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Using $HCOONH_4$ as a Reductant and Nitrogen Source in Converting PhCHO to Imine via a Continuous Condensation-Reduction Mechanism

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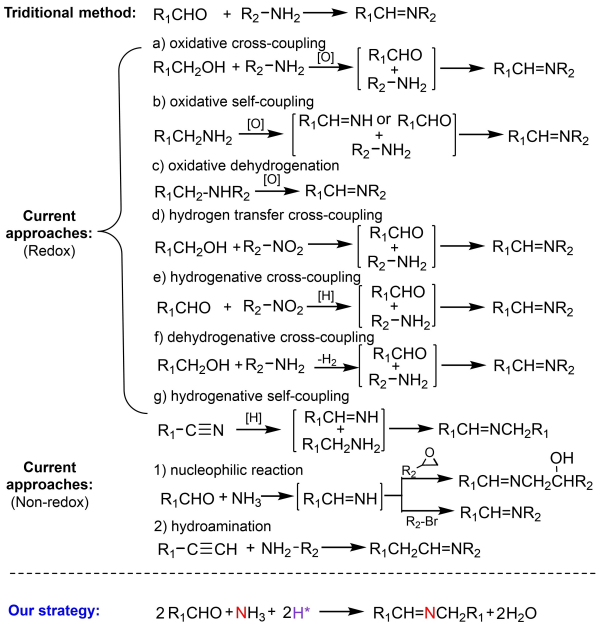
Herein, we present a novel method to synthesize imine and its derivatives using aromatic aldehydes and $HCOONH_4$ in DMSO. $HCOONH_4$ functions as both the nitrogen source and hydrogen source. And a continuous condensation-reduction (CCCR) mechanism was proposed. Moreover, the HMQC spectrum indicated the generation of $(PhCH{=}N)_2CHPh$, which was the key intermediate of the CCCR route.

Introduction

Imines are a significant class of synthetic intermediates, which are widely used as fine chemicals and biologically active compounds.[1–3] Its dominant synthesis method is the condensation of aldehydes with amines, which can be either added as substrates or in-situ generated. For imines preparation, various approaches can be divided into the following groups (Scheme 1, a–g). (a) Oxidative cross-coupling of alcohols with amines: aldehydes generated from alcohols selective oxidation react with amines to imines.[4–9] (b) Oxidative self-coupling of primary amines: RCH=NH generated from primary amine dehydrogenation or its further hydrolysis product PhCHO is generally proposed as the key intermediate.[10–13] (c) Oxidative dehydrogenation of secondary amines.[14–17] (d) Hydrogen transfer cross-coupling of nitro-compounds and alcohols: alcohols provide active hydrogen in the nitro groups reduction, and the generated aldehydes and amines react to imines.[18–20] (e) Hydrogenative cross-coupling of nitrocompounds and aldehydes: nitrocompounds are reduced to amines, which then react with aldehydes to imines.[21–24] (f) Dehydrogenative cross-coupling of alcohols with amines: aldehydes generated from alcohols dehydrogenation react with amines to imines.[25] (g) Hydrogenative self-coupling of nitriles: nitriles are selectively hydrogenated to RCH=NH and RCH_2NH_2, which condense to imines.[26–27] Furthermore, non-redox approaches with PhCHO, NH_3, and bromides or epoxides as the substrates are used to synthesize imines, and the RCH=NH generated from RCHO and NH_3 works as the key nucleophilic reagent.[28] The imines can also be synthesized via a hydroamination of terminal alkynes.[29] In these current approaches, N-contained organic substrates, bromides, and epoxides usually are used, which are generated from the corresponding alcohols or hydrocarbons via a complex organic synthesis process. In addition, catalysts are also used in some methods.[25,30–32]



Scheme 1. Imine formation approaches.

