Monatshefte für Chemie 125, 425–432 (1994)

Monatshefte für Chemie
Chemical Monthly

Ketal Mediated Diels–Alder Type Dimerization of an Arylideneacetone

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Summary. During ketalization with ethyleneglycol an arylideneacetone **1** dimerized via its ketal **2** to give a 4-acetyl-3,5-diarylcyclohexanone ketal **5**.

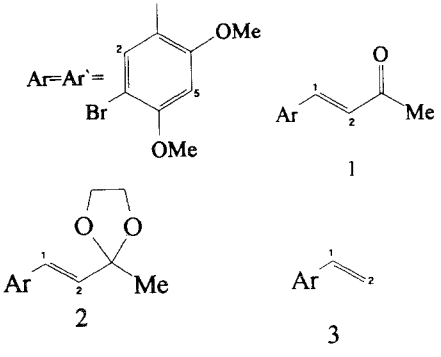
Keywords. Diels–Alder cycloaddition; Ketal-enolether equilibrium.

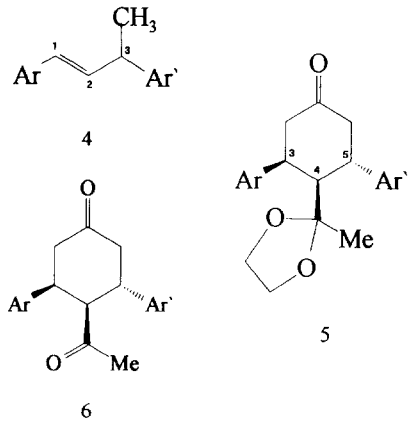
Ketal-vermittelte Diels–Alder-Dimerisierung eines Arylidenacetons

Zusammenfassung. Bei der Ketalisierung des Arylidenaceton-Derivates **1** erfolgt eine Diels–Alder-Dimerisierung des Ethylenketals **2** zu einem 4-Acetyl-3,5-diaryl-cyclohexanon **5**.

Results and Discussion

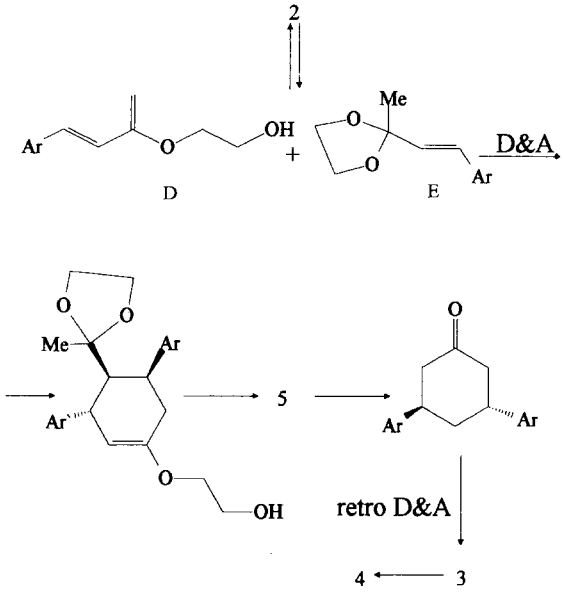
A synthetic scheme directed towards the synthesis of garugamblin II [1], a macrocyclic diarylheptanoid, required the ketalization of the enone **1** with ethylene glycol. Following the routine procedure, after 5 h reaction time the desired ketal **2** was isolated along with unchanged starting material and two apolar compounds which were identified as the styrene **3** and its dimerization product **4**. Acid catalyzed dimerization of styrene to 1,3-diphenyl-1-butene has been described earlier [2].





Prolonged reaction time seemingly did not result in the complete conversion of the starting material, only in lower yield of ketal **2**. Careful chromatography, however, revealed, that in fact the starting material was gradually replaced by a new compound of almost the same R_f value. The product was indentified as the cyclohexanone **5**, its hydrolysis gave the diketone **6**.

