Aldol Condensation in Water Using Polyethylene Glycol 400

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Efficient and environmentally friendly synthesis of chalcones and 2,6-bis(arylmethylidene)cycloalkanones was carried out by aldol condensation of ketones with aromatic aldehydes in water in the presence of polyethylene glycol 400.

From an environmental point of view, organic chemists are requested to develop clean, economical, and environmental safer methodologies. Recently, numerous methods using ionic liquids[1] and polyethylene glycol (PEG)[2,3] were reported. Toda et al. have reported the reactions in the absence of the solvent.[4] One of the most promising approaches is to utilize water as a reaction medium.[5,6]

Chalcones are potentially useful synthetic intermediates for the production of flavonoids as well as having significant pharmacological properties.[7] 2,6-Bis(arylmethylidene)cycloalkanones are known as important precursors for synthesis of bioactive pyrimidine derivatives.[8] For these reasons, the synthesis of these compounds has been extensively studied.

To the best of our knowledge, two methods have been known to prepare these compounds in water. Fringuelli et al. reported the synthesis of parent chalcone and 2,6-dibenzylidenecyclohexanone catalyzed by NaOH in the presence of cationic surfactants such as cetyltrimethylammonium chloride (CTACl).[9] Wang et al. reported the synthesis of chalcones catalyzed by Na_2CO_3 at 60–100 °C, however, good yields were limited only for the reactions of benzaldehydes bearing electron-withdrawing groups on the benzene ring.[10]

In our continuing studies concerning phase transfer catalysts,[11] we found that chalcones and bis(arylmethylidene)-cycloalkanones were prepared by aldol condensation catalyzed by NaOH in water in the presence of PEG400 having an average molecular weight of 400.[12] In this paper, we wish to report the efficiently and environmentally friendly method for aldol condensation.

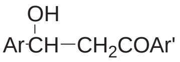
First, the reactions of aromatic aldehydes with aromatic ketones were examined in water in the presence of polyethylene glycol dimethyl ethers (PEG500DME and PEG250DME) as well as PEG400 (Table 1).[13] The reaction of 4-chlorobenzaldehyde with 4-methoxyacetophenone was chosen as a model reaction. When the reaction was conducted at room temperature in the presence of 0.1 equiv. of PEG400 for 15 min in water, aldol **3**[4] and chalcone **4**[14,15] were obtained in 59 and 40% yields, respectively, which were almost the same as those in the conventional solvent, EtOH–H_2O (1:1) (**3**, 53%; **4**, 44%) (Entries 1 and 7). Under our conditions, the reactions proceeded in a heterogeneous phase. No reaction occurred in the absence of PEG400. Formation of aldol **3** was suppressed by using 1 equiv. of PEG400 to give **4** in 97% yield (Entry 2). When 0.1 equiv. of PEG500DME was used as an additive, compounds **3** and **4** were produced in 57 and 41% yields, respectively (Entry 3). In the case of PEG250DME, the reaction proceeds more slowly than PEG500DME (Entry 5). The use of 1 equiv. of PEG500DME and PEG250DME gave **4** in quantitative yields (Entries 4 and 6). Dehydration of the initially produced aldol to chalcone occurred more easily when 1 equiv. of additives were employed. This may be attributed to the fact that coordination of polyether moieties to the sodium ion enhances the reactivities of the hydroxide ion in the organic phase of substrates in which the reaction proceeds.

ArCHO

1

Ar'$COCH_3$

2



$\mathrm{Ar\overset{OH}{C}H{-}CH_2COAr'}$

3

ArCH=CHCOAr'

4

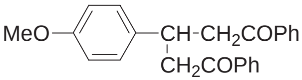


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Table 1. Reactions of aldehydes **1** with ketones **2** in water in the presence of PEG400[a]

