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STUDIES ON THE REACTION OF 1,2-DICARBONYL COMPOUNDS WITH DIMETHYL 3-KETOGLUTARATE. STERIC AND ELECTRONIC EFFECTS

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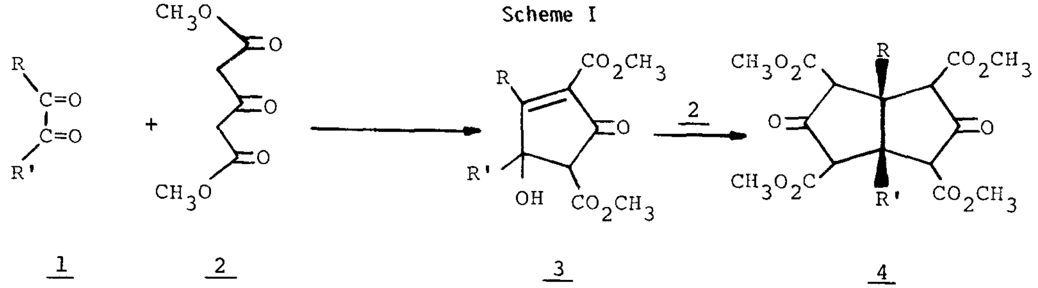
Summary: The steric and electronic influences of substituents attached to the 1,2-dicarbonyl system on the success of the reaction of 1,2-diketones with dimethyl 3-ketoglutarate 2 have been examined. It is clear from the reaction of 2 with benzil, thienil, furil, and phenanthrenequinone 5, respectively, coupled with ^{13}C NMR spectroscopy of the reaction intermediates, that steric effects play a major role in the overall success of the reaction to provide 4. This is analogous to the situation observed earlier with 1,2-diketones, R-CO-CO-R, where R represented an aliphatic or alicyclic group.

Research directed toward the synthesis of polyquinanes has grown rapidly during the past 10 years.[1a,b] New cyclopentananoid natural products have been isolated, and many novel polyquinane systems have been synthesized. For some time, we have been interested in developing a general method for the synthesis of polyquinanes,[2] which is based on the observation[3] that 1,2-dicarbonyl compounds 1 react in high yield with two molecules of dimethyl 3-ketoglutarate 2 to yield tetramethyl cis-bicyclo[3.3.0]octane-3,7-dione 2,4,6,8-tetracarboxylates represented by 4. The ease of construction of the diquinane skeleton via 1 and 2, and the wide range of substituents (R) which can be tolerated, have made this reaction the method of choice for the synthesis of a number of polyquinanes in our laboratories[4a,b,c,d] and in those of other groups.[5a,b,c,d]

Scheme I



We had previously reported that the yield of the reaction decreases as the size of the substituent increases; with 1a, R'=R=cyclohexyl, only the 1:1 adduct 3a was isolated.[6] In the case of 1a, this is due in large part to the increased steric hindrance in the intermediate 1:1 adduct 3 toward attack by the second molecule of 2. Similarly, with benzil (1b, R=R'=C_6H_5) the reaction did not proceed to the corresponding bicyclo[3.3.0]-octane-3,7-dione 4, but stopped instead at the stage of the 1:1 adduct 3b.[7] We have recently investigated the reaction of 2 with a number of fully aromatic 1,2-diketones. The results of these experiments are summarized in Table I.

