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HIGH PRESSURE PROMOTED (2+2) CYCLOADDITIONS OF KETENE ACETALS WITH CARBONYL COMPOUNDS

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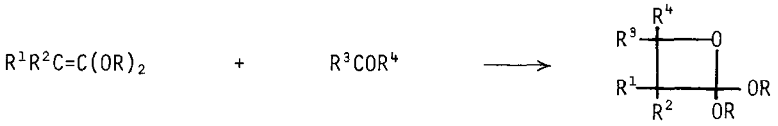
Summary. Cycloadditions of ketene acetals ($R^1R^2C{=}C(OR)_2$) with carbonyl compounds (R^3COR^4) are strongly promoted by increase or pressure. At 12 kbar oxetanes are even obtained from very polar ketene acetals (R^1,R^2=H,H or H,Cl) and - in the presence of a Lewis acid - with unactivated ketones (R^3 and R^4 = alkyl). The reaction proceeds *via* a *cisoid* dipolar transition state; when relevant mainly *trans*-substituted oxetanes are formed.

Polar (2+2)-cycloadditions show large, negative activation volumes which are in the same order of magnitude as those for Diels Alder reactions[1]. Whereas the application of Diels Alder reactions was broadly developed during the last decade[2] the exploration of polar (2+2)-cycloadditions is still at its advent. In this paper we describe the results of a study about cycloadditions of ketene acetals ($R^1R^2C{=}C(OR)_2$) with a variety of aldehydes and ketones at pressures ranging from 8-12 kbar (0.8-1.2 GPa).

The experiments were performed in a piston-cylinder, high-pressure apparatus for pressures up to 14 kbar. The reaction volume after compression is about 20 ml. The vessel is closed from below with a steel stopper and from above with a mobile piston. The vessel can be heated by pumping oil between the vessel and a second wall. More details about the apparatus and the sealing of the stopper and the piston will be given in a forthcoming publication.

For synthetic purposes 0.025 moles of a ketene acetal and 0.02 moles of a carbonyl compound were placed in a teflon ampoule of 8 ml which was further filled with dichloromethane. Two of these ampoules were inserted into the high pressure vessel filled with hexane as transmission medium. For analytical purposes ampoules of 0.5 ml were used so that the conversions in five different experiments could be followed at the same time.

Ketene acetals 1 undergo cycloadditions at normal pressure with carbonyl compounds having an electron-withdrawing α-substituent (*e.g.* R^4=CN) to yield oxetanes 2[3] according to Eqn (1).



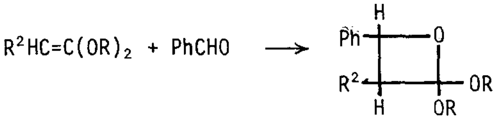
1 2

1a	$R^1=R^2=H$	R=Me	1e	$R^1=R^2=OMe$	R=Me
b	$R^1=H$, $R^2=Cl$	R=Me	f	$R^1=R^2=Me$	R=Me
c	$R^1=H$, $R^2=OMe$	R=Me	g	$R^1=H$, $R^2=Cl$	R=Et
d	$R^1=H$, $R^2=Me$	R=Me	h	$R^1=H$, $R^2=Me$	R=Et

In the presence of a Lewis catalyst unactivated aldehydes (R^4=H) can also be converted into oxetanes[3,4]; when R^1=H *cis*-substituted oxetanes appear to be the main products when the reactions are performed at low temperature in a non-polar solvent, and the catalyst is neutralized before work up. Ketones without an electron-withdrawing substituent (R^4 = alkyl) give only low yields in this reaction. The cycloaddition at normal pressure is supposed to proceed *via* a *trans*oid, dipolar transition state[3,5] (Fig 1a). This explains the observed stereochemistry and the formation of other products in the reactions of very polar ketene acetals like 1a and 1b.

The formation of oxetanes *via* Eqn (1) appeared to be strongly accelerated by an increase of the pressure (Table 1); 1d, which does not react with benzaldehyde at room temperature and normal pressure in the absence of a catalyst, is completely converted into an oxetane at 12 kbar within 30 min; 1a and 1b, which cannot be converted into oxetanes at normal pressure give mainly oxetanes at 12 kbar. Table 1 shows that considerable acceleration occurs in the range 8-12 kbar. The electronic influence of substituents (R^2) in 1 is not very large and seems mainly of inductive nature (Me accelerates, Cl and MeO retard)[7].

