

The important role of solvent vapor in an organic solid state reaction

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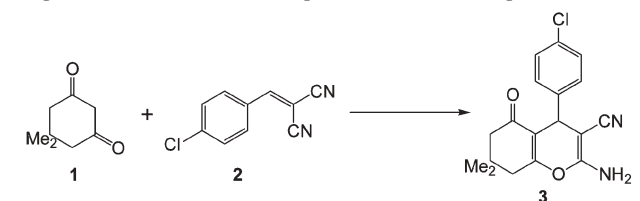
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Some organic reactions in the solid state proceeded very efficiently and selectively in the presence of a small amount of solvent vapor.

It has been well established that some organic reactions proceed efficiently and selectively in the solid state.¹ However, some solid state reactions proceed more slowly than solution reactions. Recently, we found that some solid state reactions proceed very efficiently and selectively in the presence of a small amount of solvent vapor. Since only a small amount of solvent vapor is sufficient for the acceleration of the reaction and increasing the selectivity, this method is important from the viewpoint of green and sustainable chemistry. Some phase transitions in the solid state which are accelerated by a solvent vapor have been reported.² However, organic solid state reactions which are accelerated by a solvent vapor have never been reported. Some such examples of the Michael and Br₂ addition reactions in the solid state are reported.

When a solution of 5,5-dimethylcyclohexane-1,3-dione (**1**) and 2,2-dicyano-*p*-chlorostyrene (**2**) in MeOH was kept at room temperature for 1 h, the Michael addition reaction product **3** was obtained in 71% yield (Table 1). In contrast, the reaction in the solid state gave **3** in a poor yield. For example, heating a mixture of **1** and **2** at 100 °C for 4 h gave **3** only in 21% yield. However,

Table 1 Michael reaction of **1** and **2** in the solid state at room temperature in the absence and presence of solvent vapor^a



Conditions

Solvent vapor	Reaction time/days	Yield of 3 (%)
— ^b	4	21
MeOH	1	63
MeOH	2	81
MeOH	4	90
MeCN	2	25
MeCN	4	51

^a When the reaction was carried out in MeOH solution for 1 h, **3** was obtained in 71% yield. ^b Reaction was carried out at 100 °C.

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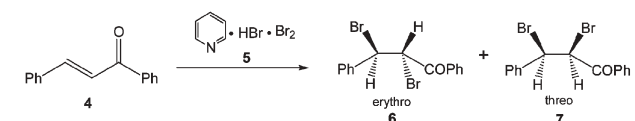
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when the reaction in the solid state was carried out at room temperature in the presence of MeOH vapor for 1 h the result was **3** in 63% yield.† By prolongation of the reaction time to 2 and 4 h, the yield increased to 81 and 90%, respectively. The efficiency of these reactions under the MeOH vapor is much better than that of the simple solid state reaction and the solution reaction in MeOH (Table 1). Although MeCN is not as effective as MeOH, it is still better than the reaction in the absence of solvent vapor.

Addition reactions of Br₂ to chalcone (**4**) were carried out by keeping a mixture of powdered **4** and a pyridine·HBr·Br₂ complex (**5**) at room temperature under various conditions (Table 2). The solid state reaction in the absence of solvent vapor for 4 h gave a 100 : 0 mixture of *erythro*- (**6**) and *threo*-addition products (**7**) in 72% yield. This result was better than that of the solution reaction in CH₂Cl₂ which gave a 91 : 9 mixture of **6** and **7** in 62% yield. The solid state reaction was also accelerated by various solvent vapors and even water vapor played an important role as did organic solvent vapors.