For the formation of compounds **3**–**6** we suggest the pathway shown in Scheme 1.



Scheme 1

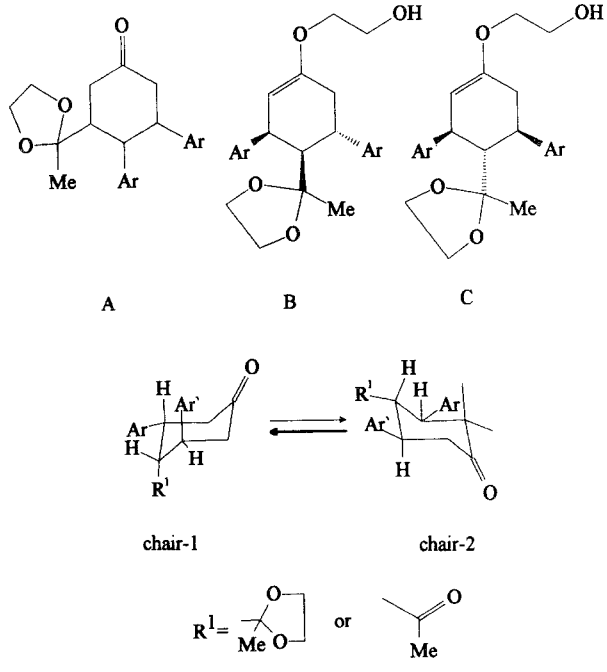
Acid catalyzed ring opening of ketal **2** or elimination of water from a hemiketal intermediate generates a diene (**D**), which then enters into Diels-Alder cycloaddition with the parent ketal to form the cyclohexanone **5**. Equilibrium of enone ethylene ketals with the corresponding 2-(2-hydroxyethoxy)-1,3-dienes is known [3]. In principle, the enol form of the parent enone (**1**) could also have served as the diene component, but we found that in the absence of ethylene glycol no reaction took place.

Formation of styrene **3** might be explained by hydrolytic loss of the 4-substituent followed by cycloreversion, but so far no experimental evidence could be provided in support of this hypothesis.

NMR Studies

Structures of compounds **1–4** could be derived from 1D NMR data (see Experimental). Elucidation of the structure of the adduct was carried out on both the primary adduct **5** and its hydrolysis product **6**. This study was simplified by the assumption that the configuration of the dienophile (**E**) was conserved in the addtion, i.e. a product with a *cis,cis* configuration could be excluded, but complicated by the possibility of the formation of two regioisomers, two diastereomers of each regioisomer and ring inversion of the cyclohexanone ring. This situation required the unambiguous assignement of ^{1}H and ^{13}C signals which was carried out by decoupling experiments, NOE, CH-COSY, DEPT and semiselective INEPT measurements [4] optimized for J(C, H) couplings of 7 Hz, suitable for the diagnosis of proton-carbon connectivities through several bonds (Tables 1–5).

Since, as said above, in **5** the disposition of the ketal side chain and one of the aryl groups must be *trans*, the main task is to determine the relative configuration of the acyl group and the second aryl group. Starting from the 2-H_2 methylene protons, multiplicity of signals and decoupling experiments assured an unambigous assignment of the protons of the cyclohexanone ring. The high value of the vicinal J(2-H_{ax},3-H_{ax}) coupling constant (12.0 Hz) indicated that the conformational equilibrium (**chair-1** ⇄ **chair-2**) was much shifted in favour of **chair-1** in which 3-Ar was equatorial (Scheme 2). From the value of J(H-3,H-4) (5.5 Hz) it is apparent that



Scheme 2

Table 1. Characteristic ^1H chemical shifts and proton–proton coupling constants (Hz) of compounds **5** and **6**