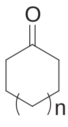
Entry	Aldehyde **1** Ar	Ketone **2** Ar′	Additive[b] (equiv.)	Time	Yield/% **3**	Yield/% **4**
1	4-ClC_6H_4	4-$MeOC_6H_4$	A (0.1)	15 min	59	40
2			A (1)	15 min	0	97
3			B (0.1)	15 min	57	41
4			B (1)	15 min	0	98
5			C (0.2)	30 min	61	38
6			C (2)	30 min	0	92
7			none	5 min	53	44
8	4-$MeOC_6H_4$	Ph	A (0.1)	48 h	0	94[e]
9			B (0.1)	72 h	0	76[f]
10			D (0.1)	4 h	0	83[g]
11	4-MeC_6H_4	Ph	A (0.1)	1 h	0	97
12	Ph	Ph	A (0.1)	24 h	0	97
13	4-ClC_6H_4	Ph	A (0.1)	15 min	0	98
14	4-$O_2NC_6H_4$	Ph	A (0.1)	5 min	0	83
15			B (0.1)	10 min	0	44
16			D (0.1)	2 h	0	28
17	Ph	4-$MeOC_6H_4$	A (0.1)	2.5 h	11	86
18			A (1)	15 min	0	97
19[c]			A (1)	15 min	0	94
20[d]			A (1)	15 min	0	89
21			B (0.1)	5 h	9	89
22			B (1)	1 h	0	98
23	Ph	4-MeC_6H_4	A (0.1)	24 h	0	98
24	Ph	4-ClC_6H_4	A (0.1)	20 min	0	95

[a] Reagents and conditions: **1** 10 mmol, **2** 10 mmol, NaOH 10 mmol, H_2O 2 mL, room temp. [b] A, PEG400; B, PEG500DME; C, PEG250DME; D, CTACl. [c] 2nd Run. [d] 3rd Run. [e] **5** (4%) was obtained. [f] **5** (14%) was obtained. [g] **5** (7%) was obtained.

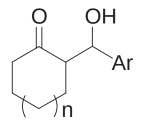
Similarly, the production of aldol **3** was suppressed by using 1 equiv. of PEG400 or PEG500DME to give **4** in good yields for the reaction of benzaldehyde with 4-methoxyacetophenone (Entries 18 and 22). The reactions of 4-methoxybenzaldehyde with acetophenone gave not only chalcone **4** but also a small amount of oligomer **5**[16] which was generated by the addition of acetophenone to **4** (Entries 8–10). The yields of chalcone **4** were decreased by the formation of polymers for the reactions of 4-nitrobenzaldehyde with acetophenone (Entries 14–16). In these cases, the best yields were obtained when PEG400 was employed (Entries 8 and 14). When CTACl was used as an additive, yields of **4** were lower compared to those of PEG400 (Entries 10 and 16). For the other examples, chalcones **4** were yielded in good yields using 0.1 equiv. of PEG400 (Entries 11, 12, 13, 23, and 24).

To check the reusability of the PEG400-NaOH system, the filtrate was evaporated and used for the next experiment. This system was reused without significant loss of activities (Entries 18–20).

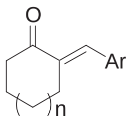
Next, the reactions of cycloalkanones with various aromatic aldehydes were examined. The results are shown in Table 2. We chose the reaction of cyclohexanone (**6**) with benzaldehyde (**1**) as a model reaction. Intermediate aldol **8** (*erythro*:*threo* = 50:50)[4,17] (31%) and (*E*)-2-benzylidenecyclohexanone (**9**)[4,17] (35%) were isolated from the reaction at room temperature for 15 min in EtOH–H_2O (1:1). When 0.1 equiv. of PEG400 was used, compounds **8** and **9** were obtained in 39 and 26% yields, respectively (Entry 5). Without PEG400, the reaction proceeded slowly to give **8** and **9** after 24 h in 43 and 19% yields, respectively. The reaction of **6** with 2 equiv. of benzaldehyde in the presence of **1** equiv. of PEG400 yielded dibenzylidenecyclohexanone (**10**)[18,19] in 98% yield (Entry 6). The use of 1 equiv. of PEG500DME did not give **10** but a mixture of **8** (30%) and **9** (38%) (Entry 8). When PEG250DME was added instead of PEG500DME, compounds **8** and **9** were produced more slowly (Entries 9 and 10). The selectivity (50:50), shown by the *erythro*:*threo* ratio of **8** obtained in the cases of PEG400, PEG500DME, and PEG250DME, was the same as that in the conventional solvent, EtOH–H_2O (1:1). The reactions of **6** with 2 equiv. of the other aromatic aldehydes **1** using 1 equiv. of PEG400 completed within 1 h to give **10** in excellent yields (Entries 2 and 4). In the case of 4-chlorobenzaldehyde, 0.1 equiv. of PEG400 was sufficient for the exclusive production of **10** (Entry 12). For the reactions of **6** with 4-nitrobenzaldehyde, only polymeric materials were obtained. This method was further applied to the condensation of cyclopentanone (**7**) with various aldehydes. Bis(arylmethylidene)cyclopentanones (**11**) were isolated in excellent yields (Entries 13–16).



