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REGIOSELECTIVITY IN REACTION OF A DIENOLATE WITH ELECTROPHILES

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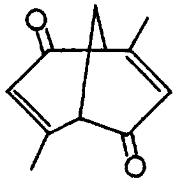
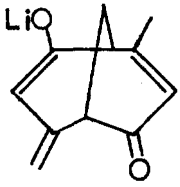
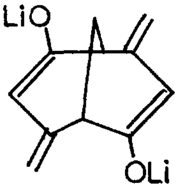
Preferential γ-alkylation of dienolates derived from αβ-unsaturated ketones is a sorely needed process'[1]. Typically with alkyl halides α-alkylation[2] is observed, although exceptions are known of γ-alkylation[3] with β-dialkylamino-αβ-unsaturated ketones, and the γ-alkylation[4] of copper enolates of αβ-unsaturated esters is well established. Indirect γ-alkylations have been achieved using bromomalonate intermediates[5], by alkylation of anions[6] derived from unsaturated nitro compounds and by carbenoid addition[7] to dienols. A recent report[1] describes the first general γ-alkylation procedure using γ-arylsulfonyl substituted αβ-unsaturated ketones. The γ-alkylation of dienolates of such ketones is efficient, but the γ-sulfonyl group is introduced in unstated yield by halogenation of the αβ-unsaturated ketone with N-bromosuccinimide followed by a displacement with sodium benzenesulfinate. The ease of removal of a γ-arylsulfonyl substituent emphasises the importance of such γ-substituted αβ-unsaturated ketones as intermediates permitting regioselective alkylation. An attractive entry to αβ-unsaturated ketones with a γ-sulfur substituent would be by reaction of an arylsulfenyl halide with the dienolate derived from an αβ-unsaturated ketone. In view of the absence of any general report concerning the likely site of reaction of an arylsulfenyl halide we now describe the nucleophilic reactivity of a dienolate of an αβ-unsaturated ketone which depending upon the halide used reacts preferentially at each of the nucleophilic sites, at oxygen, at the α-, and at the γ- positions. Reaction at the γ-position with benzenesulfenyl chloride contrasts markedly with the α-attack of alkyl halides.

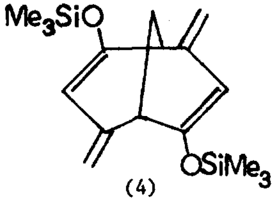
The kinetic dienolates of αβ-unsaturated ketones typically[2] undergo α'-alkylation, and complicate studies of the α/γ selectivity of the thermodynamic dienolates. A second complication with many αβ-unsaturated ketones is the possibility of proton removal from two different γ-positions. Both complications are avoided by study of 4,8-dimethylbicyclo[3,3,1]nona-3,7-diene-2,6-dione(1)[8]. The acidity of the α'-proton is decreased (Bredt's rule) and thus one equivalent of lithium diisopropylamide gives the deeply coloured dienolate (2) and 2 equivalents give the pale coloured dilithium salt (3). Only a single monolithium salt, and a single dilithium salt can be formed; hence product studies with (2) and (3) afford a simplified view of the regioselectivity of attack with a variety of reagents at the three possible sites in a dienolate.


(1)


(2)


(3)

Quenching of an enolate anion with trimethylsilyl chloride[9] typically gives a silyl ether. Following precedent the salt (3) gave the disilyl ether (4)[10]. Alkylation of (3) with methyl iodide, allyl bromide or benzyl bromide gave mixtures of the monoalkylated- and dialkylated products (5) by attack at the α-site. Under the alkylating conditions (THF, LDA, -78°) no -O- or γ-alkylation was observed.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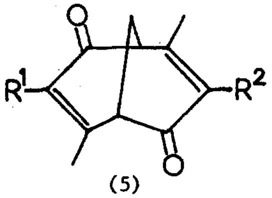
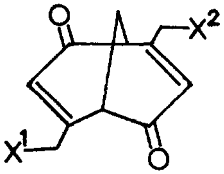