	2-H_{eq}	2-H_{ax}	3-H	4-H	5-H	6-H_{eq}	6-H_{ax}	2′-H	2″-H	5′-H	5″-H	MeO′	MeO″	Me
5[a]	1.76	2.53	3.82	3.47	3.57	2.16	2.16	7.27	7.73	6.46	6.46	3.83 3.90[c]	3.89[c] 3.93	1.56
5[b]	1.86	2.81	4.21	3.54	3.98	2.33	2.62	7.78	8.15	6.07	6.07	3.26[c] 3.31[c]	3.28[c] 3.41[c]	1.47
6[a]	2.50	3.10	3.77	3.61	3.73	2.67	2.84	7.11	7.28	6.41	6.49	3.71 3.88	3.86 3.90	1.81

J	(2-H_{ax}, 3-H)	(2-H_{eq}, 3-H)	(3-H, 4-H)	(4-H, 5-H)	(5-H, 6-H_{ax})	(5-H, 6-H_{eq})	(2-H_{ax}, 2-H_{eq})	(6-H_{ax}, 6-H_{eq})
5[a]	12.8	3.3	5.5	5.5			13.2	
5[b]	12.0	3.7	5.5	4.7	6.0	6.2	12.9	13.9
6[a]	10.5	4.7	5.0	6.0	6.0	7.7	15.6	16.0

[a] Measured at 400 MHz in $CDCl_3$

[b] Measured at 300 MHz in C_6D_6, ^4J(2-H_{eq}, 4-H) = 1.0 Hz, ^4J(4-H, 6-H_{eq}) = 1.4 Hz

[c] Tentative assignment

the C-4 substituent is axial. Orientation of Ar-5, however, could not be determined directly due to the accidental isochrony of 6-H_2 methylene protons. therefore the solvent was changed from $CDCl_3$ to C_6D_6, which exposed the coupling constants between H-5 and H_2-6 (6.0 and 6.2 Hz). This confirmed their *gauche* arrangement and consequently the axial disposition of the 5-Ar group.

Assignment of signals to individual aryl groups became possible by semiselective INEPT measurements (Table 5). Experiments starting at H_{eq}-2 and H-3 protons produced polarization transfer at C-1′, and at C-1′, C-2′, and C-6′ respectively which permitted also the assignment of methoxy and aromatic protons signals to individual aryl rings.

Table 2. Results of 1D NOE measurements for compound **5** and **6**

	Irradiated proton	NOE observed (%)
5[a]	2-H_{ax}	2-H_{eq} (22.0), 6-H_{ax} (1.7), 2′-H (10.5)
	4-H	3-H (6), 2″-H (7.9), Me (6.9)
	5-H	6-H_2 (6.2), 2″-H (3.5), Me (2.9)
	2′-H	2-H_{ax} (5.5), 2-H_{eq} (1.5), Me (1.0)
	2″-H	3-H (8), 4-H (6.8), 5-H (2.5), 6-H_{eq} (1.9)
	Me	4-H (6.2), 5-H (3.1), 2′-H (2.5)
6[b]	2-H_{ax}	2-H_{eq} (28.5), 2′-H (12.1)
	4-H	3-H (> 1), 5-H (> 1), 2″-H (4.4), Me (5.0)
	6-H_{eq}	5-H (4.0), 6-H_{ax} (> 18), 2″-H (6.0)
	2′-H	2-H_{ax} (6.7), 3-H (2.6)
	2″-H	3-H (1), 4-H (3.7), 5-H (3.0), 6-H_{eq} (3.3)
	5′-H	MeO′ (11.1 and 9.0)
	5″-H	MeO″ (12.4 and 9.0)
	Me	4-H (5.9), 5-H (4.7), 2′-H (1.2)

[a] Measured at 250 MHz in $CDCl_3$

[b] Measured at 400 MHz in $CDCl_3$

Table 3. Proton–proton 2D NOE correlations of compound **5**[a]

