Aldol Condensations in the Absence of Solvent: Acceleration of the Reaction and Enhancement of the Stereoselectivity

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Some aldol condensation reactions proceeded more efficiently and stereoselectively in the absence of solvent than in solution. When the aldol reaction was carried in an inclusion complex with an optically active host compound, diastereo- and enantio-selective reaction occurred.

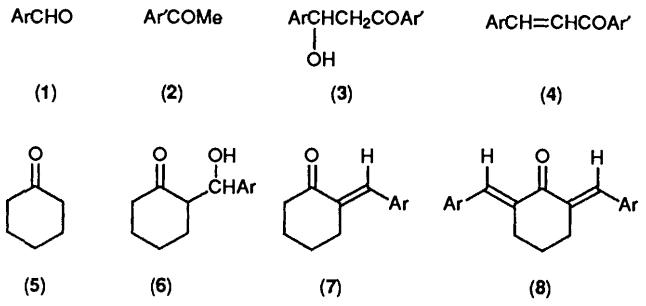
Previously we reported that Baeyer–Villiger oxidation,[1] reduction of ketones with BH_3[2] or $NaBH_4$,[3] $FeCl_3$-assisted coupling of phenols,[4] pinacol rearrangement,[5] benzylic acid rearrangement,[6] and Wittig–Horner reaction[7] proceed efficiently in the absence of solvent. We now report efficient and stereoselective aldol condensation reactions in the absence of solvent.

Results and Discussion

When a slurry mixture of *p*-methylbenzaldehyde (1.5 g, 12.5 mmol), acetophenone (1.5 g, 12.5 mmol), and NaOH (0.5 g, 12.5 mmol) was ground by pestle and mortar at room temperature for 5 min, the mixture turned to a pale yellow solid. The solid was combined with water and filtered to give *p*-methylchalcone (2.7 g) in 97% yield (Table 1, entry 2). When the condensation was carried out in 50% aqueous EtOH according to the reported procedure[8] for the same reaction time as above (5 min), the product was obtained only in 11% yield (Table 1 entry 2). Some other aldol reactions of benzaldehyde and acetophenone derivatives were carried out in the absence of solvent and in 50% aqueous EtOH (Table 1). In most cases, the condensation proceeded more efficiently in the absence of solvent than in solution. Dehydration of the initially produced aldol to chalcone occurs more easily in the absence of solvent than in solution (Table 1, entries 4 and 5).

Aldol reactions of cyclohexanone (**5**) and benzaldehydes (**1**) also proceeded more efficiently and stereoselectively in the absence of solvent than in solution (Table 2). All the solution reactions in Table 2 were carried out in water at room temperature according to the reported procedure.[9] Although the reaction in water gives the aldol (**6**) only, the reaction in the absence of solvent gives mainly the dehydration product of (**6**), (**7**) and of the doubly condensed product (**8**). The selectivity, shown by the *erythro*:*threo* ratio of (**6**), is higher when the reaction is carried out in the absence of solvent. The selectivity becomes much higher when the reaction is carried out in the inclusion complex with host compound. For example, treatment of a 1:1 inclusion complex of (**5**) and (−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**9a**) with benzaldehyde (**10**) and NaOH at room temperature by occasionally grinding with mortar and pestle gave a 20:80 mixture of *erythro* and *threo* isomers of (**11**) in 37% yield (Table 3). The product is optically active, although its optical purity is not determined. The *erythro*:*threo* ratio and $[\alpha]_D$ value of (**11**) were altered a little on changing the nature of the alkali metal hydroxide and host compound (Table 3).

In the aldol reaction of (**1b**) and (**5**) using (**9c**) as a host, the *erythro*:*threo* ratio of the product (**6b**) was essentially independent of the reactant [(**1b**) or (**5**)] included in the complex with



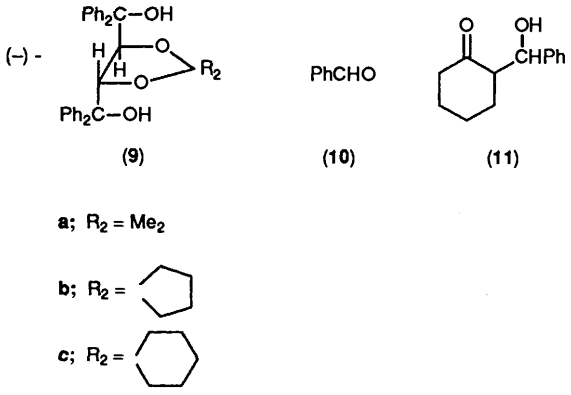
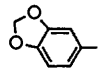