Table 1 *PERCENTAGE CONVERSION* AND CIS/TRANS RATIO (in parentheses) AFTER 20 MINUTES AT VARIOUS PRESSURES FOR THE REACTION:*



1 2

ketene acetal	12 kbar	10 kbar	8 kbar
1a, $H_2C=C(OMe)_2$	38%	25%	<5%
1d, $MeHC=C(OMe)_2$	94% (20/80)	66% (25/75)	38% (25/75)
1h, $MeHC=C(OEt)_2$	92% (30/70)	76% (30/70)	52% (30/70)
1b, $ClHC=C(OMe)_2$	18% (20/80)	<5%	
1g, $ClHC=C(OEt)_2$	31% (35/65)	25% (35/65)	<5%
1c, $(MeO)HC=C(OMe)_2$	35% (35/65)	30% (35/65)	~10%

*From solutions in $CDCl_3$ containing 2.2 mole/l of ketene acetal and 2 mole/l of benzaldehyde.

Determination of the *cis/trans* ratio in the product by NMR revealed that in all experiments the *trans*-oxetane was the main product. At normal pressure the *trans*-isomers are only isolated when the cycloaddition is performed under thermodynamic circumstances (long reaction times in a polar solvent). At high pressure the *trans*-oxetanes seem to be primary products, however; the *cis*-oxetane 2b (R^1=R^3=H, R^2=Me, R^4=Ph) prepared at room temperature did not undergo *cis*→*trans* isomerisation at 12 kbar. The results suggest that the high-pressure reaction proceeds *via* a dipolar, *cis*oid transition state, in which the bond formation between the α-carbon atoms is already far advanced (Fig 1b).

Fig 1a

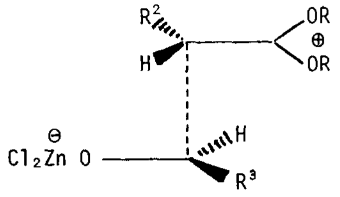
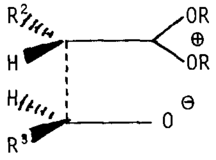


Fig 1b



Ketene acetals having two α-substituents reacted much slower. In the reaction with benzaldehyde **1e** (50% solution of equimolar amounts in $CDCl_3$) needed heating for 12 h at 50° to give 70% conversion. Under the same circumstances **1f** gave only 30% conversion. Apparently the accelerating effect of the Me-groups is counteracted by increased crowding.

Further experiments revealed that the scope of the oxetane synthesis at high pressure can be enlarged by addition of a Lewis acid as a catalyst. Simple ketones without electron-withdrawing α-substituents can then be converted in high yields into oxetanes. Some representative examples of the preparation of oxetanes *via* the uncatalyzed as well as the catalyzed reaction are given in Table 2, together with some physical data[8] of the products.

Table 2 PREPARATION OF OXETANES FROM REACTION (1) AT 12 KBAR

ketene acetal	carbonyl compound	reaction time (h) / temp (°C)	*cis/trans* ratio	b.p.[a] °C/mm	Yield (%)	NMR, δ ppm (CCl_4)
1a	C_6H_5CHO	3/25		not dist.	~70[b]	2.40-2.70 (A part of ABX); 2.87-3.27 (B part of ABX); 3.30 and 3.33 (s, 6H); 5.07-5.30 (X part of ABX); 7.03-7.43 (arom. pattern, 5H).
1d	C_6H_5CHO	1/25	20/80	77-79/ 0.2	90	see reference 3
1g	C_6H_5CHO	8/25	<5/95[c]	140/ 0.2[c]	60	1.23 (t, 3H); 1.28 (t, 3H); 3.43-4.03 (m, 4H); 4.20, 4.30, 4.97 and 5.07 (AB, J_{AB} = 6 Hz); 7.30 (b.s., 5H).
1d	c - $C_6H_{11}CHO$	8/25		56/ 0.8	80	1.00 (d, J=7 Hz, 3H); 1.00-2.00 (m, 10H); 2.50 (q, J=7 Hz, 1H); 3.20 (s, 6H).
1d	*tert.* C_4H_9CHO	8/50	<5/95	80/ 15[e]	30[f]	0.87 (s, 9H); 1.10 (d, J=7 Hz, 3H); 2.80-3.30 (m, 1H); 3.13 and 3.22 (s, 6H); 3.40 (d, J=6 Hz, 1H).
1d	cyclohexanone	5/25[d]		73/ 0.5	80	1.07 (d, J=7 Hz, 3H); 0.60-2.10 (m, 11H); 2.27-2.73 (m, 1H); 3.17 (s, 6H); 3.10-3.43 (dd partly hidden under OCH_3, 1H).
1e	cyclohexanone	15/50[d]		78/ 0.5	70	1.10-2.20 (m, 10H); 3.30 (s, 12H).
1d	$CH_3COCH_2CH_2OCOH$	8/25[d]		78/ 0.5	75	1.03 (d, J=7 Hz, 3H); 1.25 and 1.40 (s, two isomers (9/15), 3H); 1.83-2.27 (m, 2H); 2.50-3.00 (m, 1H); 3.22 (s, 6H); 4.23 (t, J=7 Hz, 2H); 7.96 (s, 1H).