Proton	Resonances showing NOE cross peaks
2-H_{eq}	2-H_{ax}(s), 3-H(m), 2′-H(w)
2-H_{ax}	2-H_{eq}(s), 3-H(w), 6-H_{ax}(w), 2′-H(m)
3-H	2-H_{eq}(m), 2-H_{ax}(w), 4-H(m), 6-H_{eq}(w), 2′-H(w), 2″-H(w)
4-H	3-H(m), 5-H(w), 2″-H(m), Me(m)
5-H	4-H(w), 6-H_{ax}(m), 6-H_{eq}(w), 2″-H(w), Me(w)
6-H_{eq}	3-H(w), 5-H(w), 6-H_{ax}(s), 2″-H(w)
6-H_{ax}	2-H_{ax}(w), 5-H(m), 6-H_{eq}(s)
Me	4-H(m), 5-H(w)
2′-H	2-H_{ax}(m), 2-H_{eq}(w), 3-H(m)
2″-H	3-H(w), 4-H(m), 5-H(w), 6-H_{eq}(w)

[a] Measured at 300 MHz in C_6D_6

Table 4. ^{13}C Chemical shifts of compounds **5** and **6**

	5[a]	**6**[b]		**5**	**6**
C-1	209.2	210.6	Me	31.8	31.8
C-2	35.5	42.2	4-C′	109.9	210.5
C-3	32.9	33.8			
C-4	53.3	53.6			
C-5	33.5	35.1			
C-6	37.7	43.4			
C-1′	124.9	122.2	MeO	55.2	55.3
C-2′	133.1	131.8		55.3	55.6
C-3′	102.7	101.9		55.6	56.2
C-4′	155.8	155.5		55.6	56.3
C-5′	96.3	96.2			
C-6′	157.5	156.9			
C-1″	128.0	125.0	OCH_2	64.0	
C-2″	132.2	131.9		64.3	
C-3″	102.4	101.8			
C-4″	155.3	155.4			
C-5″	96.8	96.6			
C-6″	157.4	156.9			

[a] Measured at 100 MHz in C_6D_6
[b] Measured at 62.5 MHz in $CDCl_3$

Table 5. $^1H/^{13}C$ Long-range correlation for compounds **5** and **6** observed by semiselective 1D INEPT measurements

	Proton	Carbon
5[a]	2-H_{eq}	C-3, C-4, C-1′
	3-H	C-1, C-2, C-4, C-1′, C-2′, C-6′, 4-C
	5-H	C-1, C-3, C-4, C-6, C-1″, C-2″, C-6″, 4-C
	2′-H	C-3, C-3′, C-4′, C-6′
	2″-H	C-5, C-3″, C-4″, C-6″
6[b]	2-H_{eq}	C-1, C-3, C-4, C-1′
	4-H	C-1′, 4-C′
	6-H_{ax}	C-1, C-4, C-1″
	2″-H	C-5, C-3″, C-4″, C-6″
	5″-H	C-1″, C-3″, C-4″, C-6″

[a] Measured at 100 MZz in C_6D_6
[b] Measured at 62.5 MHz in $CDCl_3$

The INEPT spectrum based on H-3 as anchor atom contained the signal of the quaternary carbon of the ketal group proving that this group was attached to C-4. In 1D and phase sensitive 2D NOE experiments intensity enhancements and the appearance of cross peaks at signals of sterically close protons gave further support to the proposed relative configuration and for the dominance of conformation

chair-1. Irradiation of 2′-H caused positive n.O.e. at H_{ax}-2 and CH_3 protons which permitted to conclude that in the dominant rotamer involving the C-3–C-1′ bond H-2′ was under the plane of the cyclohexanone ring. Concerning the axial orientation of the ketal group, n.O.e. effects between CH_3, H-2′ and H-5 indicated that the methyl group was turned away from the cyclohexanone ring. Since H-2″ showed n.O.e. with H-3, H-4, H-5 and H_{eq}-6 simultaneously, no preferred rotamer involving the C-5–C-1″ bond can be assumed.

Similar studies on the acetyl compound **6** showed that conformation of **5** and **6** are analogous.

