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Efficient Solvent- and Catalyst-Free Syntheses of Imine Derivatives Applying the Pressure Reduction Technique: Remarkable Change of the Reaction Rate with the Phase Transition

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Abstract

Because imines could be used as convenient starting materials in various fields, the development of an easy synthetic method of imine was strongly desired. In response to this demand, we thought that it would be an effective synthesis method if an aldehyde and an amine could be reacted to give an imine in good yield under solvent- and catalyst-free conditions. In fact, we tried the reaction of benzaldehyde with various amines under solvent- and catalyst-free conditions followed by removal of water that was produced in the reaction system by a vacuum pump, and desired imines could be obtained in good yields. Observation of this reaction using a nuclear magnetic resonance spectrometer revealed that the reaction rate was extremely fast at the initial stage but slowed over time. However, the reaction of benzaldehyde with aniline differed greatly, and the reaction rate dramatically improved in 47 - 48 minutes after the start of the reaction. At this time, we found that the reaction system underwent a phase transition from the liquid phase to the solid phase.

Keywords

Solvent-Free, Catalyst-Free, Pressure Reduction Technique, Imine, Reaction Rate, Phase Transition

1. Introduction

In recent years, because the concept of green chemistry was generalized and emphasized, the development of that technology was progressing rapidly. In particular, in the field of the organic synthesis, the progress of the study was remarkable. Among the series of investigations, it had been recognized that a solvent-free reaction was suitable for green chemistry [1]-[7]. Various solvent-free reaction systems had been developed so far, they were often accelerated by using the microwave irradiation [8]-[16], the ultrasonic method [17] [18] [19] [20] [21], or the UV lamp irradiation [1] [2] [3] [22] [23] [24] [25] in many cases. We thought that these reactions had some disadvantages. These reactions proceeded by supplying energy from the outside. Moreover, these reactions often required the catalyst. On the other hand, the neat reaction was known as another good idea for green chemistry. Although it was necessary to select a reaction system in which the reaction efficiency was extremely high and little or no by-products were generated, it was the excellent method that the desired product could be obtained by mixing the starting materials. Therefore, when researchers wanted to synthesize a useful organic compound, it was one of realistic ideas to carry out the neat reaction. In view of this point, we decided to study the development of the neat reaction. We focused on syntheses of imines (Schiff bases) from aromatic aldehydes and amines. This type of reaction had already been known. Previously, it was reported that benzaldehyde and aniline were mixed in a molar ratio of 1:1 and reacted for 15 minutes followed by the purification with alcohol to obtain the desired product in good yield [26]. In this reaction, the reaction procedure was very simple, but it was insufficient as a synthetic method from the viewpoint of the yield of the target product. On the other hand, this method was very attractive, because an imine could be a starting material for the superior building block that was used in various fields [27]-[35]. Thus, we believed it was a very useful synthetic method of various imines if this reaction system could be refined to a high performance method. As mentioned above, the main disadvantage of this system was the low yield of the corresponding imine. Then, we thought that the target compound could be obtained in high yield, if it was possible to remove generated water from the reaction system. Actually, it was found that the target compound could be obtained in high yield by the removal of water from this reaction system using a vacuum pump. This synthesis was the excellent method which could be carried out by a very simple operation that consisted of mixing materials, stirring, and reducing the pressure. In addition, comparing to other neat reactions, no activation such as heating was required at all in our method, and then it was considered to be advantageous from the viewpoint of green chemistry. In this paper, we will report the details of the reaction method.

2. Experimental

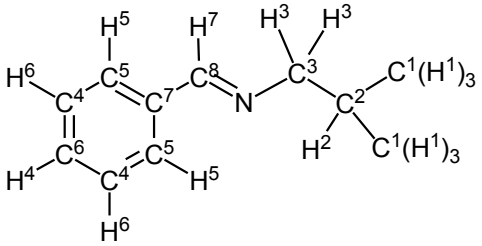
2.1. Chemicals and Instruments

Standard bench top techniques were employed for handling air-sensitive rea-

gent. Benzaldehyde and various amines were distilled under nitrogen before use. All reactions were carried out under nitrogen atmospheres. All yields of target compounds were isolated yields. ULVAC G-50DA (ULVAC KIKO Inc.) was used for carrying out this reducing pressure operation. IR spectra were recorded on an FT/IR-610 (JASCO) spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured on Bruker BioSpin AVANCE III 400 Nanobay spectrometer at 400.1 and 100.6 MHz, respectively. Chemical shifts were given in ppm relative to TMS.