(5)

(a) $R^1 = H$; $R^2 = Me$ (b) $R^1 = R^2 = Me$

(c) $R^1{=}H$; $R^2{=}CH_2CH{:}CH_2$ (d) $R^1{=}R^2{=}CH_2CH{:}CH_2$

(e) $R^1 = H$; $R^2 = CH_2Ph$ (f) $R^1 = R^2 = CH_2Ph$

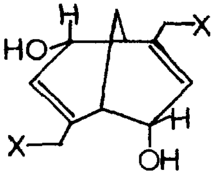
In contrast to the above results quenching of the salt (3) with bromine, benzenesulfonyl chloride and benzeneselenylbromide led exclusively to products of γ-attack. In the case of bromination the dibromide (6e) was identical with the product obtained by either treatment of (1) with bromine in methylene chloride or with N-bromosuccinimide in carbon tetrachloride. The oily disulphide (6b) was characterized by reduction to the crystalline diol (7a) m.p. 169-171°C and similarly the oily diselenide (6d) was characterized by reduction to the crystalline diol (7b).


(6)

(a) $X^1{=}$ H; $X^2{=}SPh$ (b) $X^1{=}X^2{=}SPh$

(c) $X^1{=}$ H; $X^2{=}SPh$ (d) $X^1{=}X^2{=}SePh$

(e) $X^1{=}X^2{=}Br$


(7)

(a) X = SPh

(b) X = SePh

The products of α-attack (5) require the intermediacy of βγ-unsaturated ketones which readily isomerize to the more stable αβ-unsaturated ketones. The γ-substituted products could be formed either by an initial attack at the α-position followed by a 1,3-migration of the substituent to give the observed γ-substituted products, or by direct γ-attack. If the former route were followed we believe it unlikely that 1,3-migration would proceed to the exclusion of reconjugation giving an αβ-unsaturated ketone, as observed in alkylation with alkyl halides. Analogous thermal rearrangements have little precedent, although related photochemical transpositions[11] are known. We therefore conclude that the observed products of attack at oxygen, at the α- and γ-positions are all kinetic products.

TABLE

Reagent	Conditions[a]	Product	Yield[b]
Me_3SiCl	2.2 equiv. -78° - 20°C	4	6%[c]
MeI	2.2 equiv. -78° - 20°C	5a 5b	41% 35%
$CH_2{:}CHCH_2Br$	2.1 equiv. -78° - 20°C	5c 5d	21% 33%
$PhCH_2Br$	2.0 equiv. -78° - 20°C	5e 5f	26% 28%
PhSCl	2.0 equiv. -78° - 20°C	6a 6b	13% 11%
	4.2 equiv. -78° - 20°C	6b	50%
PhSeBr	4.2 equiv. -78° - 20°C	6c 6d	43% 31%
Br_2	4.2 equiv. -78° - 20°C	6c	20%[d]

[a] Dienolate (3) prepared with LDA (2.2 equiv.) in THF at -78°C

[b] Isolated yields after preparative t.l.c.

[c] 48% yield of crude product; substantial decomposition on chromatography

[d] 54% yield of crude product; substantial decomposition on chromatography

Our results have two important consequences. The marked difference in regioselectivity of alkyl halides and benzenesulfenyl chloride emphasises the need of a general investigation of the regioselectivity of benzenesulfenyl chloride with the thermodynamic dienolates derived from αβ-unsaturated ketones. If γ-attack is general the problem of selective γ-alkylation using alkyl halides can be overcome using the method of Lansbury and Erwin. Secondly, our results contradict earlier calculations[12] concluding that α-attack on dienolates would always be favoured. Although there are particular features of (2) and (3) (greater steric hindrance at the α-site, and proximity of a second functional group at the γ-site) which are unusual our results imply that the previously accepted view of α-attack is modified by a greater preference of some electrophiles for γ-attack.

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