Rate acceleration of organic reaction by immediate solvent evaporation†

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Several types of organic reactions were accelerated by immediate evaporation of solvents because of remarkable enhancement of molecule-to-molecule contacts between reactants.

Organic reactions are usually conducted in solution, partly because better mixing is attainable when reactants are solid or immiscible with each other. Although the reactions finish quickly on occasion, a long time is required frequently. Curtailment of the reaction time is desirable from both operational and economical points of view. The reaction rate can be accelerated by elevating the reaction temperature. Another way is to increase concentration of the reaction solution so long as heat evolution is not violent. However, it is not common to condense the solution beyond the concentration level at which precipitation is triggered, because the heterogeneous reaction is conventionally regarded as being slower than the homogeneous one. Contrary to such general acceptance, we earlier disclosed dramatic rate acceleration in solventless reactions. Simple grinding of the solid reactants led to supramolecular self-assembling much faster than the normal solution reaction.[1] Rotaxanes were fabricated even without grinding once a solid film of reactants had been formed.[2] Namely, the solid reactants were dissolved in a solvent and the resulting solution was immediately evaporated to give a solid film. Merely standing the film under ambient conditions drove the reaction at a rate faster than in the case where the original solution was kept stirring.[3] During these experiments, we observed in some cases that the reaction had already occurred to a certain extent just when the evaporation was over. This suggested that a reaction might proceed faster by immediate evaporation rather than by continuing the reaction in solution and, hence, we presumed that the reaction time could be shortened by taking advantage of such rate acceleration. This is indeed the case, and we herein exemplify the validity with imine synthesis, Wittig reaction, and quaternization of tertiary phosphine and pyridine.

3,5-Dibromobenzaldehyde (**1a**) (2 mmol) and *p*-toluidine (**2**) (2.2 mmol) were dissolved in CH_2Cl_2 (4 mL). Then, the solution was immediately evaporated by means of rotary evaporator followed by vacuum pumping at rt (immediate solvent evaporation method: ISEM). It took about 5 min for complete removal of the solvent. The resulting white film was already constituted of pure imine **3a** (>99%) and a small amount of **2** on the basis of ^{1}H NMR spectroscopy, no aldehyde being detected on TLC (Table 1, entry 1). To assess this new protocol, the high concentration solution method (HCSM) which had been reported to be more efficient than the normal solution reaction for synthesis of [2]rotaxanes[4] was invoked as a control experiment. Both **1a** (2 mmol) and **2** (2.2 mmol) were dissolved in a minimum amount of CH_2Cl_2 (usually 1 mL). The solution was stirred at rt for 5 min, but **3** was formed only in 56% yield. The reaction finished after 2 h. A more marked difference was observed with 3,5-dichlorobenzaldehyde (**1b**). Upon evaporation for 5 min, a trace amount of **1b** (1%) was detected, and hence the resulting solid film was kept standing under ambient conditions for additional 30 min to complete the reaction (>99% yield based on NMR) (entry 2). The conversion of the corresponding reaction in highly concentrated solution after 5 min was only 17% and it took 24 h for the reaction to finish. *p*-Nitrobenzaldehyde (**1c**) and 2-naphthaldehyde (**1d**), also gave comparable results (entries 3 and 4) indicative of superiority of ISEM to HCSM.[5]

Wittig reaction is one of the most useful reactions in organic synthesis,[6] but a long reaction time is demanded occasionally, in particular for stabilized ylides. It has turned out that reaction between solid aldehydes and ylides undergoes a great deal of acceleration by immediate evaporation (Table 2). In a reaction of **1c** with ylide **4a** (R′ = COOEt), only a weak spot of **1c** was detected by TLC monitoring after evaporation (~2% by ^{1}H NMR). The resulting solid film was kept standing for 1 h at rt to bring the reaction to completion (entry 1). The desired olefin **5a** was isolated in 93% yield by column chromatography. On the other hand, the ratio **5a/1c** was only 70 : 30 after 5 min according to HCSM. It took 24 h to give a 92% yield, but a small amount of **1c** still remained nevertheless. Since the initial stage of reaction between **1c** and **4b** (R′ = COPh) proceeded more slowly, the conversion could be quantified more clearly by ^{1}H NMR, which revealed the ratio **5b/1c** to be 73 : 27 after evaporation according to ISEM and 53 : 47 after 5 min by HCSM (entry 2). The reaction finished in 1 h and 3 h by ISEM and HCSM, respectively. The reaction of *p*-chlorobenzaldehyde (**1e**) took place similarly but exhibited more distinct difference in the reaction rate between both protocols (entry 3). According to ISEM, the conversion was already 99% after evaporation and the reaction finished in 15 min upon additional standing. By contrast, a small amount of **1e** remained even after 24 h according to HCSM. A similar advantage of ISEM was apparent with sterically demanding 2,3-dimethoxybenzaldehyde **1f** (entry 4). Since the reaction of 9-anthraldehyde **1g** was rather slow under both conditions at rt (entry 5), evaporation by rotary evaporator was carried out at 40 °C followed by pumping *in vacuo* at rt. The ratio of the product olefin *vs.* unreacted aldehyde was found to be 80 : 20 (based on ^{1}H NMR) at this stage, and the reaction finished in 3 h while it took 24 h for completion by HCSM at 40 °C (entry 6). The utility of the higher