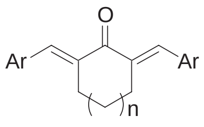
6 n = 1
7 n = 0



8 n = 1



9 n = 1



10 n = 1
11 n = 0

In fact, the products can be isolated in practically pure form simply by filtration. If the products were liquid, lathering was not observed in the extraction with EtOAc. On the other hand, phase separation is often difficult because of lathering when surfactants such as CTACl were employed. PEG400 is a cheap and relatively safe compound compared to surfactants or other phase transfer catalysts [LD_{50} (rats) of PEG400 = 30 mL/kg].[20] In addition, PEG400 possesses low vapor pressure. These facts indicate that PEG400 is a highly suitable additive.

Table 2. Reactions of cycloalkanones with aldehydes **1** in water in the presence of PEG400[a]

Entry	Ketone	Aldehyde **1** Ar	Additive[b] (equiv.)	Time	Yield/% **8**	**9**	**10**	**11**
1	**6**	4-$MeOC_6H_4$	A (0.1)	3 h	0	40	28	—
2[c]			A (1)	1 h	0	0	93	—
3		4-MeC_6H_4	A (0.1)	3 h	0	42	23	—
4[c]			A (1)	1 h	0	0	90	—
5		Ph	A (0.1)	30 min	39 (50:50)[d]	26	0	—
6[c]			A (1)	1 h	0	0	98	—
7			B (0.1)	30 min	41 (50:50)[d]	22	0	—
8[d]			B (1)	30 min	30 (50:50)[d]	38	0	—
9			C (0.2)	1 h	41 (50:50)[d]	22	0	—
10[c]			C (2)	2 h	27 (50:50)[d]	45	0	—
11		4-ClC_6H_4	A (0.1)	15 min	31 (50:50)[d]	34	33	—
12[c]			A (0.1)	30 min	0	0	90	—
13[c]	**7**	4-$MeOC_6H_4$	A (1)	20 min	0	0	—	90
14[c]		4-MeC_6H_4	A (1)	40 min	0	0	—	98
15[c]		Ph	A (1)	30 min	0	0	—	99
16[c]		4-ClC_6H_4	A (0.1)	15 min	0	0	—	97

[a]Reagents and conditions: Ketone 10 mmol, **1** 10 mmol, NaOH 10 mmol, H_2O 2 mL, room temp. [b]A, PEG400; B, PEG500DME; C, PEG250DME. [c]2 equiv. of aldehydes were used. [d]*erythro*:*threo* ratio of compound **8**.

In conclusion, we constituted an environmentary friendly methodology for the synthesis of chalcones and 2,6-bis(arylmethylidene)cycloalkanones using PEG400. In this convenient methodology, side reactions were avoided and high yields were achieved.

References and Notes

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13 A typical procedure is as follows: to a mixture of ketone **2** (1.2 g, 10 mol), NaOH (400 mg, 10 mmol), and PEG400 (400 mg, 1 mmol) in water (2 mL) was added aldehyde **1** (1.2 g, 10 mmol). After stirring at room temperature for 1 h, the mixture was poured into water (25 mL). The solid product was collected by filtration, washed with water, and dried to give **4** (2.2 g, 97%). Recrystallizaion from EtOH gave higher purity of the product (Table 1, Entry 11).
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16 Compound **5**: mp 92–93 °C; IR (KBr) 3064, 2900, 2836, 1682, 1598, 1516, 1238, 1036, 816, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.31 (2H, dd, $J = 16.5$ and 7.0 Hz), 3.46 (2H, dd, $J = 16.5$ and 7.0 Hz), 3.74 (3H, s), 4.02 (1H, t, $J = 7.0$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz), 7.43 (4H, dd, $J = 8.0$ and 8.0 Hz), 7.52 (2H, dd, $J = 8.0$ and 1.0 Hz) and 7.93–7.95 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.5, 45.1, 55.2, 114.0, 128.1, 128.4, 128.6, 133.0, 135.8, 136.9, 158.2, 198.7. Anal. Calcd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.2%. Found: C, 80.1; H, 6.3%.
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