Although molecular orbital theory [5] would suggest 1,3-diaryl substitution in the cycloaddition product **5**, alternative structures with vicinal aryl groups, such as **A** could not be completely ruled out. Note that a structure analogous to **6** (Ar = Ph) has been suggested by Gustavson and Ullenius [6] for a minor product obtained when benzylideneacetone was reacted with heterocuprates, i.e. under totally different experimental conditions.

Computational Studies

Trans disposition of the two aryl groups, i.e. one of them in axial position, is remarkable and therefore we carried out molecular mechanics calculations on the hypothetical primary enolether type adducts **B** and **C**. This confirmed what could be predicted also by simple reasoning, i.e. that the steric energy of **B** was higher (by 4.65 kcal mol^{-1}) than that of **C** [7].

Unfortunately no theoretical justification for the exclusive formation of the 1,3-diaryl regioisomer **5** was borne out of molecular orbital calculations. HOMO/LUMO interaction energy of the two modes of approch were identical within 0.037 eV. Also the values of the orbital coefficients did not indicate preference for any of the two possible regioisomers either.

Experimental Part

All melting point are uncorrected. Evaporations were carried out in vacuo, chromatography on silica gel. ^{1}H- and ^{13}C-NMR spectra were taken at 250/400 and 62.5/100 MHz respectively on Bruker AC-250 and AM-400 spectrometers at room temperature, with *TMS* as internal standard utilizing a 32 K data memory. N.O.e NOESY, DEPT and INEPT measurements were performed applying the Bruker software package.

1-(3-Bromo-4,6-dimethoxyphenyl)-1-butene-3-one (**1**)

To a solution of 3-bromo-4,6-dimethoxybenzaldehyde [8] (12.2 g, 50 mmol) in acetone (140 ml) 10% aqueous KOH solution (36 ml) was added with intensive stirring over 10 min. Stirring was continued for 1 h followed by acidification with 10% aq. HCl. On evaporation of acetone the product precipitated. It was filtered off, washed thoroughly with water, dried and recrystallized twice from methanol to give pale yellow crystals (12.4 g, 87%), m.p. 141–142 °C. ^{1}H-NMR (100 MHz, $CDCl_3$): δ = 2.25 (s, 3H, $COCH_3$), 3.91 and 3.96 (2s, 6H, $2OCH_3$), 6.62 (d, J = 16 Hz, 1H, 2-H), 6.42 (s, 1H, 5′-H), 7.64 (s, 1H, 2′-H), 7.71 (d, J = 16 Hz, 1H, 1-H). $C_{12}H_{13}BrO_3$ (285.1): calcd. C 50.54, H 4.60; found C 50.49, H 4.68.

Reaction of **1** *with Ethyleneglycol*

a) Ketalization for 5 h: Ketone **1** (12.5 g, 43.6 mmol), ethyleneglycol (7.5 ml) and *p*-toluenesulfonic acid (0.1 g) were refluxed using a Dean-Stark trap for 5 h. The solution was washed with aq. sodium

hydrogen carbonate solution, dried, evaporated and the residue chromatographed on silica gel (eluant benzene/ethyl acetate, 4:1) to give (in order of increasing polarity) *3-bromo-4,6-diemthoxyphenylethene* (**3**) as an oil, (0.18 g), *1,3-bis(3-bromo-4,6-dimethoxyphenyl)-1-butene* (**4**) (2.0 g) as a resin, and *2-methyl-2-[2-(3-bromo-4,6-dimethoxyphenyl)-1-ethenyl)]-1,3-dioxolane* (**2**) (4.7 g, 33%), as pale yellow crystals of undefined m.p. (88–100 °C) and ketone **1** (1.15 g).