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Table 1 Synthesis of imines: RCHO **1** + $H_2NC_6H_4CH_3$ **2** → RCH=N–$C_6H_4CH_3$ **3**

		ISEM[a]		HCSM[b]	
Entry	**1**	**3** : **1**[c] (after evpn., 5 min)	**3** : **1**[c] after standing (*t*/min)	**3** : **1**[c] after stirring (5 min)	**3** : **1**[c] after stirring (*t*/h)
1	**1a**	>99 : 1	—	56 : 44	>99 : 1 (2)
2	**1b**	99 : 1	>99 : 1 (15)	17 : 83	>99 : 1 (24)
3	**1c**	98 : 2	>99 : 1 (15)	30 : 70	99 : 1 (24)
4	**1d**	97 : 3	>99 : 1 (120)	46 : 54	>99 : 1 (24)

[a] Dissolve **1** (2 mmol) and **2** (2.2 mmol) in CH_2Cl_2 (4 mL); evaporation by rotary evaporator followed by pumping *in vacuo*; standing at rt. [b] Stirring a solution of **1** (2 mmol) and **2** (2.2 mmol) in CH_2Cl_2 (1 mL) at 27 °C. [c] Determined by ^{1}H NMR.

Table 2 Witting reaction: RCHO **1** + Ph_3P=CHR′ **4** → RCH=CHR′ **5**

				Yield (%)[a] of **5**			
				ISEM[b]		HCSM[c]	
Entry	**1**	**4**		**5** : **1**[d] after evpn.	Yield (time/h; *E*/*Z*[d])	**5** : **1**[d] after 5 min	Yield (time/h; *E*/*Z*[d])
1	**1c**	**4a**	**5a**	98 : 2	93 (1; 99 : 1)	70 : 30	92 (24; 97 : 3)[e]
2	**1c**	**4b**	**5b**	73 : 27	92 (1; 99 : 1)	53 : 47	93 (3; 98 : 2)
3	**1e**	**4a**	**5c**	>99 : 1	93 (15 min; 95 : 5)[f]	62 : 38	91 (24; 96 : 4)[e]
4	**1f**	**4a**	**5d**	99 : 1	93 (10 min; 92 : 8)	12 : 88	89 (24; 91 : 9)[e]
5	**1g**	**4a**	**5e**	63 : 37	94 (24; 97 : 3)[e]	11 : 89	89 (24; 96 : 4)[e]
6	**1g**	**4a**	**5e**	80 : 20	90 (3; 98 : 2)[g]	33 : 67	91 (24; 95 : 5)[h]
7	**1d**	**4a**	**5f**	91 : 9	93 (10 min; 93 : 7)[g]	63 : 37	94 (5; 98 : 2)[h]
8	**1h**	**4a**	**5g**	>99 : 1	93 (0; 94 : 6)[i]	<1 : 99	92 (24; 95 : 5)
9	**1i**	**4a**	**5h**	32 : 68	90 (7; 96 : 4)[e]	<1 : 99	81 (7; 94 : 6)[e]

[a] Isolated yield after column chromatography. [b] Dissolve **1** (2 mmol) and **4** (2.2 mmol) in CH_2Cl_2 (4 mL); evaporation by rotary evaporator followed by pumping *in vacuo*; standing at rt. [c] Stirring a solution of **1** (2 mmol) and **4** (2.2 mmol) in CH_2Cl_2 (1 mL) at 27 °C. [d] Determined by NMR. [e] Aldehyde remained by TLC monitoring. [f] Reaction was almost complete after evaporation. [g] Evaporation at 40 °C. [h] Stirring at 40 °C. [i] After evaporation.