Table 1. Aldol condensation reaction of (1) and (2) in the absence of solvent[a] and in 50% aqueous EtOH.[b]

Entry	(1) Ar	(2) Ar′	Reaction time/min	Solvent	Yield (%) (3)	(4)
1	Ph	Ph	30	—	10	0
				50%EtOH	0	36
2	*p*-MeC_6H_4–	Ph	5	—	0	97
				50%EtOH	0	11
3	*p*-MeC_6H_4–	*p*-MeC_6H_4–	5	—	0	99
				50%EtOH	0	3
4	*p*-ClC_6H_4–	Ph	5	—	0	98
				50%EtOH	18	59
5	*p*-ClC_6H_4–	*p*-$MeOC_6H_4$–	10	—	2	79
				50%EtOH	25	52
6	*p*-ClC_6H_4–	*p*-BrC_6H_4–	10	—	0	81
				50%EtOH	0	92
7		*p*-BrC_6H_4–	10	—	0	91
				50%EtOH	0	0

[a] Reaction was carried out by grinding a mixture of (1), (2), and NaOH by pestle and mortar at room temperature. [b] Reaction was carried out by keeping a solution of (1), (2), and NaOH in 50% aqueous EtOH at room temperature. When the reaction of entry 1 is carried out for 13 h, (3) is obtained in 85% yield.[8]

Table 2. Aldol condensation reaction of (1) and (5) in the absence of solvent[a] and in water[b].

(1) Ar	Solvent	Reaction time/h	Yield/%[c] (6) (*erythro*:*threo*)	(7)	(8)
a Ph	—	0.5	15 (30:70)	82	—
	H_2O	12	75 (50:50)	—	—
b *p*-MeC_6H_4–	—	0.5	—	11	31
	H_2O	24	28 (40:60)	—	—
c *p*-$MeOC_6H_4$–	—	0.5	—	15	56
	H_2O	24	3 (30:70)	8	—
d *p*-ClC_6H_4–	—	0.5	8 (30:70)	5	32
	H_2O	6	52 (50:50)	—	—
e *o*-ClC_6H_4–	—	0.5	—	88	—
	H_2O	17	50 (65:35)	—	—
f *p*-PhC_6H_4–	—	0.5	36 (30:70)	4	31
	H_2O	24	3 (30:50)	—	—

[a] All the reactions were carried out by grinding an equimolar mixture of (1), (5), and NaOH with pestle and mortar for 0.5 h. [b] All the reactions were carried out by keeping a solution of equimolar amounts of (1), (5), and NaOH in water. [c] Product ratios were determined by ^1H NMR spectroscopy.

Table 3. Aldol condensation reaction[a] of an inclusion complex[b] of (5) and (9) with benzaldehyde (10) in the absence of solvent.

Host	Base	Yield/% of (11) (*erythro*:*threo*)[c]	$[\alpha]_D$ (°)[d]
(9a)	NaOH	37 (20:80)	−2.1
(9a)	KOH	29 (40:60)	0
(9a)	$LiOH·H_2O$	20 (50:50)	−1.0
(9a)	$NaNH_2$	17 (25:75)	−2.8
(9b)	NaOH	16 (20:80)	−2.5
(9c)	NaOH	22 (20:80)	−3.7

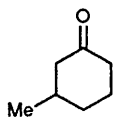
[a] All the reactions were carried out by keeping an equimolar mixture of the inclusion complex, (10), and base at room temperature for 12 h. [b] The inclusion complex of (9)[7] and (5) was prepared by recrystallization of (9) from (5). [c] The *erythro*:*threo* ratio of (11) was determined by ^1H NMR spectroscopy. [d] Measured in $CHCl_3$, but optical purity is not determined.

