# Use of Cyclohexane-1,3-dione Derivatives in the Preparation of Enaminones

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Vinylogous esters and acid halides have been compared with respect to their rates of hydrolysis and of reaction with ammonia and amines. Under alkaline conditions the vinylogous esters were hydrolysed faster than the comparable acid halides. Conversely the reaction of the vinylogous acid halides with base to give enaminones was generally faster than that of the esters. Great differences in reaction rates were observed: when tertiary enaminones are being prepared it is very advantageous to use vinylogous acid halides as starting materials.

MANY of the enaminones investigated in this laboratory have been derivatives of cyclohexane-1,3-dione (1a) or dimedone (1b). The most usual preparation here [1] and

a; R = H   b; R = Me

R¹ and R² = H, alkyl, or aryl; R³ = Me or Et; X = halogen
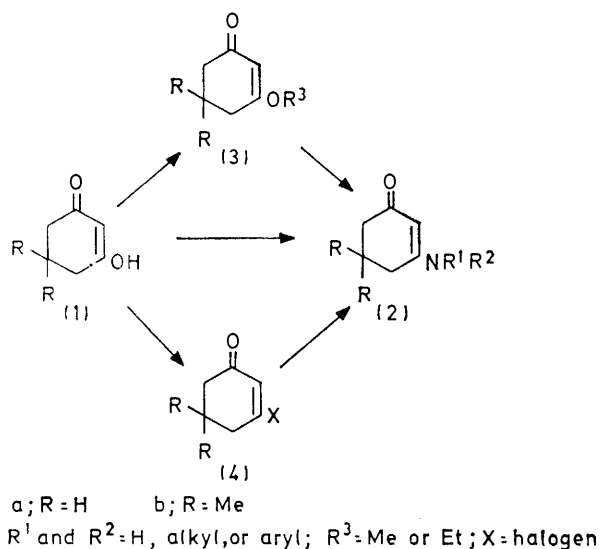
SCHEME 1

elsewhere [2] has involved the direct reaction of the dione with the amine in an aromatic solvent with azeotropic removal of the water formed. In our experience no advantage has resulted from the use of catalysts such as toluene-*p*-sulphonic acid. In a number of cases,[3] including some at present under investigation, this route has failed or has given other, unwanted products.

The diones (1) may be considered as vinylogous acids [(1a) [4] pK_a 5.26; (1b) [5] pK_a 5.22]; thus the enol ether derivatives (3) are vinylogous esters and the halides (4) are vinylogous acid halides. The vinylogous esters (3) are well known, but are most easily prepared by reaction with the appropriate alcohol in the presence of boron trifluoride.[6] A recent paper has simplified and improved the preparation of the vinylogous acid halides.[7]

Preliminary work had suggested that both these classes of compound could be used in the preparation

of enaminones, but the vinylogous acid halides reacted only slowly with aqueous alkali. It was decided to examine eight compounds under hydrolysis conditions over a range of pH values and then to study their reactions with ammonia, methylamine, and dimethylamine in alcoholic solution. These reactions are easily followed by changes in u.v. spectra.

The vinylogous esters (3) were hydrolysed at measurable rates between pH 2 and 4.5 and again between pH 10 and 11; nearer to neutrality the reactions were too slow to be followed under the conditions used. The vinylogous acid halides (4) were only hydrolysed at measurable speeds above pH 9.5. By determining rates of pseudo-unimolecular reaction at several points within these ranges, the second-order rate constants given in Table 1 were obtained.

Some typical rate constants for hydrolysis of carboxylic acid chlorides and esters (in 1 mol⁻¹ s⁻¹) are: acetyl chloride [8] (89% acetone–water; 20 °C) K_{OH} 10.9 × 10⁴, benzoyl chloride [8] (same conditions) 0.041 7 × 10⁴; ethyl acetate [9] K_{H+} 5.5 × 10⁻⁵ (25 °C), K_{OH} 6.2 × 10⁻³, methyl benzoate [9] K_{H+} 2.7 × 10⁻⁵, K_{OH} 9.0 × 10⁻³. Thus vinylogous acid halides undergo base-catalysed hydrolysis much more slowly than carboxylic acid chlorides; indeed the vinylogous esters showed greater rates of hydrolysis than the comparable vinylogous acid chlorides and bromides.

