

HIGH PRESSURE-PROMOTED CYCLOADDITIONS OF KETENE ACETALS AND α,β -UNSATURATED ALDEHYDES AND KETONES

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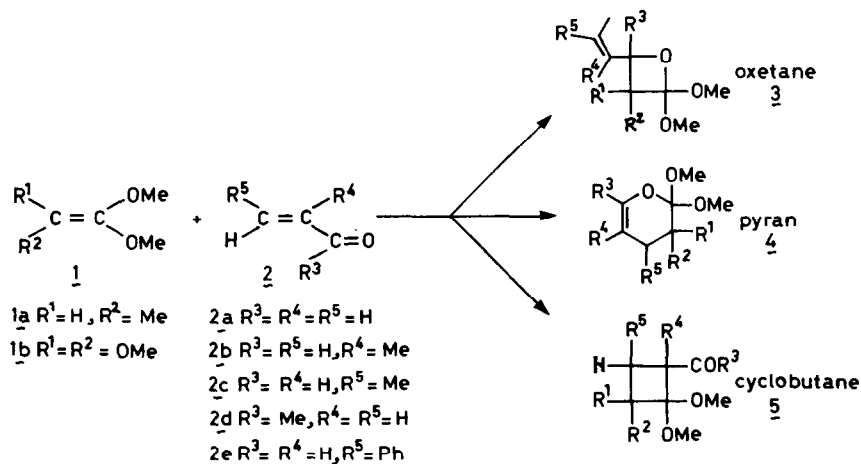
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Summary. Cycloadditions of ketene acetals with α,β -unsaturated carbonyl compounds are strongly promoted by high pressure. The influence of the solvent and the substitution pattern on the product distribution at 12 kBar has been investigated. In the polar solvent, acetonitrile, α,β -unsaturated aldehydes not having large β -substituents, yield mainly cyclobutane aldehydes, which are minor products at normal pressure. The products can be transformed under basic conditions without ring opening.

Recently, two groups reported^{1,2} that the high pressure-promoted addition of O-silylated ketene acetals to α,β -unsaturated carbonyl systems gives only conjugate addition products. This prompted us to report our results on high pressure-promoted cycloadditions of ketene acetals (1a,b) with α,β -unsaturated aldehydes and ketones (2a-e).

A priori such cycloadditions may lead to three different types of products as is depicted in Scheme I.

Scheme I



In the presence of a catalyst oxetanes 3 are mostly the kinetically determined products^{3,4}; at low temperature they can be isolated after neutralization of the catalyst. At higher temperatures the formation of oxetanes is reversible, and the thermodynamically more stable dihydropyrans (4) are ultimately formed. In the absence of a catalyst higher temperatures are necessary for notable conversions, and in general dihydropyrans (4) are the main products. In the polar solvent acetonitrile 1a gave with 2a after 20 hours at room temperature (90% conversion) a reaction mixture of 50% of 4 and 50% of 5. With 2b after 20 hours at 100° (85% conversion) the obtained

reaction mixture contained only 20% of 5. Compound 2c reacted at 100° too slow with 1a to measure the product distribution.

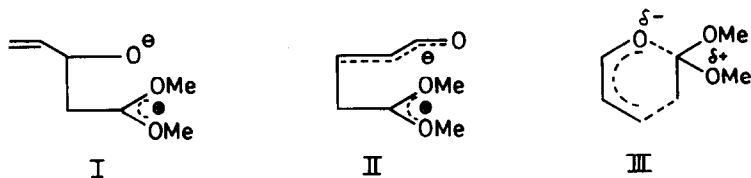
In the present investigation we studied similar reactions under neutral conditions at 12 kBar. The experiments were run in a high pressure apparatus equipped with a one wall piston-cylinder for pressures up to 14 kBar (1.4 GPa) and having an initial volume of 70 ml. For analytical purposes reactions were performed on a 1 mmole scale in sealed teflon tubes of 0.8 ml; for synthetic purposes (10-20 mmole scale) tubes of 8 ml were used.