temperature was also seen in the reaction between **1d** and **4a** (entry 7). The reaction was nearly over after evaporation at 40 °C (**5f**/**4a** = 91 : 9) and came to an end after standing for additional 10 min. In contrast, much slower reaction occurred according to HCSM. It should be noted, however, that the elevation of temperature is not always effective since in some cases, too quick evaporation hampers homogeneous mixing of reactants which is necessary for efficient contacts between reactant molecules in the solid film. Since Wittig reaction without solvent is known,[7] it may be of interest to compare ISEM with the typical solventless method in which the reactants are ground on the mortar. Although the reactions of entries 1 and 3 exhibited comparable rates in both protocols, the reaction time of other reactions in ISEM was roughly half of that in the grinding method except for the reaction of **1g** with which no reaction occurred in the latter method.

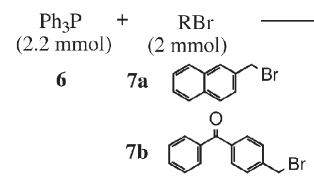
The present protocol is not restricted to solid aldehydes. When liquid benzaldehyde (**1h**) and **4a** were combined directly, no homogeneous mixture emerged causing incomplete reaction. However, a smooth but somewhat wet solid film was obtained after evaporation according to ISEM. The reaction had already finished at this stage while HCSM afforded a 92% yield after 24 h (entry 8). Notably, electron-rich aldehyde which usually reacts very slowly also enjoyed the acceleration. Thus, reaction of anisaldehyde (**1i**) was almost over in 7 h by ISEM whereas HCSM failed to drive the reaction to finish after 7 h (entry 9). The double-bond geometry of the resulting olefins deserves further comments. Nearly the same *E*/*Z* ratio was revealed for the products from both methods, thereby suggesting that the reaction mode in terms of olefin geometry is not significantly altered by suction of solvent from the conventional reaction system.

Transformation of triphenylphosphine (**6**) to phosphonium salts **8** was also accelerated.[8] As shown in Table 3, smooth alkylation occurred with 2-(bromomethyl)naphthalene (**7a**) by ISEM in contrast to unsatisfactory outcome by HCSM. On the other hand, reaction with 4-(bromomethyl)acetophenone (**7b**) required 20 h for completion (>99% yield) by standard ISEM. However, upon evaporation at 40 °C as described above, the reaction finished in 3 h. Notably, the reaction did not come to an end in 7 h in a highly concentrated solution at 40 °C.

Finally, quaternization of pyridine proved to experience rate enhancement as well (Table 4). Bipyridine derivative **9** was alkylated quantitatively in 3 h by ISEM whereas HCSM provided only a 61% conversion after 24 h.

Recently, Sharpless *et al.* put forth the "on water" method, by which various reactions take place very quickly at the macroscopic phase boundary between water and insoluble oils.[9] We found a considerable effectiveness of this on-water protocol for the reaction

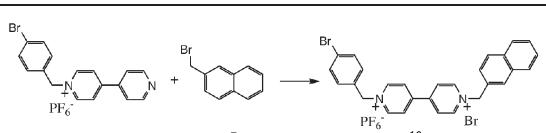
Table 3 Syntheses of phosphonium salts



	Yield/%			
	ISEM		HCSM	
	8:**7** after evaporation	Yield (time/h)	**8**:**7** after 5 min	Yield (time/h)
8a	91 : 9[a]	91[b] (2)	12 : 88[a]	87[b,c] (34)
8b	89 : 11[a]	>99[a,d] (3)	22 : 78[a]	91[a,c,e] (7)

[a] Determined by ^{1}H NMR. [b] Isolated yield by column chromatography. [c] A small amount of **7** remained on TLC. [d] Evaporation at 40 °C. [e] Stirring at 40 °C.

Table 4 Synthesis of pyridinium salt



10 : **9**[a]

ISEM		HCSM	
After evaporation	After standing (3 h)	After 5 min	After 7 h
80 : 20	>99 : 1	1 : 99	61 : 39

[a] Determined by ^{1}H NMR.