A suggested mechanism for the base-catalysed hydroly-
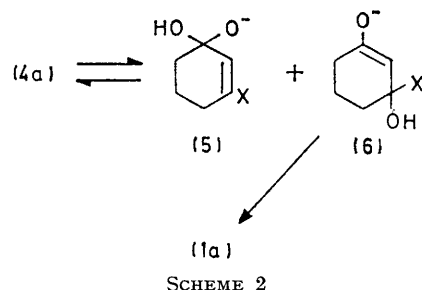
SCHEME 2

sis of the vinylogous halides is shown in Scheme 2. The vinylogous acid halide (4a) has partial positive character at two carbon atoms (1 and 3). A high ratio of C-1 to

[1] J. V. Greenhill, *J. Chem. Soc.* (*C*), 1971, 2699.

[2] I. Jirkovsky, *Canad. J. Chem.*, 1974, **52**, 55; N. J. Leonard and J. A. Adamcik, *J. Amer. Chem. Soc.*, 1959, **81**, 595; G. H. Alt and A. J. Speziale, *J. Org. Chem.*, 1965, **30**, 1407.

[3] J. V. Greenhill, *J. Chem. Soc.* (*C*), 1970, 1002.

[4] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 1940, **23**, 1147.

[5] R. P. Bell and R. R. Robinson, *Trans. Faraday Soc.*, 1961, **57**, 965.

[6] G. Hallas, *J. Chem. Soc.*, 1965, 5770.

[7] E. Piers and I. Nagakura, *Synth. Comm.*, 1975, **5**, 193.

[8] I. Ugi and F. Beck, *Chem. Ber.*, 1961, **94**, 1839.

[9] C. A. Mackenzie in ' Unified Organic Chemistry,' Harper and Row, New York, 1964, p. 335.

C-3 attack to give the intermediate (5) rather than (6) would account for the unexpectedly slow reactions of the vinylogous halides studied.
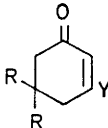
A sample of each of compounds (7)—(10) was shaken with ^{18}O-enriched water and half the theoretical quantity of sodium hydroxide. Unchanged vinylogous acid halide was extracted with ether, carefully dried, and submitted for mass spectrometry. In each case the recovered material showed incorporation of the heavy isotope approximately in proportion to its concentration in solution. This confirms that the equilibrium reaction

during the hydrolysis showed a good isosbestic point. This must mean that the intermediates (5) and (6) have only brief existence, as neither would absorb in this region. It follows that the attack of hydroxide ion on the starting material (3) or (4) is the rate-limiting step.

Acid-catalysed hydrolysis of the vinylogous esters showed rate constants 4—10 times greater than the base-catalysed reaction. However, when each of the vinylogous acid halides was kept at pH 2 no change in the u.v. spectrum was seen after two months. It seems likely in the case of the vinylogous esters that water attacks

TABLE 1

Rate constants ($\pm 10\%$) for hydrolysis of vinylogous esters and acid halides at 37 °C

Compd.	R	Y	$\lambda_{max.}$/nm	ε/l mol^{-1} cm^{-1}	$K_{H^+} \times 10^3$/ l mol^{-1} s^{-1}	$K_{OH^-} \times 10^3$/ l mol^{-1} s^{-1}	Ref.
(7)	H	OMe	254	17 640	52.1	12.0	a
(8)	H	OEt	255	16 500	39.3	8.13	b
(9)	H	Br	249	14 000		4.88	c
(10)	H	Cl	241.5	14 400		5.07	c
(11)	Me	OMe	256	16 500	3.18	0.411	d
(12)	Me	OEt	258	17 400	3.72	0.344	e
(13)	Me	Br	251.5	12 600		<0.1	f
(14)	Me	Cl	244	13 150		<0.1	f

[a] H. Stetter and W. Dieriecks, *Chem. Ber.*, 1952, **85**, 61. [b] W. F. Gannon and H. O. House, *Org. Synth.*, Coll. Vol. V, 1973, p. 539. [c] A. W. Crossley and P. Haas, *J. Chem. Soc.*, 1903, **83**, 494. [d] R. Grouper, *Chem. Ber.*, 1950, **93**, 187. [e] E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 1953, 811. [f] W. Benson and A. Pohlard, *J. Org. Chem.*, 1965, **30**, 1129.

(4a) $\rightleftharpoons$ (5) is established and the species (5) must exist for long enough to allow equilibration to take place before loss of the hydroxide ion.

Mesomeric systems may be drawn for both types of compound [(a) $\longleftrightarrow$ (c)]. Because halogen atoms are

(3) Y = OR; (4) Y = X
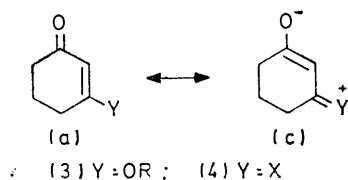
more electronegative, the contribution of form (4c) to the vinylogous acid halide will be less than the contribution of (3c) to the vinylogous ester; thus the proportion of attack at C-3 will be greater for compound (3) than compound (4). This may account for the slightly more rapid hydrolysis of the vinylogous esters studied.

