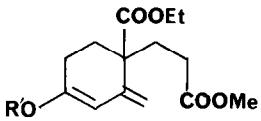
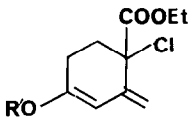
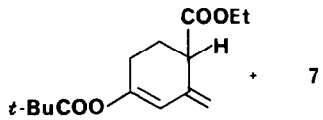
3

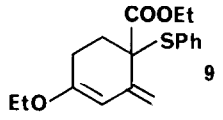


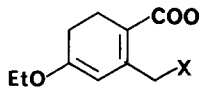
4 R,R′=Et
5 R=Et,R′=*i*-Pr
6 R=*t*-Bu,R′=*i*-Pr
7 R=Et,R′=*t*-BuCO
8 R=*t*-Bu R′=*t*-BuCO

TABLE. REACTION OF ESTER DIENOLATES WITH ELECTROPHILES.[17]



E	MeI	$CH_2=C(CH_3)CH_2I$	$I(CH_2)_3I$
	 R,R′=Et ;(95) R=*t*-Bu,R′=*i*-Pr; 93 R=Et,R′=*t*-BuCO ; 80(100)	 81	 72
E	CH_2O	$CH_2=CHCHO$	ClCOOMe
	 51	 R′=Et; 54(100) R′=*t*-BuCO; 68(100)	 R′=*i*-Pr; 57 R′=*t*-BuCO; 56
E	$CH_2=CHCOOMe$	TsCl	H_2O
	 R′=Et; 65(100) R′=*t*-BuCO; 70(100)	 R′=Et;(100) R′=*t*-BuCO;(100)	 50 + 7 37





10 X=SPh
11 X=SCSNMe$_2$
12 X=SO$_2$Ph

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(12) The methyl analogue of 4 has been prepared in 50% yield, from 1 and dimethyl sulfate in refluxing acetone over K_2CO_3.[11] In the presence of diethyl sulfate under otherwise identical conditions yields of 4 are less than 20%.

(13) A reaction conducted on a 0.12 molar scale was complete within 3 h at 20°, and quantitatively yielded a product mixture, GC analysis of which indicated that less than 8% of C-alkylated products were present therein. The dienol ether 4 was obtained by distillation of the product mixture at 103°/0.02mm. Pure samples were obtained by cooling distillates to 0°, whereupon the bulk of the enol ether crystallised as fine needles, of m.p. ∿ 8°. 4: ^{1}H NMR δ 1.28(t, J = 7 Hz, OCH_2CH_3), 1.34(t, J = 7 Hz, $COOCH_2CH_3$), 2.12-2.74(m, 2 x H-5, 2 x H-6), 2.21(s, 2-CH_3), 3.89(q, J = 7 Hz, OCH_2CH_3) 4.20(q, J = 7 Hz, $COOCH_2CH_3$), 4.96(s, H-3).

(14) 6: b.p. 90°/0.1mm. ^{1}H NMR δ 1.28[d, J = 6.1 Hz, $OCH(CH_3)_2$], 1.50(s, t-C_4H_9), 2.07-2.68 (m, 2 x H-5, 2 x H-6), 2.17(t, J = 1.5 Hz, 2-CH_3), 4.42[sept., J = 6.1 Hz $OCH(CH_3)_2$], 4.92(s, H-3).

(15) Pyridine and triethylamine are unsatisfactory. A reaction conducted on a 0.12 molar scale with respect to 1 was complete after 48 h.

(16) 7: b.p. 120-122°/0.05mm. ^{1}H NMR δ 1.23(s, t-C_4H_9), 1.28(t, J = 7 Hz, CH_2CH_3), 2.14 (m, J < 1.5 Hz, 2-CH_3), 1.9-2.8(m, 2 x H-5, 2 x H-6), 4.09(q, J = 7 Hz, CH_2CH_3), 5.33 (m, J < 1.5 Hz, H-3). 8: b.p. 158-160°/0.1mm. ^{1}H NMR δ 1.26(s, t-C_4H_9), 1.50(s, t-C_4H_9), 2.12(t, J = 1.6 Hz, 2-CH_3), 2.18-2.68(m, 2 x H-5, 2 x H-6), 5.63(t, J ≅ 1 Hz, H-3).

(17) Reactions were conducted on a 3-6 mmol scale in THF containing LDA (1.2 equiv) at -78°. After 5-10 min, the electrophile (1.1 equiv) was added. In general reaction mixtures were quenched after 20 min at this temperature. All products, with the exception of the labile α-chloro esters have been fully characterized. Because of the acid-sensitive nature of the enol function, purification by flash chromatography does result in some loss of material. Yields are quoted for products so purified; yields in parenthesis refer to crude products.

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(19) Hirsch, E.; Hünig, S.; Reissig, H-U. Chem. Ber. 1982, 115, 3687.

(20) 12 was also obtained in 70% yield by oxidation (m-chloroperbenzoic acid, ether K_2CO_3,0°) of sulfide 10.

(21) This work has been carried out by MVB, CG, AEH, GJL, GVS and H-LY as pregraduate students.

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