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Reactions of 2,6-Dibenzylidenecyclohexanone and its Derivatives in High-Temperature Water

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The reactivity of derivatives of 2,6-dibenzylidenecyclohexanone was investigated in water at 220–250°C under microwave conditions, without added catalyst. Retro-Claisen–Schmidt processes predominated. Hydrolytic attack at the benzylic position afforded a 2-benzylidenecyclohexanone derivative and liberated an aryl aldehyde. Dienones substituted with electron-withdrawing or -donating groups on the aryl rings were more susceptible to hydrolysis than was the parent 2,6-dibenzylidenecyclohexanone.

Manuscript received: 17 October 2006. Final version: 10 November 2006.

The use of water as a solvent or medium for organic reactions has attracted considerable interest since the early 1980s.^[1–5] At temperatures below 100°C, hydrophobic effects,^[4,5] hydrogen bonding,^[6] and the high cohesive energy density^[7] of water facilitate processes such as Diels-Alder reactions and Claisen rearrangements, particularly those with negative activation volumes. At higher temperatures, however, the extent of hydrogen bonding diminishes and hydrophobic effects become less pronounced. The dielectric constant of water decreases but the dissociation constant increases.[8-12] In the 1990s, the advent of pressurized microwave reactors enabled new synthetic protocols that exploited these properties to be developed.^[12,13] Processes with industrial potential included the isoaromatization of carvone to carvacrol^[14] and the intramolecular Claisen-Schmidt condensation of hexane-2,5-dione to 3-methylcyclopent-2-enone (Scheme 1).^[15]

Recently, we have employed various media including solvent-free conditions^[16] and dimethylammonium dimethyl carbamate^[17] in condensations of non-enolizable arylaldehydes and cyclic ketones. The products all have at least one enone functionality and we consider 2-benzylidenecyclohexanone (**2a**) and 2,6-dibenzylidenecyclohexanone (**1a**) as parents. The range now includes unsymmetrically substituted bis(arylidene)alkanones^[18] and dienone-based macrocycles.^[19] Palladium-catalyzed isoaromatization has afforded a new family of compounds possessing motifs with 2,6-disubstituted phenols.^[20–22]

The earlier success with carvone and hexane-2,5dione encouraged us to investigate reactions of 2,6dibenzylidenecyclohexanone (1a) in high-temperature water (see Scheme 2 and Table 1). Isoaromatization was not observed under any of the conditions employed. The



Scheme 1. Isoaromatization of carvone^[14] and intramolecular Claisen–Schmidt condensation of 2,5-hexanedione.^[15]

predominant process, as exemplified by entries 1-10 in Table 1, involved hydrolytic cleavage of one of the exocyclic double bonds to afford mono-condensed products 2 and arylaldehydes 3. Although the pathway differed from that with carvone,^[14] it seems that in both cases, addition of water across a double bond was an early step. With carvone, water addition to afford 8-hydroxy-p-6-menthen-2-one as a kinetic product was readily reversible and in the subsequent elimination step a shift in the position of the isopropenyl double bond may have occurred. Isoaromatization would have ensued through a further shift in the position of that exocyclic double bond and enolization of the keto group, to afford carvacrol as the thermodynamic product.^[14] Contrastingly, in the present study it appears that putative Markovnikov addition of water was followed by a rapid retro-aldol addition instead of by an elimination which would have afforded the starting material or an isomer thereof. Activation energy barriers for aldol additions typically are relatively low and the energy



Scheme 2. Reactions of 2,6-dibenzylidenecyclohexanones in high-temperature water.

Table 1. Reactions of benzylidenecyclohexanones in high-temperature water

Entry	Substrate	Temp. [°C]	Time [h]	Product composition [%] ^A								
				SM ^B	2a	2b	2c	2d	3a	3b	3c	3d
1	1a	220	0.5	96	2				2			
2	1a	240	0.5	93	3	_			5			
3	1a	250	0.5	54	23	_	_	_	23	_		
4	1a	220	2	54	19	_	_	_	27	_		
5	1 a	220	4	46	17	_	_	_	37	—	—	
6	1a	220	6	16	27	_	_	_	57	_		
7	1a	220	8	0	12	_	_	_	88	—		
8	1b	220	4	0		16	_	_	_	84		
9	1c	220	3	31		_	16	_	_	_	48 ^C	
10	1c	220	4	28		_	14				50^{D}	
11	1d	220	0.5	88	6	0			0	6		
12	1d	220	1.5	70	10	5	_	_	5	10		
13	1d	220	4	0	2	< 0.5			49	44^{E}		
14	1e	220	4	7	34			12	12			26 ^F
15	2a	220	2	87	G	_	_	_	13			
16	2a	220	6	85	G	_	_	_	15	_		
17	$3a + 4^{\mathrm{H}}$	220	2	95 ^I	5^{J}	—	—	—	—	_	—	_

^A Calculated from integrated area of signals measured by GC or by ¹H NMR spectroscopy. Ketone **4** could not be analyzed reliably and was not included.