This mechanism for base-catalysed hydrolysis of the vinylogous acid halides is, we think, the only possibility. In the case of the vinylogous esters, however, an O–alkyl fission could be involved. This possibility was tested for each of the esters by using sodium [^{18}O]hydroxide. In each case the alcohol recovered showed no incorporation of the heavy isotope, but the dione had the expected amount.

In each case the set of u.v. curves obtained at intervals

the protonated molecule (Scheme 3). In the case of vinylogous acid halides the very low contribution of form (4c) means that the molecule would not be protonated, so acid-catalysed hydrolysis could not occur.

These results suggested that the vinylogous esters might be the best starting materials for the preparation of enaminones.

Reactions of the eight dione derivatives with alcoholic solutions of ammonia, methylamine, and dimethylamine were followed by u.v. spectroscopy and gave the
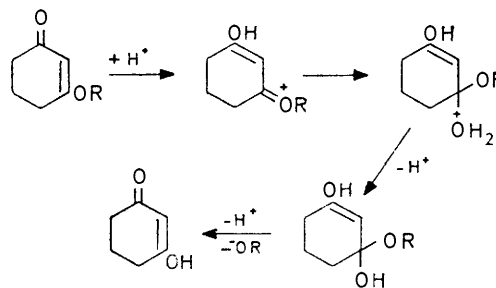
SCHEME 3

results listed in Table 2. The course of these reactions is similar to that of the base-catalysed hydrolyses. Once again the rate-determining step is attack by the base.

The vinylogous acid halides generally react faster than the vinylogous esters, but the extent of the difference is very sensitive to the bulk of the base. The smallest

TABLE 2

Rate constants (in l mol^{-1} s^{-1}; $\pm 25\%$) for enaminone formation at 37 °C

Compd.	$K(NH_3) \times 10^6$	$K(MeNH_2) \times 10^6$	$K(Me_2NH) \times 10^6$
(7)	9.42	890	26.2
(8)	4.95	526	7.15
(9)	19.6	7 840	18 200
(10)	22.8	9 710	23 200
(11)	0.545	64.5	3.29
(12)	0.405	44.7	1.47
(13)	<0.4	301	1 750
(14)	<0.4	290	2 080

base (ammonia) reacts with the halides (9) and (10) about 2—4 times as fast as with the corresponding 'esters'. The lack of a formal negative charge on the nucleophile in this case means that repulsion by the negatively charged oxygen (3a) ◄─► (3c) would not be as great as in the hydrolyses, so a higher proportion of ineffective attacks at C-1 would occur. The lower dielectric constant of the solvent (ethanol) as compared with the hydrolysis solvent (water) would mean that the charged form (3c) would make a smaller contribution to the structure of the vinylogous ester. For the dimedone halogen derivatives (13) and (14) the reactions with ammonia were too slow to be measured. In this one case, therefore, the vinylogous esters reacted faster than the halides.

Overall, methylamine reacted much faster than ammonia, reflecting its higher basicity (pK_a 10.64, cf. 9.25).[10] In the case of cyclohexanedione derivatives the halogen derivatives reacted 10—15 times faster than the 'esters' but for the dimedone derivatives this factor was between 5 and 7. The increase in this factor in comparison with the reactions with ammonia must reflect some steric interaction between the methylamine and the ether groups.

The small increase in basic strength between methylamine and dimethylamine (pK_a 10.78)[10] is probably sufficient to account for the greater rates of reaction of all four halides. However, the vinylogous esters reacted 20—75 times more slowly than with methylamine. Here the ether groups must interfere seriously with the approach of the dimethylamine.

In all the reactions studied, the dimedone derivatives reacted slower than the comparable cyclohexanedione derivatives. From a study of the dipole moments of the halogen derivatives, Pitea and Favini[11] were able to show that the gem-dimethyl system in dimedone causes distortion of the ring. In particular, rotation about the C(1)–C(2) bond occurs so that the two double bonds are not in the same plane. In the cyclohexanedione derivatives there is no distortion. This means that the inter-

mediate which has a double bond between C-1 and C-2 would have a higher energy in the dimedone derivatives than in the cyclohexanedione derivative.

