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WATER-PROMOTED ORGANIC REACTIONS. ALDOL REACTION OF SILYL ENOL ETHERS WITH CARBONYL COMPOUNDS UNDER ATMOSPHERIC PRESSURE AND NEUTRAL CONDITIONS.

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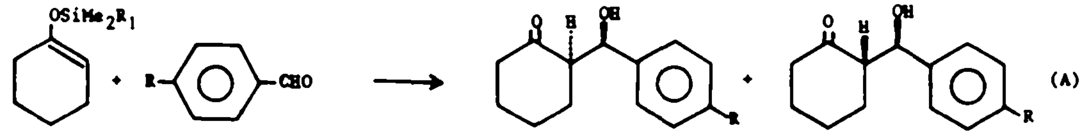
Summary

As a consequence of the hydrophobic effect, the reaction between silyl enol ethers and aldehydes are shown to proceed without a catalyst in aqueous solution and neutral conditions providing crossed-aldol products with a syn selectivity, as under pressure, that is the reverse in comparison with the acid catalysed reaction. With α,β-unsaturated aldehydes, 1,2- and 1,4-addition were observed, whereas with α,β-unsaturated ketones, only 1,4-addition occurred.

Introduction

The aldol reaction is one of the major way of forming carbon-carbon bonds for the construction of carbon chains with oxygen functionalities in 1,3-positions. This reaction known since 1838[1] has been normally carried out in protic solvents with base or acid as catalyst, but this conventional method has serious synthetic limitations, especially cross-coupling reactions. During the past two decades, several improvements of prime importance have been developed, providing crossed-aldols with good regio- and stereo-selectivity[2]. Among these new methods, the Lewis-acid promoted condensation of trimethylsilyl enol ethers with carbonyl compounds has become a popular tool in organic synthesis as it is relatively easily carried out, from readily available starting materials[3]. However, the method requires stoechiometric amount of Lewis acid such as $TiCl_4$ which could be troublesome with acid labile substrates. In addition to that, the acidic conditions led sometimes to the dehydration products. To overcome these difficulties, several modifications of the original procedure were given, such as the catalytic use of $Bu_4N^+F^-$ [4] or Me_2AlCl [5] as homogeneous catalysts or clay Montmorillonite[6] as heterogeneous catalyst. Alternatively, the reaction was shown to proceed without catalyst but under high pressure[7] to give good yield of aldol with a syn selectivity, which is the reverse in comparison with the acid-catalysed reactions.

Organic reactions between two small hydrophobic molecules promoted by water was, up to now, almost confined to the Diels-Alder reaction[8]. As part of a program of organic synthesis in aqueous solution using glyco-organic substrates[8c], we wondered if the hydrophobic effect, the well-known entropy-driven association of hydrophobic molecules in water could be used to promote other reactions than [4+2] cycloadditions. The effect of water on the rate of non-polar reaction was suggested to be related to its high cohesive energy and to the high energy necessary to create a cavity in it, because of its high interfacial energy[9]. Thus, a reaction under kinetic control, between two small hydrophobic molecules (or between the hydrophobic moities of amphiphilic molecules) for which $\Delta V^{\neq}$ is negative must be accelerated in water as it is under pressure, to occupy the smallest volume of cavity. When several transition states are possible, the more compact should be favoured. Actually, this hypothesis is verified for Diels-Alder reactions[8] and in a preliminary communication[10], one of us has shown that the reaction between 1-trimethylsilyloxy cyclohexene and benzaldehyde (eq. A) could be conducted in water without any catalyst at atmospheric pressure to give in moderate to good yield depending on the conditions the aldol products with a *syn* selectivity as under pressure. This reaction in aqueous solution occurred in a similar time, at a similar temperature providing the same *syn*/*anti* ratio than under 10 Kbars in CH_2Cl_2. In this respect it may be significant that water has a cohesive energy density of 22 Kbars.



R_1=Me **1**
R_1=tBu **2**

R=H **3**
R=NO_2 **4**
R=OCH_3 **5**

6 (*syn*)
8 "
10 "

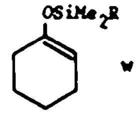
7 (*anti*)
9 "
11 "

In view of the synthetic potential of this process, and to gain more insight into the hydrophobic effect, we have undertaken further investigations and we want now to report the scope of the reaction by varying the carbonyl acceptors and the co-solvent.

Results and discussion

Table 1 shows the results obtained for the aqueous crossed-aldol reaction between silyl enol ether derivative of cyclohexanone and benzaldehyde under various conditions.

Table 1.
Reactions of



with benzaldehyde under varying conditions.