(**9c**). However, (+)- and (−)-(**6b**) were obtained when (**1b**) and (**5**) are included, respectively. Treatment of a 1:1 complex of (**9c**) with (**1b**) in the presence of NaOH in the solid state at room temperature for 12 h gave (+)-(**6b**) in 22% yield [*erythro*:*threo* = 30:70; $[\alpha]_D$ +1.8° (*c* 0.3, $CHCl_3$)]. On the other hand, the same treatment of a 1:1 complex of (**9c**) and (**5**) with (**1b**) gave (−)-(**6b**) in 28% yield [*erythro*:*threo* = 20:80, $[\alpha]_D$ −3.4° (*c* 0.48, $CHCl_3$)]. It is interesting that only the aldol condensation product (**6b**) but not its dehydration product (**7b**) is obtained when the reaction is carried out using the host-guest inclusion complex.

In order to increase the enantioselectivity of the aldol reaction, a 1:1 inclusion complex of (**9c**) and (+)-(**12**) of 81% e.e. was treated with (**1a**) and NaOH in the solid state at room temperature for 12 h to give again the dehydration product (−)-(**13**) of 81% e.e. {$[\alpha]_D$ −73.3° (*c* 0.18, $CHCl_3$)}.

Some other aldol reactions of aliphatic ketone with aliphatic aldehyde or aromatic aldehyde in an inclusion complex also gave aldol reaction product but not any dehydration product. For example, treatments in the solid state of a 1:1 inclusion complex of (**9a**) and (**5**) with paraformaldehyde and (**14**) in the presence of NaOH gave (**15**) (11% yield, $[\alpha]_D$ 0°) and (**16**) [25% yield, $[\alpha]_D$ +0.7° (*c* 0.15, $CHCl_3$)], respectively. Similar treatments of a 1:1 complex of (**9b**) and (**17**) with (**14**), and a 1:1 complex of (**9b**) and (**19**) with (**1a**) gave (**18**) (21% yield, $[\alpha]_D$ 0°) and (**20**) [35% yield, $[\alpha]_D$ +0.2°) (*c* 0.48, $CHCl_3$)]. Optical purity is again not determined.

It is important but not easy to clarify the reason why the aldol reaction proceeds more efficiently and selectively in the absence



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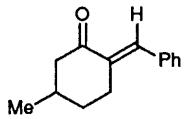

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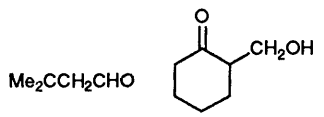

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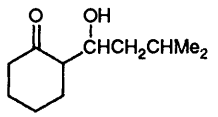

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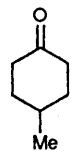

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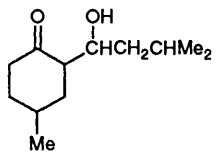

(18)

$Me_2CHCOMe$

(19)

$MeCOC(Me)_2CH(OH)Ph$

(20)

of solvent than in solution. We can say now only that the reaction in the absence of solvent has a high concentration of reagents so that the reaction goes faster, and that as the molecules are arranged regularly in the crystals the reaction proceeds more selectively.

Acknowledgements

We wish to thank for the Ministry of Education, Science and Culture, Japan, for Grant-in-Aid for Scientific Research on Priority Areas, No. 63840017.

References

1 F. Toda, M. Yagi, and K. Kiyoshige, *J. Chem. Soc., Chem. Commun.*, 1988, 958.
2 F. Toda and K. Mori, *J. Chem. Soc., Chem. Commun.*, 1989, 1245.
3 F. Toda, K. Kiyoshige, and M. Yagi, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 320; F. Toda and T. Shigemasa, *Carbohyd. Res.*, 1989, **192**, 363.
4 F. Toda, K. Tanaka, and S. Iwata, *J. Org. Chem.*, 1989, **54**, 3007.
5 F. Toda and T. Shigemasa, *J. Chem. Soc., Perkin Trans. 1*, 1989, 209.
6 F. Toda, K. Tanaka, Y. Kagawa, and Y. Sakaino, *Chem. Lett.*, 1990, 373.
7 F. Toda and H. Akai, *J. Org. Chem.*, 1990, **55**, 3446.
8 E. P. Kohler and H. M. Chadwell, *Org. Synth.*, Coll. Vol 1, 78.
9 H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310.

Paper 0/03194A
Received 16*th July* 1990
Accepted 26*th July* 1990