The conversion rate of 2 and relative amounts of 3, 4 and 5 were determined by proton NMR. Detailed proton NMR-spectra of the compounds 3 and 4 have been published before³. The oxetanes (3) show typical HCO-ring proton absorptions ($\delta=3.9-4.3$ ppm), whereas the dihydropyrans (4) have characteristic vinyl ether proton absorptions ($\delta=4.3-4.8$ ppm, HC=C-O and 5.9-6.2 ppm⁶, C=CHO-). The cyclobutanes (5) are characterized by an aldehyde proton absorption at higher field ($\delta=9.5$) than that of 2a,b,c,e. The conversion rate of 2 was measured from the disappearance of the aldehyde proton and appearance of the characteristic protons of the products 3, 4 and 5.

The results of the analytical experiments are given in Table I. It appears that high pressure has a strong accelerating effect, as was previously found for (2+2) cycloadditions of 1 with simple carbonyl compounds⁷. Comparison of the product distribution at high pressure with that at normal pressure shows that formation of (2+2) cycloadducts is favoured at high pressure. From the possible (2+2) cycloadducts 5 is the main product when α,β -unsaturated aldehydes without large β -substituents are used and the reaction is performed in a polar solvent (acetonitrile). In the non-polar hexane formation of oxetanes (3) and dihydropyrans (4) become more important.

Results from the literature show that polar (2+2) cycloadditions have large negative activation volumes exceeding those of Diels-Alder reactions⁸. Whereas dihydropyrans (4) can be formed in a concerted (4+2) cycloaddition *via* a less polar transition state (III) oxetanes (3) and cyclobutanes (5) have to be formed *via* the dipolar intermediates, I and II, respectively (see Figure 1).

Figure 1



Although 4 may also be formed *via* II, the solvent effect suggests that it is formed *via* III. The preferential formation of 5 (*via* II) in a polar solvent suggests that the transition state in the cyclobutane formation at high pressure is more polar than in the oxetane formation.

As expected, the formation of 5 is diminished by substituents at the β -carbon atom of 2. In the reaction of cinnamaldehyde (2e) with 1a a cyclobutane could not at all be detected in the reaction mixture. Another extreme result was obtained in the reaction of methyl vinyl ketone (2d) in which both cyclobutane and oxetane formation are depressed. This may be ascribed to the greater stability and lower electron-withdrawing ability of the ketone function.

The tendency to cyclobutane formation of ketene acetal 1b having a symmetrical π electron distribution is even higher⁹ than that of 1a. Due to its low reactivity¹⁰ 1b does not yield cycloadducts at 12 kBar, 20 °C, with croton- or cinnamaldehyde.

Preparative experiments were done in those cases, where 5 was the main product. To that aim two Teflon ampoules (8 ml) were charged with 0.022 mole of 1 and 0.02 mole of 2a or b, further filled with acetonitrile, and inserted into the cylinder which was filled with hexane as a transmission medium. After the appropriate reaction time the solvent was evaporated and 5 distilled at low pressure with 'micro spaltrohr' column of 15 theoretical plates. Under neutral or basic conditions the cyclobutanes appeared to be sufficiently stable for further derivatisations indicated in Eqn. 1. The possibilities were applied to get pure end products in those cases where 5 could not completely be liberated from 4. In the reaction of 1a and 2a the impure aldehyde (5aa) could be converted into the pure alcohol 6aa; other aldehydes were further characterized as the corresponding dimethylhydrazones 7 (see Table II).

Eqn. 1

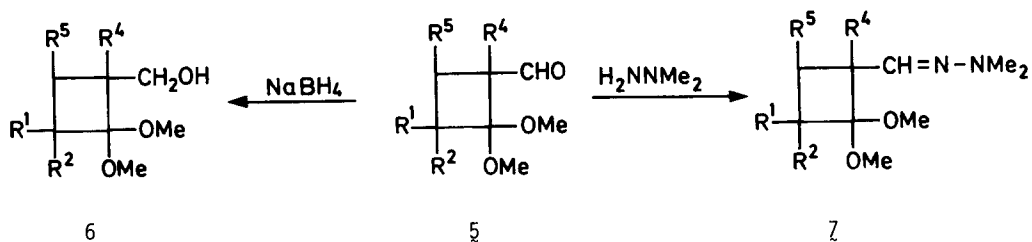


Table I CYCLOADDITIONS OF 1a AND 1b WITH α, β -UNSATURATED CARBONYL COMPOUNDS 2a-e AT 20 °C AND 12 kBar IN ACETONITRILE OR HEXANE (20% SOLUTIONS, 1 IN 10% EXCESS).