TABLE I

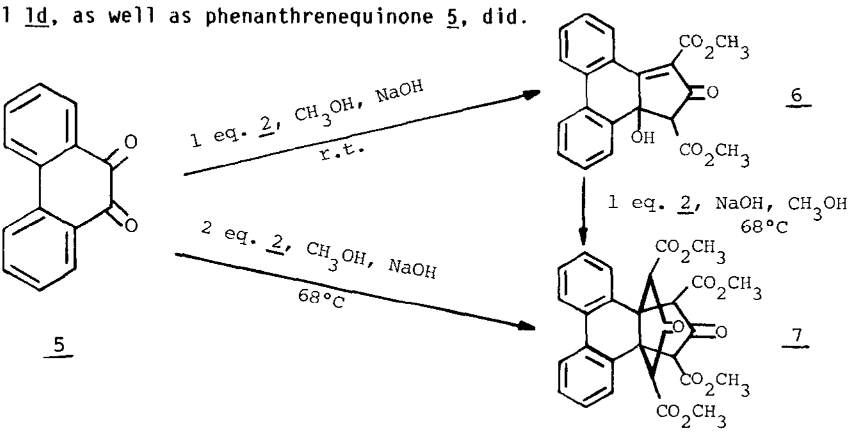
1,2-DIKETONE	R = R' =	1:1 ADDUCT (% YIELD)	1:2 ADDUCT (% YIELD)
1a	Cyclohexane	3a(61)	4a(0)
1b	Phenyl	3b(70)	4b(0)
1c	2-Thienyl	3c(77)	4c(0)
1d	2-Furyl (1 eq. 2)	3d(56)	-----
1d	2-Furyl (2 eq. 2)	-----	4d(60)

When the 1,2-diones 1a-1d were stirred with two equivalents of 2 in a solution of methanolic sodium hydroxide at reflux only 1d gave a 1:2 adduct, characterized as 4d.[8] Under analogous conditions, diones 1a-1c yielded the corresponding 1:1 adducts 3a-3c. All four of the dicarbonyl compounds 1a-1d, however, gave 1:1 adducts 3a-3d, respectively, when reacted with one equivalent of 2. The above results could be due to either steric or electronic influences on the reactivity of 2 toward 1 or 3. It was difficult to resolve whether these observations were due to steric congestion in the intermediate (as in the case where R=R'=cyclohexyl), or whether electron release (*via* resonance) lowered the reactivity of the enone system of the 1:1 adducts 3b or 3c toward Michael addition by another molecule of 2. Previously, it was felt that both electronic and steric effects were important on the success of the condensation to 4 because 1b and phenanthrenequinone 5 yielded only 1:1 adducts upon reaction with excess 2.[7] In the case of 5, however, the effect of steric congestion should be less important than in that of 1b since the aromatic substituents of 5 are tied back in a ring system which occupies a molecular volume similar to cyclohexane-1,2-dione at the site of reaction.[4c] The ability of furil 1d to proceed to the 1:2 adduct, in contrast to the behavior of benzil 1b and thienil 1c which only gave 1:1 adducts was intriguing. Examination of models of these substituents indicated that benzene and thiophene are similar in molecular volume both being larger than furan. In the 1:1 intermediates 3a-3d considered here, the electronic effects deemed important were those which would alter the electron density of the β position of the enone system. Groups capable of donating electrons to this site should tend to decrease the rate of Michael addition of 2 to 3 in favor of the formation of undesirable by-products such as cyclopentadienones. To evaluate the effect of R on the electron density of the β carbon atom, ^{13}C NMR spectroscopy was employed. Through proton-coupled ^{13}C NMR spectroscopy, it was possible to determine the chemical shifts of the β carbon atoms for the series of 1:1 adducts (3a-3d). The chemical shifts in ppm (from TMS) are listed in Table II.

TABLE II

Substituent R=R'	β Carbon, ^{13}C-Chemical Shift (ppm)	Aldehyde	Carbonyl, ^{13}C-Chemical Shift (ppm)
3a Cyclohexane	186.5	Cyclohexane carboxaldehyde	202.7[9a]
		Acetaldehyde	200.5[9a]
3b Phenyl	175.0	Benzaldehyde	190.7[9a]
3c 2-Thienyl	164.1	2-Thienaldehyde	182.9[9b]
3d 2-Furyl	153.0	2-Furylaldehyde	178.2[9c]

