Zinc Chloride Catalysis in Cycloadditions between Ketene Acetals and Electron-Poor Olefins; Synthesis of Highly Substituted 1,1-Dimethoxycyclobutanes

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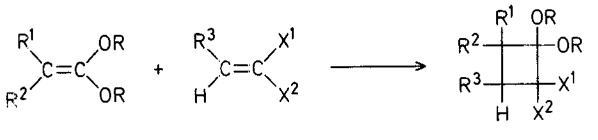
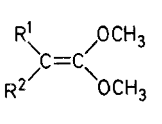
Ketene acetals (**1**)[1] have proved to be useful components for cycloadditions[1-4] with electron-poor olefins (**2**); the cycloaddition products (**3**) have been used for the preparation of tetraalkoxycyclobutenes and tetraalkoxybutadienes[5] (when $R^1 = R^2 = OR$), cyclobutanones[6], cyclobutenediones[7] (again, when $R^1 = R^2 = OR$), and several types of γ-functionalized esters[8,9].



1 **2** **3**



1a $R^1 = CH_3$; $R^2 = H$
1b $R^1 = Cl$; $R^2 = H$
1c $R^1 = R^2 = OCH_3$
1d $R^1 = R^2 = CH_3$

With unsubstituted ketene acetals (**1**, $R^1 = R^2 = H$), the [2+2]-cycloaddition seems to be quite generally applicable: even weakly electron-poor olefins like acrylonitrile (**2**, $R^3 = X^2 = H$, $X^1 = $—CN) or acrylic esters (**2**, $R^3 = X^2 = H$, $X^1 = COOCH_3$) can be converted into cyclobutanes with these ketene acetals. Substituted ketene acetals (e.g. **1**, $R^1 = R^2 =$ alkyl or alkoxy) generally require higher temperatures in such cycloadditions, and cyclobutanes can only be obtained[3,9] with electrophilic olefins containing at least two electron-withdrawing substituents one of which should have the electron-withdrawing ability of a cyano group.

We have already shown[10] that analogous cycloadditions between ketene acetals and electron-poor *carbonyl compounds* can be strongly accelerated by the addition of small amounts of Lewis acids such as zinc chloride; under these conditions, oxetanes can even be obtained from simple aldehydes or ketones. Zinc chloride is preferentially bonded to the carbonyl oxygen, thus lowering the LUMO energy of the electron-poor component[11,12]. Polymerization of ketene acetals remains slow in the presence of this Lewis acid. We report here the use of zinc chloride catalysis in cycloadditions between ketene acetals and electron-poor *olefins*. A prerequisite for Lewis acid catalysis in these cycloadditions is the presence of a substituent in the electron-poor component which can be bonded to the Lewis acid (e.g. —CN, —$COOCH_3$, —NO_2).

Experiments were performed with a series of four 1,1-dimethoxyalkenes (**1**, ketene dimethyl acetals) of the following order of reactivity: R^1, $R^2 = CH_3$, H > Cl, H > CH_3, $CH_3 \approx OCH_3$, OCH_3. It was found that in the presence of zinc chloride ketene acetal **1a** reacts with acrylonitrile and with methyl acrylate (Table), with the former even at room temperature. Ketene acetal **1b** also reacts smoothly with relatively electron-poor olefins whereas the less reactive ketene acetals **1c** and **1d** which in the absence of zinc chloride do not undergo cycloaddition with acrylonitrile (3 days at reflux temperature) give cycloaddition products with weakly electrophilic olefins in satisfactory yields at a reaction temperature of ~80°C in the presence of zinc chloride.

It is a general experience that cyclobutanes obtained from ketene acetals having a more symmetrical π-electron distribution (**1c**, **1d**) are more stable than those obtained from less symmetrically substituted ketene acetals (**1a**, **1b**). Cycloaddition of the latter with particularly electron-poor olefins[9] may lead to products which are derived from dipolar intermediates. This different behavior is also observed in the Lewis acid-catalyzed cycloadditions of **1a** and **1c** with β-nitrostyrene: the reaction of **1c** yields the expected stable [2+2]-cycloaddition product (**3**) whereas the reaction of **1a** leads to the formation of the instable 5,6-dihydro-4*H*-1,2-oxazine 2-oxide **4**.