[a] Distilled with a vigreux column of 15 cm x 10 mm.

[b] See note 9.

[c] Obtained from bulb to bulb distillation of a reaction mixture with a *cis/trans* ratio of 35/65. The *cis*-compound decomposes partly during the distillation.

[d] In the presence of ~1 mole % of $ZnCl_2$. The catalyst was neutralized with triethylamine before work up.

[e] Bulb to bulb distillation.

[f] Conversion of the reaction is 50%.

The oxetanes are reactive cyclic orthoesters which can be easily hydrolyzed into stable β-hydroxy esters[5,6]. In the hydrolysis of 2 (R=Me, $R^1=R^2=R^3=H$, $R^4=Ph$) the β-hydroxy ester is contaminated (~20%) with cinnamic acid methyl ester, because 2 decomposes partly during removal of the solvent *in vacuo*[9]. In all other cases, however, the hydroxy esters are obtained as pure compounds[10].

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7. At normal pressure when the (2+2) cycloaddition is probably more frontier orbital controlled higher differences in reactivity between the ketene acetals 1b and 1c have been observed which can be ascribed to the expected higher HOMO energy of 1c.
8. All oxetanes have been fully characterized from their NMR, IR and Mass spectra and by comparison with data from the literature. For typical spectroscopic data, see reference 3. Due to their thermal instability and their sensitivity for moisture elemental analyses were only obtained from the more stable oxetanes derived from 1e.
9. In the NMR-spectrum of the concentrated reaction mixture the presence of compound PhCHOH-CH=C$(OMe)_2$ (~20%) was indicated from the absorbtions at δ(CCl_4), 5.43 (d, J=9 Hz, H-COH); 3.80 (d, J=9 Hz, H-C=C) and 3.63 (b.s., OCH_3).
   It was suggested before that this compound is formed *via* a proton shift in the dipolar intermediate and that it decomposes in the presence of acid into cinnamic acid methyl ester[3]. The compound could probably be detected because the high pressure reaction is carried out under neutral conditions. Due to the presence of this compound the hydrolysis of the oxetane leads to a mixture of the β-hydroxy ester and the cinnamic acid methyl ester.
10. The synthesis of the β-hydroxy esters has been described in reference 6. Some constants of β-hydroxy esters which have not been described before are given below.
    $C_6H_5CHOHCHClCOOC_2H_5$, b.p. 110°/0.5 mm (bulb to bulb distillation), NMR δ ppm (CCl_4), 1.03 and 1.20 (t, J=7 Hz, 3H, two isomers); 3.70 (b.s., OH); 3.92-4.43 (m, 3H); 4.80-5.13 (s, 1H); 7.30 (s, 5H).
    c-$C_5H_{10}COHCHCH_3COOCH_3$, b.p. 65°/0.5 mm, δ($CCl_4$), 1.00-1.85 (m, 10H); 1.20 (d, J=7 Hz, 3H); 2.40 (q, 1H); 2.80 (s, 1H); 3.70 (s, 3H).
    c-$C_5H_{10}COHC(OCH_3)_2COOCH_3$, b.p. 85°/ 0.5 mm, δ($CCl_4$), 1.50-2.33 (m, 10H); 3.20 (s, 6H); 3.80 (s, 3H); OH-proton partly hidden under CH_3O.

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