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REGIOSPECIFIC SYNTHESES OF QUINONES USING VINYLKETENE ACETALS DERIVED FROM UNSATURATED ESTERS

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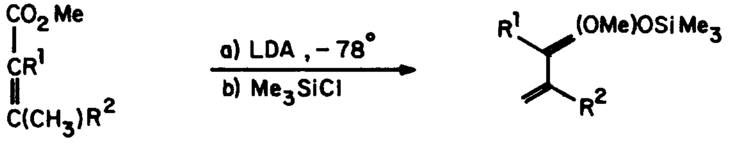
Abstract - A general method of annellating quinones in high yield has been devised using mixed vinylketene acetals obtained directly from the enolate ions of unsaturated esters.

Recently several types of vinylketene acetals have been devised in order to effect simple syntheses of highly substituted naturally occurring quinones. The preparation of the appropriate diene for each of the substitution patterns desired however usually required a different approach[1-5]. An ideal method of producing a variety of these synthons, capable of reproducing most of the arrangements of substituents observed in these natural products can readily be envisaged using enolate ions[6,7] generated by the action of strong bases on unsaturated esters or acids. The corresponding vinylketene alkyl trialkylsilyl acetals have been mentioned only briefly in the literature[6b,8] except in the case of those particular structures required for Claisen rearrangements[9]. On the other hand, the formation of ketene acetals from carboxylic acids and esters has been studied and is attended by numerous difficulties. The nature of the base and of the silylating agent as well as the structure, isolation and stability of the products have been examined in detail[6,7].

A number of substituted α,β-unsaturated esters 1-4 have now been converted to their enolates and thence to the corresponding 1-methoxy-1-trialkylsiloxybutadienes 5-8. (A similar reaction involving an unsubstituted crotonate had been reported earlier[6b].) The most convenient procedure consisted in treating the ester in dry tetrahydrofuran at -78°C with lithium diisopropylamide followed by chlorotrimethylsilane. Careful fractionation of the reaction mixture gave the required dienes 5-8 (40%-85%). Sodium bis(trimethylsilyl)amide in ether at -60°C gave comparable results, at least in the case of compounds 5 and 6. Other bases such as lithium cyclohexylisopropylamide or tetramethylpiperidide were undoubtedly more efficient but gave products that could not be separated readily from the liberated amines.



1 $R^1 = H$, $R^2 = Me$

2 $R^1 = H$, $R^2 = OMe$

3 $R^1 = OMe$, $R^2 = Me$

4 $R^1 = Cl$, $R^2 = OSiMe_3$

5 $R^1 = H$, $R^2 = Me$

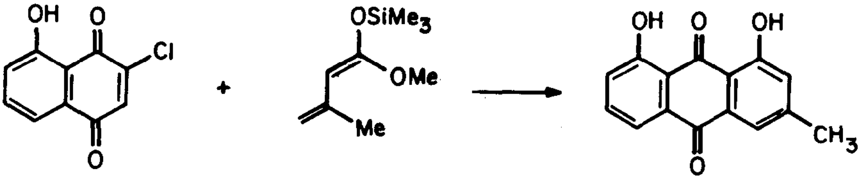
6 $R^1 = H$, $R^2 = OMe$

7 $R^1 = OMe$, $R^2 = Me$

8 $R^1 = Cl$, $R^2 = OSiMe_3$

The various procedures were explored for the preparation of the following vinylketene acetals among others: 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene (5) from methyl 3-methyl-2-butenoate (1), b.p. 80-82°C/16 mm, δ 0.21 (9H, s, 1-OTMS), 1.91 (3H, m, 3-Me), 3.51 (3H, s, 1-OMe), 4.24 (1H, br s, 2-H), 4.50, and 4.74 (2 x 1H, 2m, 4-H_2); 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene (6) from methyl (E)-3-methoxy-2-butenoate[10] (2), b.p. 57-62°C/0.8 mm, δ 0.24 (9H, s, 1-OTMS), 3.54 and 3.55 (2 x 4H, 2s, 1,3-OMe), 3.98 (1H, dd, J = 1.5, 1.5 Hz, 4-H), 4.03 (1H, d, J = 1.5 Hz, 4-H), and 4.33 (1H, d, J = 1.5 Hz, 2-H); 1,2-dimethoxy-3-methyl-1-trimethylsiloxy-1, 3-butadiene (7), as a mixture of isomers, from methyl 2-methoxy-3-methyl-2-butenoate[11] (3), b.p. 38-44°C/0.5 mm, δ 0.22 and 0.24 (2s, 1-OTMS), 1,71 (br s, 3-Me), 3.32 and 3.36 (2s, 2-OMe), 3.57 (br s, 1-OCH_3), 4.53 and 4.81 (2m, 4-H_2); 2-chloro-1-methoxy-1,3-bis-trimethylsiloxy-1, 3-butadiene (8), from methyl 2-chloroacetoacetate[12], b.p. 74-82°C/0.6 mm, δ 0.21 and 0.24 (2 x 9h, 2s, 1,3-OTMS), 3.50 (3H, s, 1-OMe), 4.22 and 4.36 (2 x 1H, 2m, 4-H_2)[13].