Herein, we give our strategy (Scheme 1, bottom). It just involves an accessible O-contained substrate of aromatic aldehyde and the simplest nitrogen source of NH_3. In addition, active hydrogen species should be introduced for balancing this reaction. In our exploration of this strategy, $HCOONH_4$ is chosen as both the nitrogen source and the reductant, which

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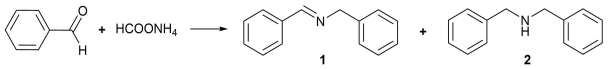
could avoid the use of volatile ammonia[33–35] and high-pressure H_2.[36] We discovered that the PhCH=NCH$_2$Ph could be synthesized using PhCHO and HCOONH$_4$ in DMSO without catalyst or extra additive. And 79.2% yield of PhCH=NCH$_2$Ph was obtained in 3 h at 80 °C. Furthermore, we describe a new continuous condensation-reduction route (CCCR) to synthesize imines from aldehyde, ammonium, and active hydrogen source via the (PhCH=N)$_2$CHPh intermediate, which may provide more understanding about the imine and its derivatives.

Results and Discussion

First, we tested the effect of solvent on the reaction. For the imine formation from PhCHO and HCOONH$_4$ at 80 °C, DMSO was the best among the different solvents (DMSO, H_2O, CH_3OH, C_2H_5OH, CH_3CN, DMF, THF, PhCl, 1,4-dioxane, HFIP, and EtOAc) (Table 1). Next, we explored the effect of temperature on the reaction in DMSO. The benzaldehyde couldn't be completely converted in 10 h at 60 °C. Only imine was produced in the first 8 h, and imine could be reduced to dibenzylamine with time extension (Figure 1A). The benzaldehyde could be completely converted after 4 h at 80 °C. And 79.2% GC yield of PhCH=NCH$_2$Ph was obtained in just 3 h at 80 °C (Figure 1B). When the temperature was increased to 100 °C, dibenzylamine would become the main product as the reaction time was prolonged (Figure 1C). In other words, the selectivity of the N-containing product can be turned with the change of reaction temperature and time.

To explore the reaction, the gas phase products were first checked at 80 °C by MS (Figure 2). The m/z 17 (NH_3) and m/z 16 (NH_2) signals were higher than the m/z 18 signal (H_2O). It showed the existence of NH_3 in the gas phase.[37] Referring to the equation (HCOONH$_4$→HCOOH + NH_3), HCOOH should exist in the DMSO. Compared with the standard reaction conditions (Figure 3, entry 1), the partial replacement of HCOONH$_4$ with HCOONa or HCOOH could decrease the yield of imine (Figure 3,

Table 1. The synthesis of PhCH=NCH$_2$Ph in different solvents.[a,b]



Entry	Solvent	Conv./%	Yield/%	
			1	2
1	DMSO	>99	49.5	45.7
2	H_2O	67.8	0.0	0.0
3	CH_3OH	80.6	9.3	0.0
4	C_2H_5OH	79.3	21.9	0.0
5	CH_3CN	74.8	23.2	0.0
6	DMF	98.7	32.6	10.6
7	THF	67.7	5.1	0.0
8	PhCl	52.1	0.0	0.0
9	1,4-dioxane	68.2	6.7	0.0
10	HFIP	64.9	4.1	0.0
11	EtOAc	64.6	6.4	0.0

[a] Reaction conditions: HCOONH$_4$ 0.5 mmol, PhCHO 0.5 mmol, solvent 2.0 mL, 80 °C, Ar 1 atm, 10 h.
[b] GC yields. Note: DMSO = Dimethylsulfoxide. DMF = N,N-Dimethyl formamide. THF = Tetrahydrofuran. HFIP = Hexafluoroisopropanol.