Reactants	Solvent	Reaction time	% conversion of <u>2</u>	Relative product amounts (%)		
				<u>3</u>	<u>4</u>	<u>5</u>
<u>2a</u> + <u>1a</u>	acetonitrile	30 min	100	-	35	65
	hexane	30 min	100	-	80	20
<u>2a</u> + <u>1b</u>	acetonitrile	24 h	100	-	30	70
<u>2b</u> + <u>1a</u>	acetonitrile	30 min	70	10	10	80
	hexane	30 min	35	30	30	40
<u>2b</u> + <u>1b</u>	acetonitrile	48 h	70	-	-	>95
<u>2c</u> + <u>1a</u>	acetonitrile	30 min	60	20	60	20
	hexane	30 min	20	30	70	-
<u>2d</u> + <u>1a</u>	acetonitrile	12 h	100	-	>90	-
<u>2d</u> + <u>1b</u>	acetonitrile	24 h	<5	not determined		
<u>2e</u> + <u>1a</u>	acetonitrile	12 h	100	50	50	-
	acetonitrile	24 h	<5	not determined		

Table II CHEMICAL, PHYSICAL AND SPECTROSCOPIC DATA OF CYCLOBUTANE ALDEHYDES (5) FORMED IN HIGH PRESSURE REACTIONS 1 AND 2, OF A CORRESPONDING ALCOHOL (6aa) AND SOME N,N-DIMETHYL-HYDRAZONES (7)

Starting compounds	Product	Yield (%)	b.p. (°C/mm)	¹ H NMR (δ in ppm, CDCl ₃)
1a + 2a	5aa	a		1.65-2.65 (m, 2H, CH ₂); 2.75-3.35 (m, 1H, HC-CO); 3.20 (s, 3H, OCH ₃); 3.30 (s, 9H, OCH ₃); 9.50 (d, J = 3 Hz, 1H, HCO)
1b + 2a	5ba	60	65/0.5 ^c	0.85-1.30 (m, 6H, 2 CH ₃); 1.45-2.65 (m, 3H, CH and CH ₂); 3.05-3.35 (m, 6H, 2 OCH ₃); 9.45 and 9.55 (2s, 1H, isomer ratio 7:13, CHO)
1a + 2b	5ab	75	33/0.5 ^d	1.20 (s, 3H, CH ₃); 1.45 and 1.65 (A part of AB, J = 12 Hz); 2.25 and 2.45 (B part of AB, J = 12 Hz, AB of CH ₂); 3.25 (s, 6H, 2 OCH ₃); 3.30 (s, 6H, 2 OCH ₃); 9.55 (s, 1H, HCO)
1b + 2b	5bb	65	43/0.3	1.05 (b.d., 3H, CH ₃); 1.15-2.80 (m, 4H); 3.10, 3.15 and 3.20 (3s, 6H, 2 OCH ₃); 3.35 (b.d., J = 7 Hz, 2H, CH ₂ OH (-OH was exchanged with D ₂ O)
5aa (impure)	6aa	80 ^b	46/0.8	1.06 (d, J = 7 Hz, 3H, CH ₃); 1.27 (s, 3H, CH ₃); 1.57 and 1.67 (A part of ABC, 1H); 2.11-2.67 (m, BC part of ABC); 2.71 (s, 6H, N(CH ₃) ₂); 3.11, 3.18 and 3.27 (3s, 6H, OCH ₃); 6.73 and 6.80 (2s, 1H, HC=N-, isomer ratio 3:2)
5ab (impure)	7ab	75 ^b	54/0.4	1.80-2.30 (m, 2H, CH ₂); 2.75 (s, 6H, N(CH ₃) ₂); 2.90-3.20 (m, 1H, HC-C=N-); 3.30 (b.s., 6H, OCH ₃); 3.35 (s, 6H, OCH ₃); 6.60 (d, J = 6 Hz, HC=N-)
5ba	7ba	80	84/0.5	1.25 (s, 3H, CH ₃); 1.30 and 1.68 (A part of AB, J = 12 Hz, 1H); 1.92 and 2.10 (B part of AB, J = 12 Hz, 1H, CH ₂); 2.80 (s, 6H, N(CH ₃) ₂); 3.20 (b.s., 12H, OCH ₃)

^aThe product could not be separated from the corresponding dihydropyran 4aa (product ratio 65:35)

^bBased on the amount of 5 present

^cKugelrohr distillation

^dContaminated with ca 20% 4ab

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