In order to make the contact with solvent vapor efficient, the solid state reaction of various chalcone derivatives **8** with **5** was carried out in the presence of various solvent vapors by mixing every hour with a spatula (Table 3). The efficiency and the selectivity of all reactions were much better than those of the corresponding solid state reactions in the absence of solvent vapor. Finally, the satisfactory contact of the solvent vapor with **8** and **5** was found to be important. When the reaction of **8b** with **5** in

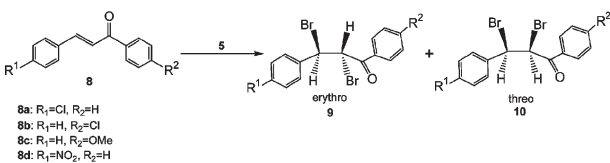
Table 2 Addition reaction of Br₂ to **4** in the solid state at room temperature in the absence and presence of solvent vapor^a



Conditions		Products	
Solvent vapor	Reaction time/h	Yield (%)	6 : 7 Ratio
—	4	72	100 : 0
CH ₂ Cl ₂	1	95	99 : 1
MeCN	2	82	100 : 0
CHCl ₃	1	94	98 : 2
MeOH	2	88	100 : 0
EtOH	2	81	99 : 1
benzene	4	95	95 : 5
H ₂ O	4	73	100 : 0
Et ₂ O	2	93	100 : 0
Hexane	4	71	100 : 0

^a When the reaction was carried out in CH₂Cl₂ and MeCN solution for 1 h, **6** and **7** were obtained in 62 (91 : 9) and 67% (100 : 0) yields, respectively, in the **6**:**7** ratios indicated.

Table 3 Addition reaction of Br₂ to **8** in the solid state at room temperature in the absence and presence of solvent vapor^a



8a: R₁=Cl, R₂=H
 8b: R₁=H, R₂=Cl
 8c: R₁=H, R₂=OMe
 8d: R₁=NO₂, R₂=H

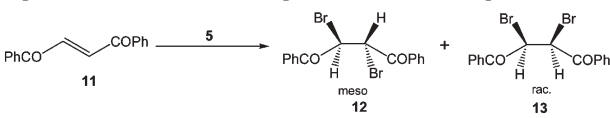
Conditions		Products	
Solvent vapor	Reaction time/h	Yield (%)	9 : 10 Ratio
8a	—	9	100 : 0
	CH ₂ Cl ₂	85	100 : 0
8b	—	4	100 : 0
	CH ₂ Cl ₂	93	100 : 0
8c	—	6	100 : 0
	CH ₂ Cl ₂	87	100 : 0
8d	—	0	100 : 0
	CH ₂ Cl ₂	70	93 : 7

^a All reactions were carried out by mixing every one hour by spatula.

CH₂Cl₂ was carried out at room temperature for 3 h, a mixture of **9b** and **10b** (93 : 7 ratio) was obtained in 69% yield. These data again support that the solid state reaction in the presence of solvent vapor has many advantages.

The reaction of (*E*)-dibenzoyl ethylene (**11**) and **5** which gives a mixture of *meso*- (**12**) and *rac*-addition products (**13**), also proceeded efficiently and selectively in the presence of solvent vapor. When a solution reaction of **11** and **5** was carried out in CH₂Cl₂ for 2 h, a 50 : 50 mixture of **12** and **13** was obtained in 73% yield. Although the selectivity increased to 83 : 17 when the reaction was carried out in the solid state for 20 h, the yield was only 38%. In contrast, the yield and the selectivity were improved by carrying out the solid state reaction under CH₂Cl₂ vapor and a 89 : 11 mixture of **12** and **13** was obtained in 88% yield (Table 4). Nevertheless, MeOH and EtOH vapor was not as effective as CH₂Cl₂ vapor (Table 4). Such a difference is also observed sometimes in solution reactions as a solvent effect. The possibility that the difference depends on the solubility of the Br₂ generated from **5** in the solvent used can be neglected, since Br₂ is freely soluble in all these solvents. However, it is not clear whether the solvent effect in the solution reaction is similar or not to that in the solid state reaction.

Table 4 Addition reaction of Br₂ to **11** in the solid state at room temperature in the absence and presence of solvent vapor^a



Conditions		Products	
Solvent vapor	Reaction time/h	Yield (%)	12 : 13 Ratio
—	20	38	83 : 17
CH ₂ Cl ₂	2	88	89 : 11
MeOH	2	34	88 : 12
EtOH	2	36	91 : 9

^a When the reaction was carried out in CH₂Cl₂ for 2 h, a 50 : 50 mixture of **12** and **13** was obtained in 73% yield.