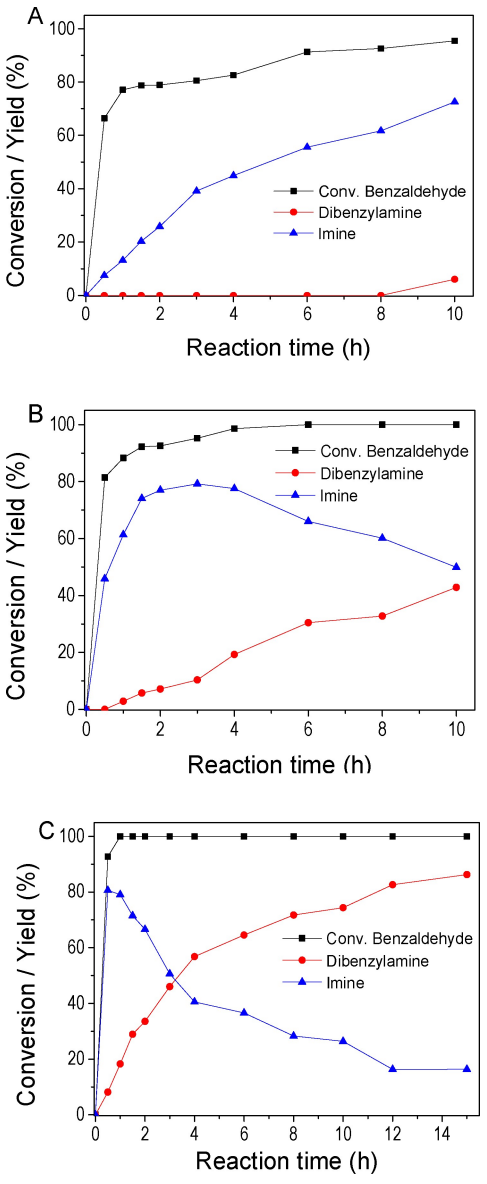


Figure 1. The synthesis of PhCH=NCH$_2$Ph with PhCHO and HCOONH$_4$ at different temperatures. Reaction conditions: HCOONH$_4$ 0.5 mmol, PhCHO 0.5 mmol, DMSO 2.0 mL, Ar 1 atm. (A) 60 °C, (B) 80 °C, (C) 100 °C.

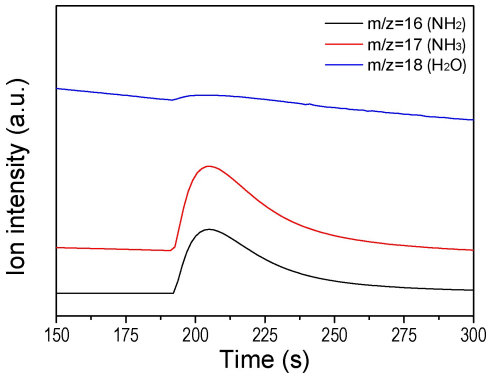


Figure 2. The gas phase analysis of the sample (HCOONH$_4$ + DMSO) at 80 °C by MS.

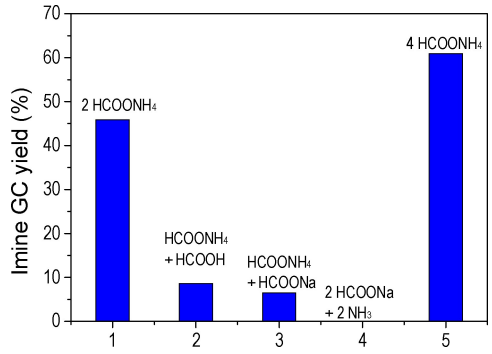


Figure 3. The effect of $HCOONH_4$ on the PhCHO transformation. Reaction condition: PhCHO 0.50 mmol, DMSO 2.0 mL, Ar, 80 °C, 30 min. (1) $HCOONH_4$ 0.50 mmol; (2) $HCOONH_4$ 0.25 mmol, HCOOH 0.25 mmol; (3) $HCOONH_4$ 0.25 mmol, HCOONa 0.25 mmol; (4) HCOONa 0.50 mmol, NH_3 0.50 mmol; (5) $HCOONH_4$ 1.00 mmol.

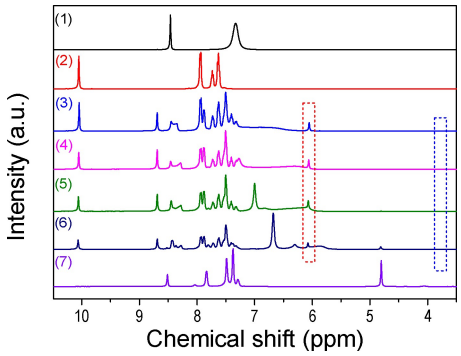


Figure 4. The in-situ ^1H NMR spectrums of the reaction. (1) $HCOONH_4$ + DMSO; (2) PhCHO + DMSO; (3) $HCOONH_4$ + DMSO + PhCHO at 25 °C for 20 min; (4) $HCOONH_4$ + DMSO + PhCHO at 40 °C for 5 min; (5) $HCOONH_4$ + DMSO + PhCHO at 60 °C for 5 min; (6) $HCOONH_4$ + DMSO + PhCHO at 80 °C for 5 min; (7) PhCH=NCH_2Ph + DMSO.