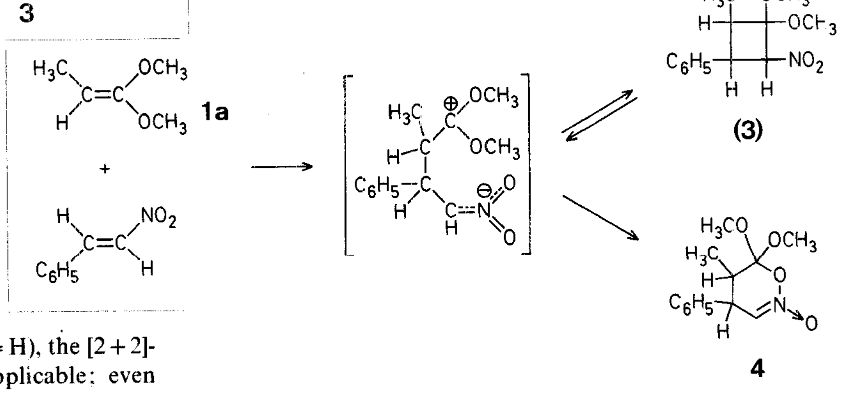


Table. 1,1-Dimethoxycyclobutanes (**3**; R = CH_3) from Ketene Acetals (**1a–d**) and Electron-Poor Olefins (**2**) in the Presence of Zinc Chloride (5 mol-%)

Ketene acetal	Product 3 (R = CH_3)					Reaction conditions (time, temperature [°C], solvent)	Yield [%]	b.p. [°C]/torr or m.p.	Molecular formula[a] or Lit. data	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[b] δ [ppm]
	R^1	R^2	R^3	X^1	X^2					
1a	CH_3	H	—CN	H	—CN	1 h, 25°, acetonitrile	80	sirup	$C_9H_{12}N_2O_2$ (180.2)	1.25, 1.29 (d, J = 7 Hz, CH_3, two isomers); 2.6–3.7 (m, 3 H, CH—CH—CH); 3.23, 3.28, 3.49 (s, 6 H, OCH_3)
1a	CH_3	H	H	Cl	—CN	30 min, 25°, acetonitrile	80	b.p. 74°/1	$C_8H_{12}ClNO_2$ (189.6)	1.23 (d, J = 7 Hz, 3 H, CH_3); 2.1–3.0 (m, 3 H, $CHCH_2$); 3.33, 3.46 (s, 6 H, OCH_3)
1a	CH_3	H	H	—CN	H	4 h, 25°, acetonitrile	60	b.p. 56–58°/0.7	$C_8H_{13}NO_2$ (155.2)	1.07, 1.17 (d, J = 7 Hz, CH_3, two isomers); 1.4–3.1 (m, 4 H, CH—CH_2—CH); 3.18, 3.21, 3.39 (s, 6 H, OCH_3)
1a	CH_3	H	H	—$COOCH_3$	H	4 h, 80°, acetonitrile	70	b.p. 60–62°/1	$C_9H_{16}O_4$ (188.2)	1.15, 1.25 (d, J = 7 Hz, CH_3, two isomers); 1.3–3.3 (m, 4 H, CH—CH_2—CH); 3.04, 3.14, 3.20, 3.23 (s, 6 H, OCH_3); 3.60 (s, 3 H, OCH_3)
1b	Cl	H	H	Cl	—CN	2 h, 25°, acetonitrile	80	b.p. 57–58°/0.1	$C_7H_9Cl_2NO_2$ (209.1)	2.2–3.4 (m, 2 H, CH_2); 3.40, 3.57, 3.63 (s, 6 H, OCH_3, two isomers); 4.1–4.8 (m, 1 H, CHCl)
1c	OCH_3	OCH_3	H	—CN	H	3 h, 80°, neat	70	m.p. 50–52°	$C_9H_{15}NO_4$ (201.2)	2.05–2.40 (AB part of ABX, 2 H, CH_2); 2.50–3.10 (X part of ABX, 1 H, CH—CN); 3.21, 3.29, 3.46, 3.54 (s, 12 H, OCH_3)
1c	OCH_3	OCH_3	—CN	H	—CN	2 h, 80°, neat	70[c]	m.p. 135–136°	m.p. 136–138°[2]	3.20 (s, 2 H, CH—CN); 3.33, 3.45 (s, 12 H, OCH_3)
1c	OCH_3	OCH_3	H	Cl	—CN	3 h, 70°, neat	70	m.p. 62–64°	$C_9H_{14}ClNO_4$ (235.7)	2.23, 2.45 (part of AB, 1 H, CH_2); 2.70, 2.92 (part of AB, 1 H, CH_2); 3.24, 3.49 (s, 12 H, OCH_3)
1c	OCH_3	OCH_3	4-O_2N—C_6H_4—	H	—NO_2	4 h, 80°, neat	65	m.p. 122–125°	$C_{14}H_{18}N_2O_8$ (342.3)	3.23, 3.40, 3.50, 3.57 (s, 12 H, OCH_3); 4.27, 4.42 (part of AB, CH—C_6H_4—NO_2); 4.90, 5.05 (part of AB, 1 H, CH—NO_2); 7.45, 7.60, 8.08, 8.23 (AB with fine splitting, $C_6H_4(NO_2)$
1c	OCH_3	OCH_3	C_6H_5	H	—NO_2	5 h, 80°, neat	60	sirup	$C_{14}H_{19}NO_6$* (297.3)	3.20, 3.35, 3.47, 3.53 (s, 12 H, OCH_3); 4.13, 4.30 (part of AB, 1 H, $C\underline{H}$—C_6H_5); 4.88, 5.04 (part of AB, 1 H, CH—NO_2); 7.30 (bs, 5 H, C_6H_5)
1c	OCH_3	OCH_3	—$(CH_2)_3$—CO—		H	7 h, 70°, acetonitrile	60	b.p. 82–85°/1	$C_{12}H_{20}O_5$* (244.3)	1.6–2.5 (m, 7 H, CH_2—CH_2—CH_2—CH); 2.80, 2.90 (part of AB, 1 H, CH—CO); 3.23, 3.27, 3.34, 3.37 (s, 12 H, OCH_3)
1c	OCH_3	OCH_3	H	—$COOCH_3$	H	8 h, 80°, neat	50	b.p. 76–79°/0.6	$C_{10}H_{18}O_6$ (234.25)	1.7–3.2 (m, 3 H, CH_2—CH); 3.21, 3.32, 3.65 (s, 12 H, OCH_3)
1d	CH_3	CH_3	H	—CN	H	12 h, 100°, neat	50	b.p. 99–100°/15	$C_9H_{12}NO_2$ (166.2)	1.20 (d, J = 7 Hz, 6 H, CH_3); 1.73, 1.90 (AB part of ABX with δ_{AB} small 2 H, CH_2); 2.86–3.20 (X part of ABX, 1 H, CH—CN); 3.30, 3.43 (s, 6 H, OCH_3)