2.2. Typical Experimental Procedure 1 (Scheme: R = Isobutyl, Reaction of Benzaldehyde with Isobutylamine)

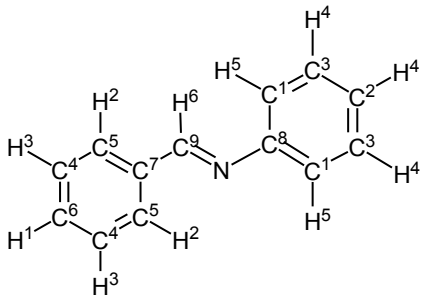
To a stirring benzaldehyde (2.12 g, 20.0 mmol) was added dropwise isobutylamine (1.46 g, 20.0 mmol) at room temperature. The reaction mixture was sampled at 10 minutes after the start of the reaction and was measured by ^{1}H-NMR. After 20, 30, 40, 50, and 60 minutes, the mother liquor was sampled in a same manner and these reaction mixtures were analyzed by ^{1}H-NMR. After 60 minutes, the reaction system was connected to a vacuum pump, the pressure was reduced to 1.0 mmHg and stirred for three hours. After then, the crude mixture was taken out from the reaction vessel and it was purified by the silica gel chromatography (*n*-hexane/Et_2O = 10/1) to yield the desired compound as pale yellow clear oil in 95.2% yield (3.07 g). All physical properties of this product were completely consistent with literature values [36] [37]; Rf = 0.42 (*n*-hexane/Et_2O = 10/1); IR (neat): 693, 752, 1029, 1311, 1386, 1450, 2870, 2955, 3027, 3063 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (d, J = 6.72 Hz, 6H, H^1), 2.00 (sept, J = 6.68 Hz, 1H, H^2), 3.43 (t, J = 6.68 Hz, 2H, H^3), 7.38 - 7.40 (m, 3H, H^4 and H^5), 7.70 - 7.74 (m, 2H, H^6), 8.22 (s, 1H, H^7); ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.72 (C^1), 29.60 (C^2), 69.85 (C^3), 128.08 (C^4), 128.59 (C^5), 130.46 (C^6), 136.38 (C^7), 160.88 (C^8).



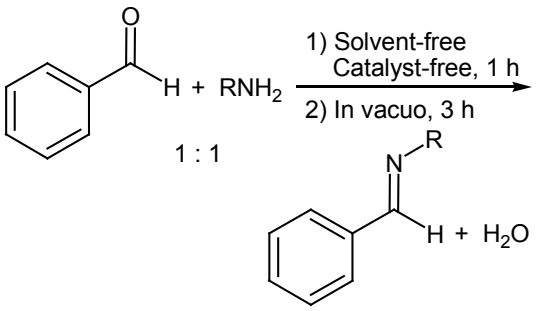
2.3. Typical Experimental Procedure 2 (Scheme: R = Phenyl, Reaction of Benzaldehyde with Aniline)

To a stirring benzaldehyde (2.12 g, 20.0 mmol) was added dropwise aniline (1.86 g, 20.0 mmol) at room temperature. The reaction mixture was sampled at 10 minutes after the start of the reaction and was measured by ^{1}H-NMR. After 20, 30, 40, 50, and 60 minutes, the mother liquor was sampled in a same manner and these reaction mixtures were analyzed by ^{1}H-NMR. After 60 minutes, the reaction system was connected to a vacuum pump, the pressure was reduced to

1.0 mmHg and stirred for three hours. After then, the compound was taken out from the reaction vessel and recrystallized from dichloromethane and hexane to obtain the desired imine as pale yellow crystals (3.45 g, 95.2%). All physical properties of this product were completely consistent with literature values [38] [39] [40]; IR (KBr): 435, 519, 541, 692, 765, 869, 906, 976, 1072, 1170, 1193, 1590, 1627, 2890, 3061 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.19 - 7.25 (m, 3H, H^1 and H^2), 7.35 - 7.42 (m, 2H, H^3), 7.43 - 7.50 (m, 3H, H^4), 7.87 - 7.93 (m, 2H, H^5), 8.45 (s, 1H, H^6); ^{13}C-NMR ($CDCl_3$) δ (ppm): 120.85 (C^1), 125.92 (C^2), 128.75 (C^3), 128.78 (C^4), 129.13 (C^5), 131.37 (C^6), 136.16 (C^7), 152.04 (C^8), 160.41 (C^9).