^B Unreacted benzylidenecyclohexanone.

^C Salicylaldehyde accounted for 4%.

^D Salicylaldehyde accounted for 8%.

^E p-Hydroxybenzaldehyde accounted for 5%.

^F Unidentified compounds accounted for 8%.

^G Starting material was **2a**.

^H 1:1 Mixture.

^I Benzaldehyde (3a).

^J 1a not detected.

wells for the starting materials and the aldol adducts are of comparable magnitude.^[23] These circumstances facilitate ready reversibility of aldol addition processes.

Difficulties associated with mono-condensation of an arylaldehyde with cyclohexanone (4) to afford products 2 are well documented.^[17] With base catalysis in particular, monocondensed products 2 typically are more reactive than 4 toward arylaldehydes and reactions tend to afford disubstituted products 1.^[17] Here, 2,6-dibenzylidenecyclohexanone (1a) underwent gradual hydrolytic degradation in hightemperature water. Its half-life was ~4 h at 220°C (entry 5, Table 1) and somewhat surprisingly, 2-benzylidenecyclohexanone (2a) was a significant product (e.g. entries 3 and 5). In water at 220°C, after 2 and 6 h (entries 15 and 16), 87% and 85% respectively, of 2a remained. Benzaldehyde (3a) was the only product detected. These results strongly suggested that under the conditions 2a was more stable than 1a and that an equilibrium involving 2a, benzaldehyde (3a), and cyclohexanone (4) had become established. That conclusion was reinforced when aldehyde 3aand ketone 4 partially condensed in water at 220°C to give 2benzylidenecyclohexanone (2a) with no detectable 1a (entry 17). It was also consistent with results of Zhu et al., who recently reported that aldehydes including 3a and 3b condensed with 4 in water at 250 and 280°C to form primarily the mono-condensed products 2a and 2b, respectively.^[24]

Next, the influence of electron-withdrawing or -donating groups on the aryl moieties was explored with regard to the hydrolytic behaviour of compounds **1**. Two symmetrically substituted dienones, **1b** and **1c** as well as two unsymmetrically substituted dienones, **1d** and **1e** were employed. These substrates were heated in water at 220°C under microwave conditions for up to 4 h (entries 8–14). Hydrolysis of **1b**, which contained two electron-donating groups, was facile and neared completion after 4 h (entry 8). That of **1c** proceeded less readily, probably because the sterically bulky 2 and 2'-methoxy groups inhibited attack of water at the benzylic positions. Minor changes in composition between reaction mixtures after 3 h (entry 9) and 4 h (entry 10), again suggested the establishment of an equilibrium. Interestingly, hydrolytic cleavage of the methoxy group of **3c** was also apparent, as salicylaldehyde was present among the products after 4 h (entry 10).

Unsymmetrically substituted dienone **1d** underwent complete hydrolysis after 4h (entry 13) to give aldehydes **3a** and **3b** predominantly. Shorter reaction times returned considerable amounts of starting material (entries 11 and 12). After a lag phase, 4-hydroxybenzaldehyde was detected as a minor component and it appears that it acid-catalyzed the hydrolysis.

When the electron-donating methoxy group of 1d was replaced with an electron withdrawing nitro group, the resultant unsymmetrical dienone 1e also was prone to hydrolysis (entry 14). Aqueous attack occurred readily and more regioselectively than was the case for 1d, preferentially at the benzylic position proximal to the electron withdrawing group. Consequently, *p*-nitrobenzaldehyde (3d) and enone 2a were the two major products.

To summarize, when heated in water at 220–250°C, dienones 1 underwent hydrolytic attack at the benzylic positions to afford 2-benzylidenecyclohexanone derivatives 2 and arylaldehydes 3. 2,6-Dibenzylidenecyclohexanone (1a) was more reactive than the mono-substituted enone 2a. The presence of either electron withdrawing or donating groups at the *ortho* or *para* positions on the aryl rings of 1, rendered substituted dienones 1b–1e more susceptible to hydrolysis than the unsubstituted parent molecule 1a. In some cases, equilibria were readily established and these appeared to influence the product distributions. These preliminary experiments further demonstrate the chemoselectivities possible with reactions in high-temperature water and the multiple roles that water can play including as solvent/medium, reactant and catalyst depending upon the conditions.