2: ^{1}H-NMR (60 MHz, $CDCl_3$): $\delta = 1.55$ (s, 3H, CCH_3), 3.03 and 3.88 (2s, 6H, $2OCH_3$), 3.96 (s, 4H, CH_2CH_2), 6.03 (d, $J = 16.0$ Hz, 1H, 1-H), 6.41 (s, 1H, 5′-H), 6.82 (d, $J = 16.0$ Hz, 1H, 2-H), 7.53 (s, 1H. 2′-H). $C_{14}H_{17}BrO_4$ (329.2): calcd. C 51.08, H 5.20; found C50.98, H5.13.

3: ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.85$ and 3.90 (2s, 6H, $2OCH_3$), 5.17 (dd, $J = 11.0$, 1.4 Hz, 1H, (*E*)-2-H), 5.61 (dd, $J = 17.6$, 1.4 Hz, 1H, (*Z*)-1-H), 6.44 (s, 1H, 5′-H), 6.88 (dd, $J = 11.0$, 17.6 Hz, 1H, 1-H), 7.60 (s, 1H, 2′-H). ^{13}C-NMR (62.5 MHz, $CDCl_3$): $\delta = 55.8$ and 56.3 (OCH_3), 96.4 (C-5′), 102.3 (C-3′), 113.3 (=CH_2), 120.9 (C-1′), 129.9 (C-1), 130.3 (C-2), 156.1 and 157.0 (C-4′ and C-6′). $C_{10}H_{11}BrO_2$ (243.1): calcd. C 49.40, H 4.56; found C 49.30, H 4.38.

4: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (d, $J = 7$ Hz, 3H, CH_3), 3.85 (3H), 3.86 (3H), 3.90 (6H) (4s, $4OCH_3$), 3.93 (m, 1H, 3-H), 6.22 (dd, $J = 16.0$, 6.5 Hz, 1H, 2-H), 6.58 (dd, $J = 16.0$, 1.5 Hz, 1H, 1-H), 6.43 and 6.48 (2s, 2H, 5′, 5″-H), 7.30 (s, 1H, 2″-H), 7.55 (s, 1H, 2′-H). ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 20.1$ (C-4), 35.0 (C-3), 55.85, 55.87, 56.38 and 56.44 ($4OCH_3$), 96.59 and 96.9 (C-5′ and C-5″), 101.9 and 102.4 (C-3′ and C-3″), 121.0 (C-1′), 121.4 (C-1), 128.2 (C-1″), 130.3 (C-2′), 131.4 (C-2″), 134.0 (C-2), 154.8, 155.5, 156.6, and 156.9 (C-4′, C-4″, C-6′ and C-6″). $C_{22}H_{22}Br_2O_4$ (510.2): calcd. C 51.79, H 4.37; found C 51.53, H 4.42.

b) Ketalization for 16 h: When ketalization, as described under a) was continued for 16 h and the product subjected to chromatography (eluant hexane/ethyl acetate, 4:1) *3,4-cis-4,5-trans-3,5-bis-(3-bromo-4,6-dimethoxyphenyl)-4-(2-methyl-1,3-dioxolan-2-yl)-cyclohexan-1-one* **5** was isolated in about 60% yield, m.p. 168–170 °C. NMR data in Tables 1–5. $C_{26}H_{30}Br_2O_7$ (614.3): calcd. C 50.83, H 4.92; found C 51.02, H 4.80.

3,4-cis-4,5-trans-4-Acetyl-3,5-bis-(3-brom-4,6-dimethoxyphenyl)-cyclohexan-1-one (**6**)

Ketal **5** (200 mg, 0.16 mmol) was refluxed in a mixture of 1,2-dimethoxyethane (4 ml) and 5% hydrochloric acid for 20 min. Evaporation and crystallization of the residue from diethylether/hexane gave **6** (140 mg, 76%), m.p. 102–104 °C. NMR data in Tables 1–5. $C_{24}H_{26}Br_2O_6$ (570.3): calcd. C 50.54, H4.60; found C50.45, H4.48.

Acknowledgement

Thanks are due to the National Research Fund (OTKA grant no. 1639) for financial assistance.

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Received November 3, 1992. Accepted Jaunary 11, 1993