Other imines obtained in this study were synthesized by the same method as typical experimental procedures. In addition, the physical properties of the obtained imines were perfectly consistent with those reported in literature [41]-[48].



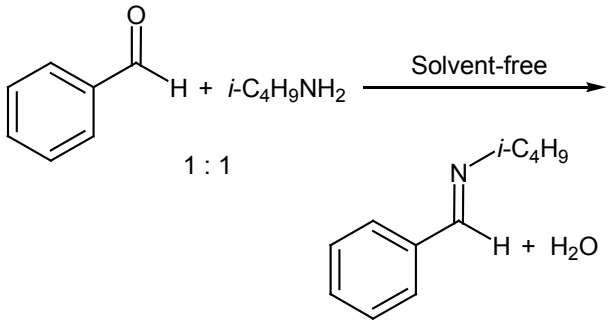
Scheme. Solvent- and catalyst-free syntheses of imine derivatives.

3. Results and Discussion

First, benzaldehyde and isobutylamine were chosen as substrates, and the reaction conditions of this reaction were investigated by using a nuclear magnetic resonance (NMR). In NMR, ^{1}H nucleus was observed and the conversion to imine was determined using the ratio of the integral value of the aldehyde proton to the imine proton. The results were shown in **Table 1**.

In this reaction system, we found that the formation of the imine and water were observed, and no by-products including the structural isomer of imine were detected by ^{1}H-NMR. The reaction mother liquor was sampled at 10

Table 1. Reaction of isobutylamine with benzaldehyde.



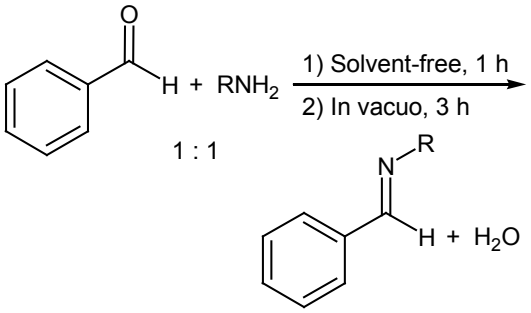
Entry	Time (min.)	Conversion[a)] (%)
1	10	94.8
2	20	95.7
3	30	95.9
4	40	96.0
5	50	96.1
6	60	96.1

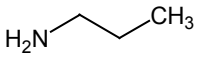
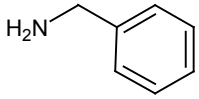
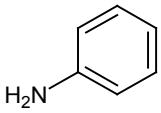
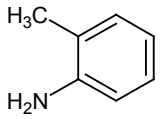
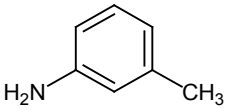
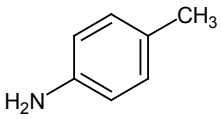
[a)]Conversion data were calculated by ^{1}H-NMR spectrum.

minutes after the start of the reaction and the reaction mixture was measured by ^{1}H-NMR. As a result, benzaldehyde was found to be converted to the corresponding imine at 94.8% (Entry 1). In this system, the amount of the imine was increased as the reaction time passed. When samplings from the mother liquor were carried out in 20 minutes, 30 minutes, 40 minutes, 50 minutes and 60 minutes after the start of the reaction and these reaction mixtures were analyzed by ^{1}H-NMR, we could find that the degree of the conversion to the imine gradually improved (Entries 2 - 6). It could be found that the change of the conversion value became gentler over time by comparing the results at each time. From these results, although the reaction rate at the initial stage of this reaction was very fast and more than 90% of the substrate reacted within 10 minutes, the reaction rate decelerated from around 10 minutes. When the reaction vessel was decompressed to 1.0 mmHg using a vacuum pump and water in the reaction system was removed over 3 hours, only a trace amount of benzaldehyde was observed. Thus, it was thought that the reaction progressed further in the reduced pressure. In this case, the desired imine was isolated in 95.2% yield. In the previous study, the synthesis of this target compound had been reported, and the study showed that the yield of the imine was 100% [49]. However, because acetic acid and methanol were used as a catalyst and a solvent in that study, it could be said that our reaction system was more useful, because only starting materials were used.

Next, we applied this reaction to syntheses of various imines. The results were shown in **Table 2**.

Table 2. Syntheses of various imines.