The efficiency of the solid state reaction in the presence and absence of CH₂Cl₂ vapor was compared by monitoring the reaction by IR spectral measurements (Fig. 1). In the presence of CH₂Cl₂ vapor, as the reaction proceeds, νC=O of **11** at 1650 cm⁻¹ decreased and almost disappeared after 1 h and νC=O at 1670 cm⁻¹ of the product increased. Since the amount of CH₂Cl₂ vapor is very small, its absorption did not appear in the spectra. In the latter, however, no significant change occurred after 30 and 60 min.

In some cases, however, solvent vapor retarded the solid state reaction. For example, when the reaction of (*E*)-stilbene (**14**) and **5** was carried out under solvent vapor at room temperature it gave the pure *trans*-addition product (**15**) in the yields indicated (Table 5). These yields are lower than those by the solid state reaction in the absence of the solvent vapor. Nevertheless, all these solid state reactions gave the *meso*-isomer (**15**) as the sole product, but not any *rac*-isomer (**16**), although the solution reaction in CH₂Cl₂ for 16 h gave a 97 : 3 mixture of **15** and **16** in 76% yield. Nevertheless, when the complex PhN⁺Me₃·Br⁻·Br₂ (**17**) is used as a reagent instead of **5** for the bromination reaction of **14** in the presence of CH₂Cl₂ vapor, **15** was obtained selectively in 96% yield, although the reaction in the absence of CH₂Cl₂ vapor gave **15** in 49% yield (Table 5).

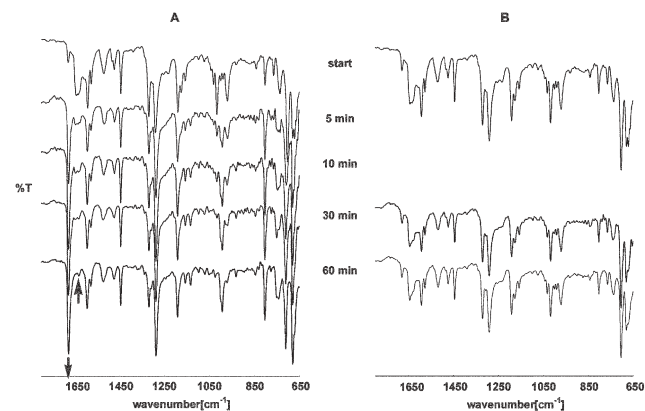
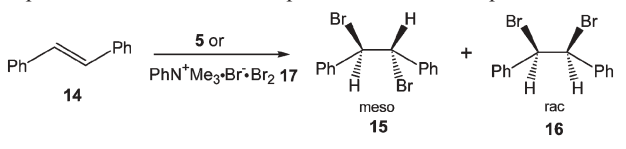


Fig. 1 Monitoring of the solid state reaction of **11** with **5** in the presence (A) and absence (B) of CH₂Cl₂ vapor by the ATR method.

Table 5 Addition reaction of Br₂ to **14** in the solid state at room temperature in the absence and presence of solvent vapor^a



Conditions		Products	
Reagent	Solvent vapor	Reaction time (h)	Yield/% 15 : 16 Ratio
5	—	48	68 100 : 0
5	CH ₂ Cl ₂	48	36 100 : 0
5	MeOH	18	31 100 : 0
5	EtOH	18	41 100 : 0
5	MeCN	18	40 100 : 0
17	—	24	49 100 : 0
17	CH ₂ Cl ₂	16	96 100 : 0

^a When the reaction was carried out in CH₂Cl₂ for 16 h, a 97:3 mixture of **15** and **16** was obtained in 76% yield.