R=CH_3 **1**
R=tBu **2**

entry	silyl enol ether (eq)	solvent	temp. °C	time	conditions	yields %	syn:anti	ref
1	**1** (1)	CH_2Cl_2	20	2 h	$TiCl_4$	82	25:75	3
2	**1** (1)	id	60	9 days	10 Kbars	90	75:25	7
3	**1** (0.5)	H_2O	20	5 days	ST[a] or US[b]	23	85:15	
4	**1** (2)	H_2O-THF	60	2 days	ST	47[c]	73:27	
5	**1** (2)	id	55	1 day	US	76[c]	74:26	
6	**1** (2)	H_2O-DME	id	id	id	46	69:11	
7	**1** (2)	H_2O-CH_3CN	id	id	id	37	55:45	
8	**1** (2)	H_2O-MeOH	id	id	id	35	65:35	
9	**1** (2)	MeOH	id	id	id	30	57:43	
10	**2** (2.5)	H_2O-THF	100	16 h	ST	84	57:43	

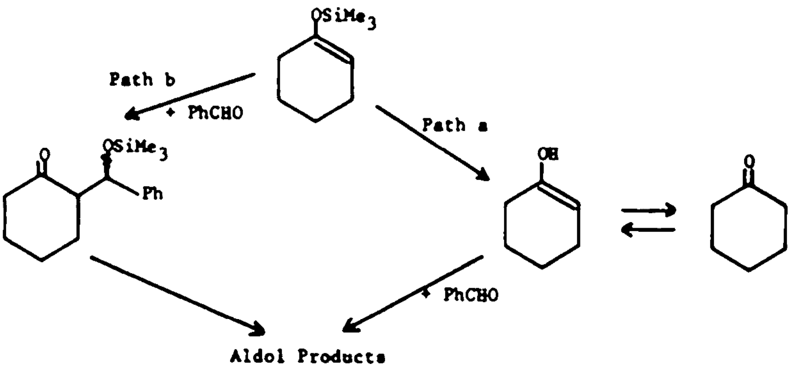
[a] Vigorous magnetic stirring or violent shaking. [b] Sonication using a Bransonic 220, 50-kHz cleaning bath. [c] Isolated yield

Starting from the 1-trimethylsilyloxy cyclohexene **1**, the best yield in aldol products was obtained when the reaction was conducted in a water-THF mixture (1:1) under ultrasonic waves (entry 5). In these conditions, the reaction mixture was heterogeneous and it could be assumed that the role of ultrasonic waves was only to disperse the organic phase in water as this way of mixing is without significant effect when the reaction was conducted in pure water (entry 3). This ability for ultrasound to generate extremely fine emulsions for mixture of immiscible liquids has been recognized for a long time[11].

It must be noted that in all cases, the reaction goes to completion, - i.e. complete disparition of the silyl enol ether - and the only side product is the cyclohexanone resulting from the competitive hydrolysis of the silyl enol ether. This side reaction could be reduced using the *t-butyl dimethylsilyl* enol ether 2 (entry 10). In this case, higher temperature is required for completion of the reaction and the yield increased to 84% but with concomitant loss of *syn* selectivity. In all cases, *syn* selectivity was observed, as under pressure; that is, it is the reverse of the selectivity observed under conditions of acidic catalysis (entry 1). We assumed that the reaction proceeded through a six-membered transition state and that the acceleration of the reaction in water is due to steric compression of the transition state in a cavity of the water structure, giving rise predominantly to the boat shaped transition state as under pressure[7], due to its tight character. This effect of the water structure is supported by varying the co-solvent. First we may note for instance that the reaction did not proceed in any other solvent than water, such as toluene, THF, CH_2Cl_2, CH_3CN as well as formamide or glycerol which have been shown to be somewhat structured as measured by the Hildebrandt parameter[12]. Moreover, the co-solvent added to water is important, for instance, MeOH, which could be considered as "structure-breaker", lowered the yield to 35% (entry 8). Pure methanol gave a low *syn* selectivity along with a low yield (entry 9).

At this point, due to the physicochemical implications of this reaction, it is of importance to ascertain the mechanism. Two possible pathways are depicted in scheme 1. In path a, slow hydrolysis of the silylenol ether give rise to the enol form of cyclohexanone which could be trapped by benzaldehyde. In path b, a six-membered transition state favored by the hydrophobic effect led to C-C bond formation with transfer of the Me_3Si group followed by hydrolysis of the trimethylsilyl ether.

Scheme 1

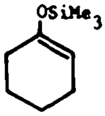


In favor of path b, in addition to the role of the solvent, we may note for instance that cyclohexanone itself didn't give any aldol condensation. Moreover, addition of acid (AcOH 1%) inhibited the reaction. Likewise, slow hydrolysis of 1-trimethylsilyloxycyclohexene in CH_2Cl_2 by wet silica gel in the presence of a large excess of benzaldehyde gave only traces of aldol products.