Entry	RNH_2	Isolated Yield (%)
1		95.1
2		94.0
3		95.2
4		94.9
5		94.5
6		94.0

When this reaction was carried out using propylamine, the desired imine was obtained in 95.1% (Entry 1). Then, we used benzylamine as a substituent. It was found that the corresponding target compound could be obtained in high yield (Entry 2). The maximum yields of imines synthesized from propylamine or benzylamine reported in the past papers were 96% [50] (in the propylamine system) and 92% [51] (in the benzylamine system), but in these reactions, they were necessary to use a solvent and an acid catalyst so on. At this point of view, our method was considered to be superior. This reaction system could also be applied to aromatic amines. When aniline was used as a substrate, the target Schiff base could be obtained in high yield (Entry 3). In the case of a solvent-free reaction that was reported previously, the yield of the target product was about 87% [26], so it was clear that our method was more effective [52]-[59]. Even if *o*-toluidine, *m*-toluidine and *p*-toluidine were used as aromatic amines, synthetic reactions proceeded smoothly. These reactions gave target compounds in high

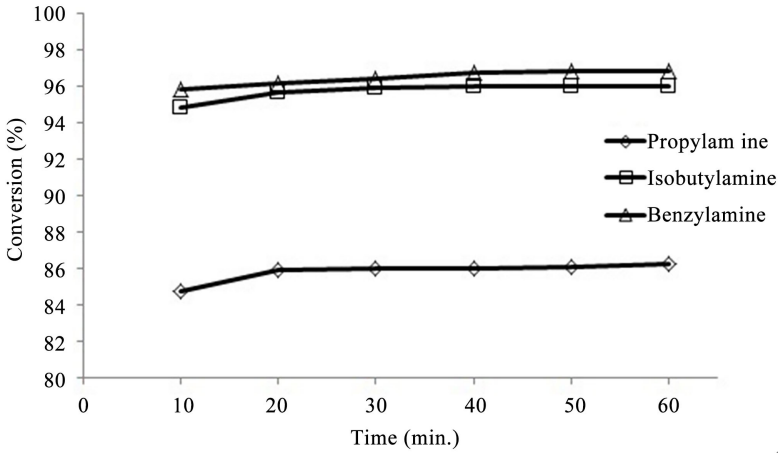
yields regardless of the substitution position of the methyl group (Entries 4 - 6). Some methods of synthesizing imines derived from toluidines had been reported. Target compounds were obtained in 92% (*o*-toluidine) [60], 100% (*m*-toluidine) [59], and 98% (*p*-toluidine) [61] [62] [63], respectively. Although the yields of imines were high in these reaction systems, they still had some disadvantages that a solvent and/or a catalyst were necessary, or the microwave irradiation was needed for the promotion of synthetic reactions. Thus, our reaction systems were considered to be more useful for imine syntheses. From above results, it was revealed that we could use various amines as substrates in this reaction system, and it was an excellent method to easily obtain the desired imines with high yields.

In the reaction of isobutyamine, the starting material (benzaldehyde) was rapidly converted to the corresponding imine at about 10 minutes after the start of the reaction, and thereafter the conversion rate became slowly. Therefore, we investigated that this phenomenon could be observed similarly when other amines were used. The time profiles of the conversion to various imines using aliphatic amines were shown in **Graph 1**.

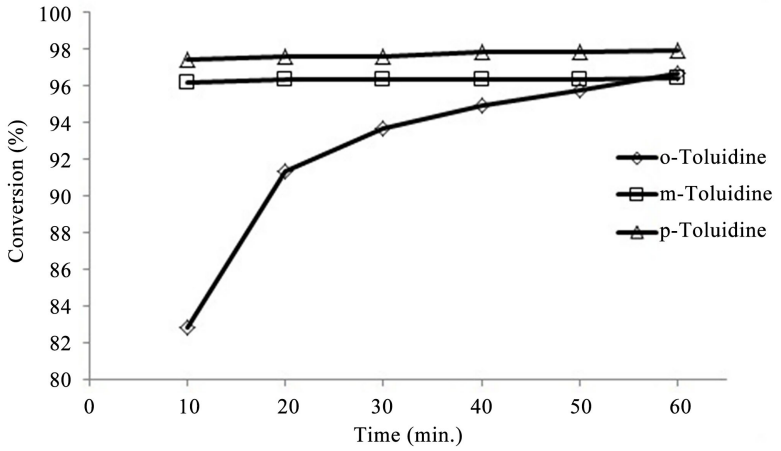
The graph of isobutylamine system was based on the data of **Table 1**. These studies were carried out by ^{1}H-NMR measurement. In addition, the horizontal axis of this graph showed the time after the start of the reaction, and the vertical axis showed the degree of the conversion to imine derivatives. As shown in **Graph 1**, time profiles of reaction systems with aliphatic amines were similar to each other. These results indicated that various imines were formed rapidly within 10 minutes after the start of the reaction, after which the conversion rate became slow. The cause of the difference in the degree of the conversion to the imine using aliphatic amines has not been clarified at present. We will further investigate in future.