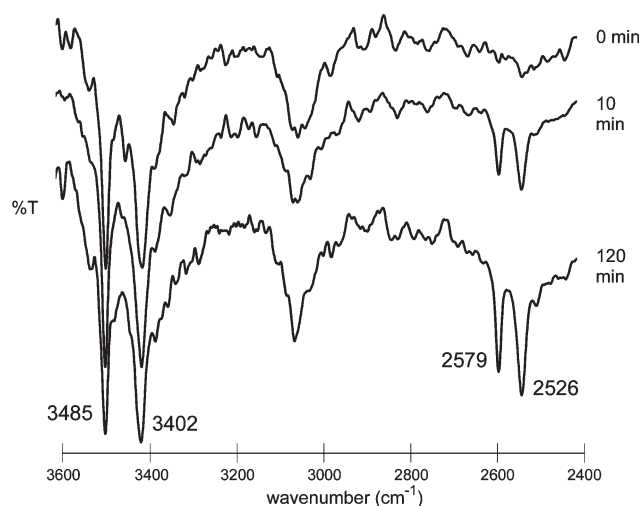


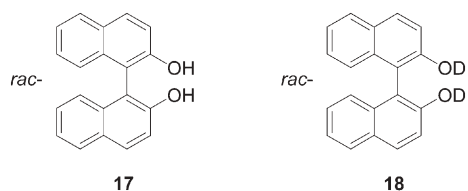
Fig. 2 Monitoring by the ATR method at room temperature of the deuterium exchange reaction between powdered **17** and MeOD vapor.

All the solid state reactions under solvent vapor atmosphere were carried out in a sealed flask filled with air and solvent vapor. For example, when a mixture of **4** or **11** and an equimolar amount of **5** was kept in a sealed flask filled with air and a 0.4 mmol amount of CH_2Cl_2 vapor at room temperature for 1 h, **6** and **7** in a 99 : 1 ratio (95% yield), and **12** and **13** in a 89 : 11 ratio (88% yield) were obtained after recrystallization in the yields indicated, respectively. In a previous paper, we reported that co-crystallization by grinding in the solid state is accelerated by addition of a small amount of solvent.³ However, it is very interesting that a small amount of solvent vapor accelerates the solid state reaction and increases its selectivity.

It has been well established that gas–solid reactions proceed efficiently, and mechanistic studies of these reactions have been carried out by Kaupp and his co-workers using AFM techniques.⁴ However, the AFM technique is available only to study the surface reaction of the solid. In order to clarify the mechanism of the important role of the solvent vapor in the organic solid state reaction, we studied how the solvent molecule easily comes into the crystal. Powdered *rac*-2,2'-dihydroxy-1,1'-binaphthyl (**17**) is exposed to MeOD vapor at room temperature and deuteration of the OH group of **17** was monitored by measurement of IR spectra in the solid state (Fig. 2). At the beginning of the measurement, only the νOH absorptions of **17** appeared at 3485 and 3402 cm^{-1} , which have been assigned to inter- and

intramolecular hydrogen bonded OH groups, respectively.⁵ After 10 min, new inter- and intramolecular hydrogen bonded νOD absorptions of deuterated **18** appeared at 2579 and 2526 cm^{-1} , respectively. After 120 min, about a half of the molecules of **17** were deuterated (Fig. 2).

These data show that MeOD vapor comes into the crystal of **17** and H–D exchange occurs easily. Finally, it is reasonable to consider that solvent vapor comes into the crystal of the reactant together with the reagent molecule and solid state reaction occurs efficiently. It is also probable that some solvent vapors come into the crystal easily and some do so with difficulty.



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Notes and references

† Experimental details: All solid state reactions under solvent vapor atmosphere were carried out in a sealed flask filled with air and solvent vapor roughly in a 1 : 1.2 : 0.25 molar ratio of reactant : reagent : solvent vapor. For example, a mixture of powdered **4** (200 mg, 0.96 mmol), and **5** (369 mg, 1.15 mmol) was kept in a flask (2 ml volume) filled with CH_2Cl_2 vapor (20 mg, 0.24 mmol) for 1 h. The reaction product was washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ to give the product (336 mg, 95%) as a mixture of **6** and **7** in a 99 : 1 ratio. All the ratios of isomers were determined by ^1H NMR spectra.

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