The principal object of this study, which consisted in establishing a simple and general method for the preparation of naturally occurring quinones and other useful intermediates, was based on the well-established regiospecificity of reactions involving vinylketene acetals[1-5]. The process is exemplified by the following scheme for the synthesis of chrysophanol (19).



11 5 19

The dienes 5-8 (1.0 mmol) combined rapidly at room temperature with 2,5- and 2,6-dichlorobenzoquinone (9) (1.0 mmol) in anhydrous tetrahydrofuran (10 ml), however the efficiency of the procedure was improved considerably by conducting the reactions at -30°C. Upon evaporation of the solvent, the condensations could then be completed by consecutive pyrolysis of the residue at 80-140°C followed by treatment of the intermediate by a 2.5% solution of concentrated hydrochloric acid in tetrahydrofuran at reflux temperature (10 min). It was later found that similar results with better yields were obtained by slowly percolating (0.5-1.5 h) a benzene solution of the crude adduct through silica gel (~ 30 g; Woelm, act 3, for dry column chromatography). With less reactive substrates such as 2-chloronaphthoquinone (10) and 3-chlorojuglone (11) the most satisfactory conditions consisted in bringing together the reactants (1 mmol of quinone and 2 mmols of diene) at room temperature without solvent (10-20 min) and completing the reaction in the prescribed way. Some of the results are presented in the Table.

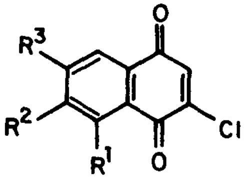
Whereas previously prepared vinylketene dimethyl acetals, being highly reactive, generally behaved unsatisfactorily and gave poor results with benzoquinones[3b], the annellations involving mixed acetals proceeded more smoothly and afforded much higher yields even when the improved technique for inducing aromatization was not used. Mixtures of 5-hydroxylated and 5-methoxylated

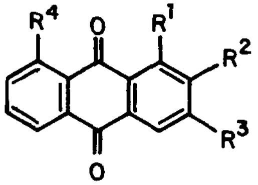
Reactants	Products	Yield, %	m.p., °C
5 + 9	12	76	190-191
	13	14	174.5-175.5
6 + 9	14	93	177(177-178)[5a]
	15	6	205-207(208-209)[3b]
7 + 9	16	62	155.0-155.5
	17	<1†	123.5-124.0
8 + 9§	18	23	dec. 194-195
5 + 11	19	63	194-195(192-193)[14]
	20	4	187-189
6 + 10	21	99	193.5-194.5(193-194)[15]
7 + 10§	22	65	167-168
	23	6	201
7 + 11	24	77	214-215

TABLE: Preparation of quinones using vinylketene mixed acetals

(All compounds were fully characterized by their spectral properties. Yields given are for isolated products.) † Aromatization through pyrolysis increases the yield to ~ 6%.

§ These reactions have not been repeated using the more effective procedure for the aromatization step.





10 $R^1 = R^2 = R^3 = H$

11 $R^1 = OH$, $R^2 = R^3 = H$

12 $R^1 = OH$, $R^2 = H$, $R^3 = Me$

13 $R^1 = OMe$, $R^2 = H$, $R^3 = Me$

14 $R^1 = OH$, $R^2 = H$, $R^3 = OMe$

15 $R^1 = R^3 = OMe$, $R^2 = H$

16 $R^1 = OH$, $R^2 = OMe$, $R^3 = Me$

17 $R^1 = OH$, $R^2 = OMe$, $R^3 = CH_2Cl$

18 $R^1 = R^3 = OH$, $R^2 = Cl$

19 $R^1 = R^4 = OH$, $R^2 = H$, $R^3 = Me$

20 $R^1 = OMe$, $R^2 = H$, $R^3 = Me$, $R^4 = OH$

21 $R^1 = OH$, $R^2 = R^4 = H$, $R^3 = OMe$

22 $R^1 = OH$, $R^2 = OMe$, $R^3 = Me$, $R^4 = H$

23 $R^1 = OH$, $R^2 = OMe$, $R^3 = CH_2Cl$, $R^4 = H$

24 $R^1 = R^4 = OH$, $R^2 = OMe$, $R^3 = Me$

naphthoquinones were usually formed in which the former was by far the major constituent. Additions to naphthoquinones 10 and 11 proceeded very slowly in solution thus reflecting the decreased reactivity of these substrates towards nucleophilic species. As expected, 3-chloronaphthoquinones methoxylated in the 5 or 5 and 7 positions were extremely inert and did not give yields exceeding 2.5% under the most vigorous conditions. Finally, an abnormal by-product was consistently encountered with the use of diene 7. All reactions investigated so far have produced small amounts, up to 6%, of an unexplained chloromethyl derivative, i.e. 17 or 23, as established unambiguously by n.m.r. and mass spectroscopy. The amounts of the latter can generally be decreased by aromatizing the adduct over silica gel.

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