The time profiles of the conversion to the imine using *o*-toluidine, *m*-toluidine and *p*-toluidine were shown in **Graph 2**. These reaction systems were also examined by ^{1}H-NMR. A typical example of our synthetic method was the reaction of *o*-toluidine. The conversion to the imine at the initial stage of the reaction system was very rapid, and its speed became slower over time. Although there was a difference in a reaction rate, this phenomenon could be observed in the reactions of *m*-toluidine or *p*-toluidine as well. It was considered that the conversion rate varied depending on the substitution position of the methyl group because of its steric hindrance. The methyl group acted as the steric-hindered substituent, suppressed nucleophilic attack, and it was considered that the converting speed decreased as approaching the reaction center at the *p*-, *m*-, *o*-position.

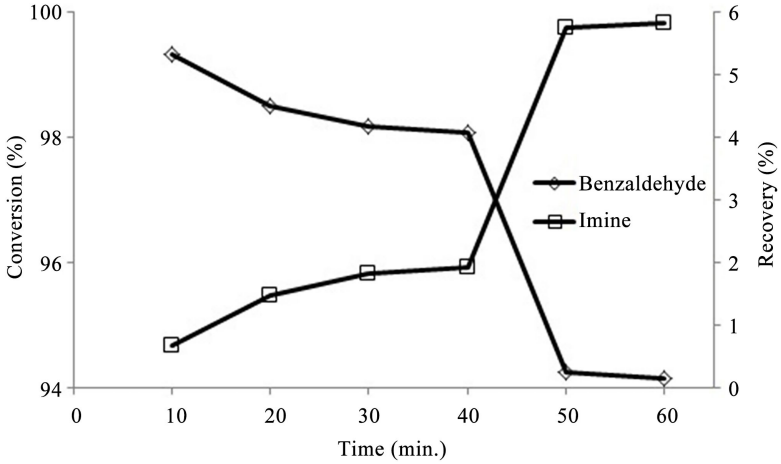
Interestingly, the time course of the conversion to the imine using aniline was different from reactions using aliphatic amines and toluidines. **Graph 3** showed the time profiles of the degree of the conversion to the imine and the recovery of benzaldehyde. In this graph, the vertical axis showed the degree of the conversion



Graph 1. Time profiles of conversions in cases of aliphatic amines.



Graph 2. Time profiles of conversions in cases of toluidine derivatives.



Graph 3. The time profile of the reaction of benzaldehyde with aniline.

to the imine and the recovery of benzaldehyde. In the early stage of this reaction, the conversion to the imine and the consumption of benzaldehyde proceeded very rapidly as in other reaction systems. It was similar to other reaction systems

in that its rate became slow from about 10 minutes after the start of the reaction. However, between 40 minutes and 50 minutes, it was found that the degree of the conversion to the imine was dramatically improved. Along with this phenomenon, the degree of the recovery of benzaldehyde had dramatically decreased. When we observed the state of the reaction between 40 minutes and 50 minutes, we found that the mother liquor solidified at once at around 47 - 48 minutes. It meant that the phase transition of the reaction system had occurred between 40 minutes and 50 minutes. In other reaction systems, such phenomenon including the phase transition had not been observed at all and it could be seen that the reaction using aniline was very specific. To the best of our knowledge, there had been no report of any significant change in degrees of the conversion and the recovery when phase transition was involved. It seemed that dramatic change in the reaction rate accompanied by the phase transition. We would like to further study this phenomenon in future and to clarify the cause.

4. Conclusion

We studied the neat reaction of an aldehyde and an amine. In this system, it was found that the desired imine could be obtained in high yield by removing water under reduced pressure conditions. We found that this reaction proceeded very rapidly in the initial stage, but its rate decreased with the passage of time. It was found that the reaction of benzaldehyde with aniline had a specificity that the phase transition occurred. We will be planning to investigate reactions using various aldehydes and amines. Now we could not investigate the mechanism of this synthetic method from 0 to 10 minutes, because the reaction rate was very fast. Thus, we will elucidate the mechanism at the initial stage of this reaction with various analytical methods in the next investigation. Moreover, we will try to develop the suitable purification of the target compound without organic solvents.

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