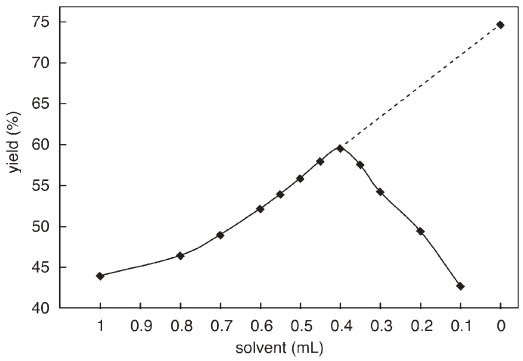


Fig. 1 Concentration effect: Yields of Wittig reaction of **1f** with **4a** in HCSM after 5 min.

of **4a** with **1h**, yet its reaction rate (75% and >99% yields of **5g** based on ^{1}H NMR after 5 min and 1.5 h, respectively, at 27 °C) was slower than that obtained with ISEM.[10]

To get further insight into characteristics of ISEM, the concentration effect of the reaction of entry 4 in Table 2 was scrutinized. The reaction between **1f** (1.0 mmol) and **4a** (1.1 mmol) in various amounts of CH_2Cl_2 at 27 °C was monitored by ^{1}H NMR spectroscopy.[11] The yields 5 min after mixing of the two reactants were determined (Fig. 1) because the solvent evaporation in ISEM finishes within 5 min or it may be that the evaporation has finished actually within 2–3 min. The reaction mixture was homogeneous when the amount of the solvent was between 2.00–0.40 mL, while a part of the reactants precipitated in less than 0.40 mL of the solvent. As expected from the concentration effect, the relationship of yield *vs*. solvent volume exhibited an uphill slope under homogeneous conditions, and the slope was reversed downhill under heterogeneous conditions. Extrapolation of the uphill slope of the homogeneous region (concentration between 1.00 mmol/0.55 mL and 1.00 mmol/0.40 mL) by use of the least square method[12] to the putative solventless extreme leads to the 75% yield (dotted line), an outcome suggesting that the rate enhancement in ISEM does not simply result from the concentration effect. The downhill slope indicates that the concentration effect does not hold in the region below 0.40 mL. Therefore, it is not reasonable to expect such a big leap in the yield (from 60 to 99%) as found in ISEM on the basis of the concentration effect. The present outcome, if being qualitative, clearly shows that ISEM gives rise to the higher yield than that expected to be attained at the ultimate high concentration in solution. Practically, the advantage of ISEM over HCSM is apparent if the limitation of HCSM due to the saturated solubility is taken into account as is evident from the 60% maximum yield in the present case.

Notably, ISEM works on a large scale as well. When the same reaction was carried out on a 20 mmol scale, the solvent (20 mL) was removed at 27 °C in 10 min to leave a dry film which consisted of **5d** : **1f** in a 91 : 9 ratio. The reaction was complete after 15 min upon standing the resulting film at room temperature.

It is not clear enough at present what plays a pivotal role for the acceleration of the reaction rate by ISEM. It can be said that molecule-to-molecule contacts between the respective reactants are made easier by the evacuation of solvent molecules which have joined reactants through solvation. In addition, the overall reaction time is saved by quick reaction in the solid film.[2] Solventless reactions are free from the de-solvation process which is inevitable in a solution reaction. It is fully recognized that solvation heavily decreases the reaction rate.[13] Furthermore, smaller entropy change during the reaction in the solid state may serve for lowering the activation energy. Since 0.4 mL of CH_2Cl_2 is equivalent to 6.7 mmol, each substrate (2.1 mmol in total) is estimated to be solvated at most by three or four molecules of CH_2Cl_2 on average in the saturated solution. It follows that removal of the final portions of the solvent molecules may give rise to a substantial leap of rate increase. The downhill slope under heterogeneous conditions also suggests the effectiveness of ISEM, by which the substrates are once dissolved so as to be completely intermingled at the molecular level. On the other hand, under the above heterogeneous conditions or normal solventless conditions (grinding method), the contacts between the reactants are achievable only at the level of mass particles.

It is now apparent that immediate evaporation of the solvent can conduct reaction faster than running it in solution. The reaction is completed immediately after solvent evaporation in some cases, but not always. If not, standing the resulting film drives the reaction to completion again faster than the solution reaction. Such a simple operation is of great use from the synthetic point of view. Since the rate acceleration by ISEM is deviated from the simple extrapolation of normal solution reaction, the present protocol provides a new facet on organic reaction mechanisms. In conclusion, we propose to reconsider the reactions in the light of the immediate evaporation method when their reaction rate is too slow in solution. The reaction time in solution may well be shortened. Of course, this protocol is not always effective for any reactions, yet shortening of reaction time is basically feasible for a number of reactions which require a long time in solution.

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