Our previous experience has shown that the chemistry of vinylogous amides (enaminones) is not predictable from the chemistry of amides. We have now shown that vinylogous acid halides are hydrolysed much more slowly than their carboxylic counterparts, although the vinylogous esters studied had rates of reaction roughly similar to those of 'normal' esters. Nevertheless the vinylogous halides are usually to be preferred for the preparation of enaminones which are not easily obtained directly from the dione, but the vinylogous esters are also useful reagents, likely to react rapidly on heating with all but the the bulkiest amines.

EXPERIMENTAL

Samples of the vinylogous esters and acid halides were prepared as reported (see Table 1) and each was purified by two distillations.

Rates of Hydrolysis.—The buffer solution was prepared according to the method of Teorell and Stenhagen.[12] Citric acid (6.403 g), N-phosphoric acid (3.26 g), boric acid (3.45 g), and N-sodium hydroxide (343 ml) were dissolved in water and the solution was diluted to 1 l. A portion (20 ml) of this solution and a suitable amount (73.3—14.5 ml) of 0.1N-hydrochloric acid were diluted to 100 ml (to give pH range 2—11). A ca. 6.5 × 10^{-3}M-solution of the vinylogous ester or acid halide was prepared in water and 1.0 ml of this was accurately transferred to ca. 95 ml of the appropriate buffer pre-warmed to 37 °C. This operation was taken to occur at zero time. The volume was quickly made up to 100 ml with water pre-heated to 37 °C, and the flask was maintained at 37 ± 0.1 °C throughout the experiment. A sample of the solution was transferred to a 1.0 cm silica cell and the u.v. spectrum was recorded with a Unicam SP 800 spectrometer having a thermostatically controlled cell carrier. The spectrum was recorded immediately and at suitable time intervals to give at least six more readings. Under acidic conditions, the vinylogous esters and derived diones absorb at the same wavelength. In these experiments, therefore, the solutions were 20 times more concentrated with respect to the vinylogous esters; 5 ml samples plus N-sodium hydroxide (0.1—0.3 ml) were accurately diluted to 100 ml and the spectra were recorded. This gave final solutions of pH 9—10 which ensured that essentially all the dione present was converted into its anion, which absorbs at longer wavelength. A Pye Dynacap pH meter was used to check the solutions at the beginning and end of each run. In no case did the pH change by more than 0.1 unit.

For each solution the optical density at $\lambda_{max.}$ was plotted against time; extrapolation gave the optical density at zero time and hence the molar extinction coefficient.

Pure samples of each dione produced on hydrolysis subjected to the same conditions of pH and temperature showed no change in u.v. spectrum during the time of the hydrolysis runs. At any time (*t*), therefore, the proportion of starting

[10] H. S. Harned and B. B. Owen, *J. Amer. Chem. Soc.*, 1930, **52**, 5079.

[11] D. Pitea and G. Favini, *J.C.S. Perkin II*, 1972, 142.
[12] T. Teorell and E. Stenhagen, *Biochem. Z.*, 1938, **299**, 416.

material remaining (x) is given by [13] $(D - d')/(d - d')$, where D represents the optical density at time t at the $\lambda_{max.}$ of the starting material, and d and d' are the optical density at the same wavelength at times zero and infinity respectively. Rate constants for pseudounimolecular reaction were obtained from plots of t vs. $\log_{10} x$, and the second-order rate constants quoted in Table 1 were determined from at least four first-order constants.

Rates of Reactions with Amines.—Stock solutions of ammonia, methylamine, and dimethylamine in absolute ethanol were prepared and assayed with 0.1N-hydrochloric acid (Methyl Orange). To a solution (1.0 ml) containing the substrate (*ca.* 6×10^3 mol l^{-1}) was added a carefully measured volume of stock solution and absolute ethanol to give a total volume of 100 ml. The concentration of base in the final solution was 0.1—5% w/v. The solutions were

all maintained at 37 $\pm$ 0.1 °C and the reactions were followed by techniques similar to those for the hydrolysis.

Analytically pure samples of the enaminones produced [1] were used to determine their molar extinction coefficients in ethanolic solutions containing various concentrations of the bases employed in the kinetic runs. Then for an accurately weighed sample of vinylogous ester or acid halide, the optical density at infinite time could be deduced, and the proportion of starting material remaining (x) at time t is given by $1 - x = (D - d')/(d - d')$, where the symbols have the same meaning as above. It was necessary to read the spectra at the $\lambda_{max.}$ of the enaminones produced by the reaction since the bases interfered with the peaks due to the starting materials.

The second-order rate constants are presented in Table 2.

[13] K. Dixon and J. V. Greenhill. *J.C.S. Perkin II*, 1974, 164.