While it is true that ^{13}C chemical shifts do not depend entirely on electron density, the correlation between the two is often good. For example, it is the decreased electron density at the β carbon atom of α,β unsaturated ketones which is responsible for the downfield shift of this signal (165.2 ppm for 2-cyclopentenone vs. 130.8 ppm for cyclopentene).[9d] The trend of chemical shifts which we observed for 1:1 adducts 3a-3d parallels the order of those observed for the corresponding aromatic aldehydes, as illustrated in Table II. In addition, there is a reasonable correlation between the chemical shifts of these carbon atoms in the ^{13}C spectra and the σ^+ values (phenyl 1.0, thienyl -0.85, furyl -0.95) for these substituents.[10] These pieces of evidence, taken together, would then tend to rank the electron density on the β carbon of the enone system of the 1:1 adducts (1b-1d) in the order of 2-furyl > 2-thienyl > phenyl. This should be opposite to their ability to act as Michael acceptors, for the higher electron density on the β-carbon atom of 1d would be expected to render this center less reactive toward nucleophiles than 1c, etc. On this basis, the 1:1 adduct 3b should be better suited electronically to accept the second molecule of 2 than the corresponding 2-furyl compound 3d. This trend is exactly opposite the experimental observations! This result suggests that the predominant effect in conversion of 3 into 4 in the 1,2-diones (1, R=R'=Ar) rests on steric factors, as was the case earlier with 3a (R=R'=cyclohexyl). For this reason, the ^{13}C spectrum of the 1:1 adduct 6 of phenanthrenequinone 5 was recorded, and the β-enone carbon atom found to resonate at 169.4 ppm. In terms of the ability of the substituents to donate electron density to the enone, this value should place the reactivity of the 1:1 adduct 6 between those of the analogous benzil 3b and 2-thienil 3c compounds. Furthermore, since steric interactions in 5 are necessarily smaller than those in 1b, the former compound should be capable of conversion into the 1:2 adduct 7. With this information in hand, it was decided to reexamine the reaction[7] of 2 with 5 under the more vigorous reaction conditions employed to prepare 3a-3d.[7] When the condensation of 2 with 5 was carried out (NaOH, MeOH, r.t.), it was found that the sodium salt of the 1:1 adduct 6 precipitated from the solution. The earlier inability to convert 5 into 7 might have been due to solubility problems with intermediate 6, followed by decomposition of this 1:1 adduct. To circumvent this problem, 5 (Scheme II) was reacted (NaOH, MeOH, 68°C) with 2 at higher dilution and higher temperature to provide a white solid (mp>300°C). Treatment of this material with cold dilute HCl gave the desired 1:2 adduct in 53% yield.[11] It is important to emphasize that under the vigorous reaction conditions (NaOH, CH_3OH, 68°C), the bulkier diones 1a, 1b and 1c did not yield 1:2 adducts, whereas, furil 1d, as well as phenanthrenequinone 5, did.



On the basis of these results it appears that steric factors play a much greater role in the reaction of 1 with 2 (via 3) to 4 than the electronic character of the R groups. Undoubtedly, these substituents may be capable of altering the rate of addition of a second molecule of 2, but the overall success or failure of the conversion of the 1:1 adduct 3 into the desired cis-bicyclo[3.3.0]octanedione system 4 is based primarily on the size of the R groups. It is important to remember, however, that 1,2-diones such as 1a-1d and 5 are not soluble in aqueous systems; hence, the condensations in these cases were carried out in sodium hydroxide-methanol at reflux. The conditions are much more vigorous than those (aqueous buffer) successfully employed in our hands in the aliphatic and alicyclic cases reported earlier.[2,3,4] This successful alteration in conditions is important for it permits a more thorough study of steric effects on the scope of the reaction, as well as expands the use of the condensation to less soluble and less reactive 1,2-diketones.

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11. 7 m.p. 235°C dec. ($CHCl_3$/hexane); IR (KBr), 2680, 1745, and 1619 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ2.90 (6H,s), 4.02 (6H,s), 4.71 (2H,s), 7.26 (4H, m), 7.65 (2H,m), 7.75 (2H,m), 11.37 (2H,s,br); Mass spectrum (CI/CH_4) m/e 521 (M+1, 26.6%), 489 (-MeOH, 67.2%), 457 (-2MeOH, 100%).

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