entries 2 and 3). And no imine was obtained with HCOONa and NH_3 (Figure 3, entry 4). Moreover, increasing the amount of $HCOONH_4$ could increase the yield of imine (Figure 3, entry 5). These results indicated the NH_3 and HCOOH are both necessary in the imine generation.

Given the fact that PhCHO and $HCOONH_4$ were the only substrates in PhCH=NCH_2Ph generation, there should be four possible routes for imine generation (Scheme 2). (1) CRC route: PhCH=NH generated from PhCHO and NH_3 was reduced to $PhCHNH_2$, which reacted with another PhCHO to the final PhCH=$NHCH_2$Ph. (2) CCR-1 route: without C=N bond reduction, PhCH=NH reacted with PhCHO to PhCH=NCH(OH)Ph, which was then reduced with HCOOH to the final imine after losing an H_2O. (3) CCR-2 route: different from CCR-1 route, PhCH=$NCH(NH_2)$Ph generated from the self-coupling of PhCH=NH was reduced with HCOOH to the final imine after losing an NH_3. (4) CCCR route: the possible PhCH=$NCH(NH_2)$Ph intermediate condensed with a PhCHO to $(PhCH=N)_2CHPh$, which was reduced to the final imine after losing a PhCH=NH.

For further confirming the main route of imine generation, the in-situ ^1H NMR (Figure 4) and ^{13}C NMR (Figure S6) were employed to track the reaction. When the PhCHO was added in the mixture of $HCOONH_4$ and DMSO (Figure 4, entry 3), a signal at 6.04 ppm appeared in the ^1H NMR and a signal at 92.6 ppm appeared in the ^{13}C NMR spectrum (Figure S6A). The HMQC spectrum (Figure 5) showed the correlation between the mentioned H signal and the C signal. According to the standard spectrums of the compounds that appeared in the proposed reaction routes (Figure S1-S5, Table 2), signals at 6.04 ppm and 92.6 ppm indicated the generation of $(PhCH=N)_2CHPh$, which was a key intermediate of the CCCR route. In addition, when the temperature was increased to 80 °C, the signal of product

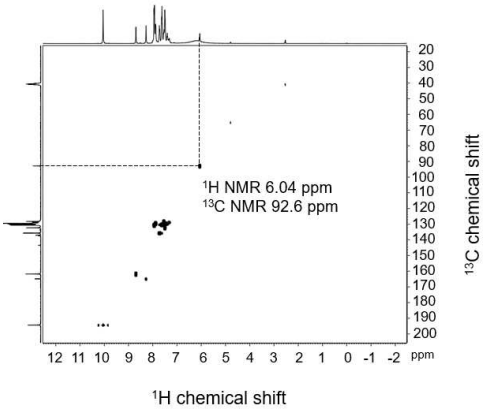
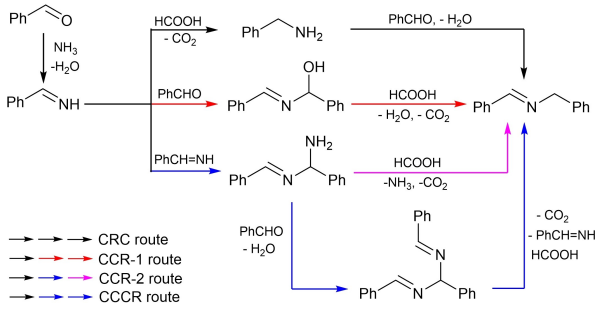


Figure 5. The HMQC spectrum of the $HCOONH_4$ + DMSO + PhCHO at 25 °C for 20 min.