Experimental

All solvents, reagents and starting materials were used as purchased. ¹H and ¹³C NMR spectra were recorded on a Bruker Advance DRX 400 spectrometer at 400 and 100 MHz, respectively, using CDCl3 or TMS as an internal standard. GC analyses were carried out using a Hewlett Packard Series 5890 GC equipped with a FID and a Hewlett Packard HP 3396A Integrator. The column was a SGE BPX5 fused silica column (25 m \times 0.32 mm ID, 0.5 μ m film thickness). The injector and detector temperatures were 220 and 250°C, respectively. The oven temp was programmed as follows: initial temp 70°C, increasing to 280°C at 10°C min⁻¹ and holding for 5 min. Helium was the carrier (2 mL min⁻¹) and nitrogen was the makeup (28 mL min⁻¹) gas. GC-MS spectra were obtained with a ThermoQuest TRACE DSQ GC-MS using EI with an ionization energy of 70 eV. The column was a SGE BPX5 fused silica column ($25 \text{ m} \times 0.32 \text{ mm}$ ID, $0.25 \mu \text{m}$ film thickness). The injector temp was 250°C and the transfer line was set to 250°C. The oven temp was programmed as follows: initial temp 50°C for 2 min, increasing to 250°C at 20°C min⁻¹, and holding for 16 min. High-purity

helium was used as the carrier gas with a flow rate of 0.8 mL min⁻¹. Microwave experiments were conducted in a MicroSYNTH (Microwave Organic Synthesis Labstation, Milestone) that was operable up to 250°C and that could withstand reaction pressures of at least 5 MPa. Compounds **1a**-**1c**,^[25] **2a**-**2b**,^[17] **2c**,^[26] and **2d**^[27] were prepared according to literature methods. Dienones **1d**-**1e** were prepared by reaction of 2benzylidenecyclohexanone (**2a**) with aldehyde (**3b** or **3d**) in 4% NaOH in 95% EtOH at rt overnight. All compounds were known and had satisfactory physical and spectral characteristics.^[17,25-29] ¹H and ¹³C NMR spectral data of dienones **1d** and **1e** are presented for the first time, below

Typical Procedure for the Reaction of Benzylidenecyclohexanones in High-Temperature Water

The substrate (1.5 mmol) and water (40 mL) were placed in a pressureresistant microwave reaction vessel (100 mL capacity). The mixture was stirred and rapidly microwave-heated for 3 min to the desired temp (220– 250°C), held at this temp for the designated time (0.5–8 h) and cooled. The product mixture was extracted with an organic solvent and the combined organic phase was dried (anhyd. MgSO₄) and concentrated for analysis by GC, GC-MS, and ¹H NMR spectroscopy.

2-Benzylidene,6-(4-methoxybenzylidene)cyclohexanone (1d): $\delta_{\rm H}$ 7.79 (1H, t, J 2, CH), 7.77 (1H, t, J 2, CH), 7.48–7.45 (4H, m, Ar), 7.42–7.38 (2H, m, Ar), 7.35–7.31 (1H, m, Ar), 6.96–6.92 (2H, m, Ar), 3.85 (3H, s, OCH₃), 2.95–2.91 (4H, m, CCH₂), 1.83–1.77 (2H, m, CH₂). $\delta_{\rm C}$ 190.4, 160.2, 137.2, 137.1, 136.6, 136.5, 136.3, 134.4, 132.5, 130.5, 130.5, 128.9, 128.6, 128.5, 55.5, 28.8, 28.6, 23.2.

2-Benzylidene,6-(4-nitrobenzylidene)cyclohexanone (1e): $\delta_{\rm H}$ 8.25 (2H, m, Ar), 7.82 (1H, t, J 2, CH), 7.77 (1H, t, J 2, CH), 7.58 (2H, m, Ar), 7.49–7.46 (2H, m, Ar), 7.44–7.40 (2H, m, Ar), 7.37–7.34 (1H, m, Ar), 2.97–2.94 (2H, m, CCH₂), 2.92–2.88 (2H, m, CCH₂), 1.85–1.79 (2H, m, CH₂). $\delta_{\rm C}$ 189.8, 147.3, 142.7, 139.5, 138.1, 135.8, 135.8, 133.9, 130.9, 130.6, 129.1, 128.6, 123.7, 28.6, 28.5, 22.9.

Acknowledgments

We thank Angela Ziebell and Dr Ulf Kreher for conducting a preliminary experiment, Anthony Rosamilia for providing a sample of **2b**, the Australian Research Council (ARC) for funding this research through the ARC Special Research Centre for Green Chemistry, and an Australian Postgraduate Award (to L.T.H.), The People's Republic of China for supporting sabbatical leave (for X.J.B.), and Milestone (Italy) for the loan of microwave reactors and ancillary equipment. Drs Carl Braybrook and Jo Cosgriff of CSIRO Molecular & Health Technologies are thanked for performing GC-MS analyses.

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