Then, we turned our attention to the electrophilic character of the carbonyl acceptor. First of all, we must note that ketones are totally unreactive in this type of reaction. The same observation has been made for the reaction under high pressure in CH_2Cl_2 [13].

1 12 (8)

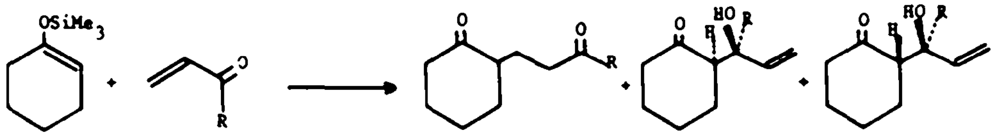
The results in table 2 show that the best yield was obtained with the strong electrophilic paranitrobenzaldehyde **4** (entry 13), whereas the yield was only modest with formaldehyde (eq. B) which exists in water, almost completely, in its hydrated form (entry 16).

Table 2
Reaction of  with various carbonyl acceptors.

entry	carbonyl compound (eq.)	solvent	temp. °C	time	conditions	yield %	<u>syn</u>:<u>anti</u>
11	pNO_2PhCHO (2)	H_2O	90	1.5 days	ST	66	60:40
12	id	H_2O-THF	60	id	ST	70	60:40
13	id	id	55	id	US	82[a]	70:30
14	$pCH_3OPhCHO$ (2)	id	60	id	ST	17	63:37
15	id	id	55	id	US	29[a]	70:30
16	HCHO (2)	id	55	21 h	id	55[a]	-

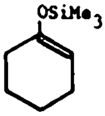
[a] Isolated yields

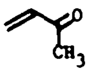
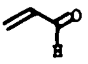
Next, we examined the regioselectivity with α,β-unsaturated carbonyl compounds (eq. C) for which the results are summarized in table 3.


(C)

1 R=Me **13** R=H **14** → **15** **16** + - **17** (syn) + - **18** (anti)

Whereas acrolein gave rise to 1,2- and 1,4-additions, methyl vinyl ketone only gave 1,4-addition in agreement with the lack of reactivity of ketones in these water-promoted crossed-aldol reactions.

Table 3
Reaction of  with α,β-unsaturated carbonyl acceptors.

entry	carbonyl compounds (eq.)	solvent	temp °C	time (days)	conditions	yields %	1,4-add:1,2-add (<u>syn</u>:<u>anti</u>)
17	 (2)	H_2O-THF	55	2	US	18	100:0[a]
18	id (4)	id	id	1	id	32[b]	100:0[a]
19	 (2)	H_2O	60	2	ST	8	83:17 (nd)
20	id (2)	H_2O-THF	60	2	ST	14	46:54 (75:25)
21	id (2)	id	55	2	US	38[b]	23:77 (65:35)

[a] as judged by tlc, glc and NMR examination. [b] Isolated yields

In spite of the moderate yield, it must be emphasized that these smooth conditions allowed us to prepare the new compounds 17 and 18 which are very sensitive either in acidic or basic conditions, giving rise to the dehydration products.

In conclusion, after the Diels-Alder reaction, we present here a new example of a reaction which is accelerated when water is the solvent due to the hydrophobic effect. Owing to the smooth and neutral conditions which are required for this water-promoted crossed-aldol reaction and which could led to very sensitive products, this type of reactions could gain synthetic applications. Other reactions having a negative activation volume are being examined in our laboratory.

Experimental

Water was distilled twice before use. All organic solvents (reagent grade) were used as received. Identification of products was made by conventional methods using NMR spectroscopy (Bruker model AM 250 or Perkin Elmer model R-32 spectrometer) after purification by liquid chromatography and comparison with literature data. In repetitive experiments, the yield and the syn:anti ratio were determined either by NMR integration or analytical HPLC (Waters model 590 equipped with a differential refractometer model 410) using internal standard.

1-trimethylsilyloxy cyclohexene[14] and 1-terbutyl dimethylsilyloxy cyclohexene[15] were prepared according to the literature procedures and purified by distillation. Elemental analyses of new compounds were performed by the Service Central de Microanalyse du CNRS.

Standard procedure

A mixture of the silyl enol ether (3 mmol) and the specified amounts of carbonyl compounds (see tables 1, 2 and 3) in water (5 ml) or the specified aqueous solution (water - organic solvent, 1:1, v/v, 5 ml) in a screw-capped tube was either stirred at the specified temperature or immersed in an ultrasonic cleaning bath (Bransonic 220, 50 KHz) at 55°C. The reaction was monitored by silica gel tlc. After disparition of the silyl enol ether, the aqueous mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried, filtered and evaporated. Silica gel column chromatography afforded the aldol products in pure form.