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[a] The microanalyses of products **3** (except those marked with an asterix) were in satisfactory agreement with the calculated values: C, ±0.35; H, ±0.25; N, ±0.23. The mass spectra of all products **3** gave characteristic peaks for $M^+ - CH_3$, $M^+ - OCH_3$, and $M^+ - R^1R^2C{=}CR^3H$.

[b] Varian T60 spectrometer.

[c] Yield 56% after 3 days at 100°C without solvent[2].

A similar reaction has been observed in cycloadditions between enamines and nitroalkenes[13].

From the reaction conditions (Table) it appears that the reactivity of the electron-poor components used decreases, roughly, in the order: $H_2C{=}C(Cl){-}CN$, $NC{-}CH{=}CH{-}CN$ > $Ar{-}CH{=}CH{-}NO_2$ > $H_2C{=}CH{-}CN$ > $H_2C{=}CH{-}COOCH_3$. Further reduction of the reactivity by introduction of substituents which enhance the LUMO energy or reduce the LUMO coefficients[11,12] of the olefinic compounds **2** [as in $C_6H_5{-}CH{=}CH{-}CN$, $H_3C{-}CH{=}CH{-}COOCH_3$, and $H_2C{=}C(CH_3){-}COOCH_3$] precludes the formation of cyclobutanes from **2** and ketene acetals **1** even in the presence of zinc chloride. This applies also to the reactive ketene acetal **1a**; in attempted cycloadditions of this acetal with the above-mentioned electron-poor olefins, the reaction conditions required (8 h at 90°C) led mainly to polymerization of **1a** under the influence of the catalyst, less than 10% of the desired cyclobutane being present in the reaction mixture according to N.M.R. analysis.

1,1-Dimethoxycyclobutanes (3, R = CH_3); General Procedure:
To a stirred mixture of a ketene dimethyl acetal (**1**; 110 mmol) and an electron-poor alkene (**2**; 100 mmol) is added zinc chloride (0.7 g, 5 mmol), either neat or dissolved in acetonitrile (5 ml). Stirring is continued under the conditions given in the Table. The mixture is then cooled to room temperature, a solution of triethylamine (1 g) in ether (50 ml) is added, and the precipitate ($ZnCl_2$-triethylamine salt) is filtered off. The solvent is removed in vacuo. If the residue remains fluid it is distilled through a 20 cm × 10 mm Vigreux column; if it is crystalline or syrupy it is washed several times with pentane, and the residual pentane is removed in vacuo. Syrupy products are not further purified. Crystalline products are recrystallized from methanol.

6,6-Dimethoxy-5-methyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (4):
A mixture of methylketene dimethyl acetal (**1a**; 1.1 g, 11 mmol), *β*-nitrostyrene (1.5 g, 10 mmol), and zinc chloride (0.06 g) is stirred for 1 h at 60°C. Work-up as described above affords the crude product **4** which cannot be further purified because of its instability; yield: 1.9 g (80%); purity (^{1}H-N.M.R.): ~90%.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.72$, 0.93 (d, $J = 7$ Hz, CH_3, two isomers, 45:55); 3.39, 3.47, 3.53 (s, 6H, OCH_3); 2.0–2.8 (m, 1H, $HC{-}CH_3$); multiplet of $HC{-}C_6H_5$ is hidden under OCH_3 absorptions; 6.26, 6.40 (d, $J = 3$ Hz, $HC{=}N$, two isomers); 7.23 ppm (br. s, 5 H_{arom}).

Received: April 11, 1983

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