2-[hydroxy(phenyl)methyl]cyclohexanone[3]

6 (syn) : m.p. 104°C (isopropanol) ^{1}H NMR (90 MHz, $CDCl_3$) : δ 5.40 (d, J = 2.5 HZ, 1 H, CHOH)

7 (anti) : m.p. 74°C (ether-hexane) ^{1}H NMR (90 MHz, $CDCl_3$) : δ 4.80 (d, J = 9 Hz, 1 H, CHOH).

2-[hydroxy(4-nitrophenyl)methyl]cyclohexanone.

In this case, the literature data are discordant[4, 16], so we give a complete description for both syn and anti isomers including elemental analyses.

8 (syn) : m.p. 132°C (ether-hexane) ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.2 (d, J = 9 Hz, 2 H, Ph), 7.5 (d, J = 9 Hz, 2 H, Ph), 5.50 (br s, 1 H, CHOH), 3.25 (d, J = 3 Hz, 1 H, OH); 1.5-2.8 (m, 9 H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; O, 25.67. Found : C, 62.91; H, 6.18; N, 5.32; O, 25.79.

9 (anti) : m.p. 152°C (ether-hexane) ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.2 (d, J = 9 Hz, 2 H, Ph), 7.5 (d, J = 9 Hz, 2 H, Ph), 4.9 (dd, J = 2, 8 Hz, 1 H, CHOH), 4.1 (d, J = 2 Hz, 1 H, OH), 1.5-2.7 (m, 9 H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; O, 25.67. Found C, 62.52; H, 6.06; N, 5.41; O, 25.60.

2-[hydroxy(4-methoxyphenyl)methyl]cyclohexanone[4]

10 (syn) : m.p. 117°C (ether-hexane) ^{1}H NMR (250 MHz, $CDCl_3$) : δ 5.32 (d, J = 3 Hz, 1 H, CHOH)

11 (anti) : m.p. 76°C (ether-hexane) ^{1}H NMR (250 MHz, $CDCl_3$) : δ 4.73 (d, *J* = 9 Hz, 1 H, $C\underline{H}OH$).

2-hydroxymethyl cyclohexanone 12[17].

Oil, ^{1}H NMR (90 MHz, $CDCl_3$) : δ 3.57 (dd, *J* = 4.6, 12 Hz, 1 H, $C\underline{H}_2OH$), 3.76 (dd, *J* = 6.4, 12 Hz, 1 H, $C\underline{H}_2OH$).

2-(3-oxobutyl)cyclohexanone 15[18].

Oil, ^{1}H NMR (90 MHz, $CDCl_3$) : δ 1.1-2.6 (m, 16 H, with a singlet at 2.12).

2-(3-oxopropyl)cyclohexanone 16[19].

Oil, ^{1}H NMR (90 MHz, $CDCl_3$) : δ 1.1-2.6 (m, 13 H), 9.72 (br s, 1 H).

2-(1-hydroxy 2-propenyl)cyclohexanone.

17 (syn) : oil, ^{1}H NMR (250 MHz, $CDCl_3$) : δ 1.5-2.5 (m, 9 H), 3.12 (br s, 1 H, OH), 4.6 (br s, 1 H, $C\underline{H}OH$), 5.15 (dt, *J* = 2, 10 Hz, 1 H, $CH{=}C\underline{H}_2$), 5.29 (dt, *J* = 2, 17 Hz, 1 H, $CH{=}C\underline{H}_2$), 5.84 (ddd, *J* = 5.5, 10, 17 Hz, 1 H, $C\underline{H}{=}CH_2$). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; O, 20.75. Found : C, 69.18; H, 8.97; O, 21.79.

18 (anti) : oil, ^{1}H NMR (250 MHz, $CDCl_3$) : δ 1.3-2.5 (m, 9 H), 3.75 (d, *J* = 2 Hz, 1 H, OH), 4.28 (br t, *J* = 7 Hz, 1 H, $C\underline{H}OH$), 5.15 (ddd, *J* = 1, 1.5, 10 Hz, 1 H, $CH{=}C\underline{H}_2$), 5.25 (dt, *J* = 1.5, 17 Hz, 1 H, $CH{=}C\underline{H}_2$), 5.83 (ddd, *J* = 7, 10, 17 Hz, 1 H, $C\underline{H}{=}CH_2$). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; O, 20.75. Found : C, 69.25; H, 9.24; O, 21.57.

Acknowledgments

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