Scheme 2. The possible reaction routes of the PhCH=NCH_2Ph generation from PhCHO and $HCOONH_4$. (The C stands for the condensation and R for the reduction).

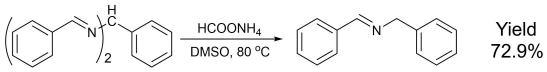
Table 2. The characteristic information for important compounds.

Entry	Compound	^1H NMR	^{13}C NMR
1	PhCHO	10.0	
2	PhCH=NCH_2Ph	4.80	65.0
3	$PhCH_2NCH_2Ph$	3.80	
4	$(PhCH=N)_2CHPh$	6.04	92.6
5	$PhCH_2NH_2$	3.80	
6	PhCH=NCH(OH)Ph	5.80	

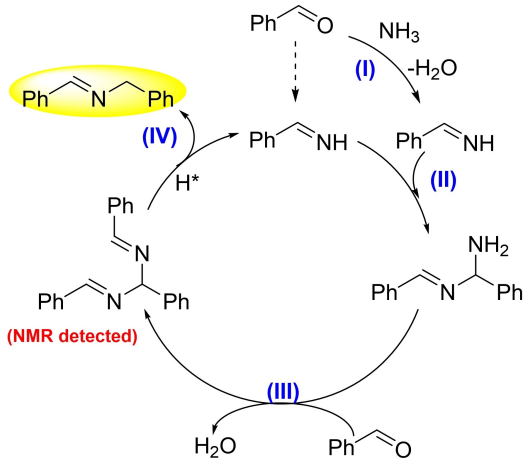
PhCH=NCH$_2$Ph at 4.80 ppm was obvious(Figure 4, entry 6), and the signal of (PhCH=N)$_2$CHPh at 6.04 ppm

weakened. In this process, no signals at 5.8 ppm and 3.8 ppm were observed, which were the representative signals of the PhCH=NCH(OH)Ph in the CCR-1 route and PhCH$_2$NH$_2$ in the CRC route. Signals at 7.39 ppm and 7.31 ppm belonged to the aromatic hydrogen of the (PhCH=N)$_2$CHPh. The signals at 7.27, 7.00, 6.68, and 6.30 ppm could be attributed to the active H of HCOOH, NH$_3$, and other N-contained intermediates respectively. The NMR results indicated the possibility of the CCCR route as the main route.

Furthermore, reduction of the condensation product (PhCH=N)$_2$CHPh with HCOONH$_4$ at 80 °C in DMSO offered imine product with 72.9% yield in 30 min (Scheme 3). Based on the results obtained above, the CCCR route with (PhCH=N)$_2$CHPh as the key intermediate is the main route for the imine generation.



Scheme 3. The transformation of the (PhCH=N)$_2$CHPh. Reaction condition: (PhCH=N)$_2$CHPh 0.167 mmol, DMSO 2.0 mL, HCOONH$_4$ 0.5 mmol, Ar, 80 °C, 30 min.



Scheme 4. The generation of imine from PhCHO and HCOONH$_4$ via the possible CCCR mechanism.

Table 3. Condensation-reduction of aldehydes with HCOONH$_4$ to imines.[a,b]

Entry	Substrate	R=N-R	Yield/%
1	4-fluorobenzaldehyde		70.7
2	4-methoxybenzaldehyde		82.7
3	4-methylbenzaldehyde		85.0
4	2-methylbenzaldehyde		83.2
5	3,4-dimethoxy benzaldehyde		76.3

[a] Reaction condition: RCHO 0.5 mmol, HCOONH$_4$ 0.5 mmol, DMSO 2.0 mL, 80 °C, 3 h, Ar.
[b] The yields were detected by ^{1}H-NMR.

As shown in Scheme 4, a possible mechanism for the PhCH=NCH$_2$Ph generation in the CCCR route is proposed: (1) The NH$_3$ generated from HCOONH$_4$ decomposition firstly condenses with PhCHO to PhCH=NH; (2) The condensation of two PhCH=NH to provide a PhCH=NCH(NH$_2$)Ph; (3) The condensation product further condenses with benzaldehyde to (PhCH=N)$_2$CHPh; (4) (PhCH=N)$_2$CHPh is then reduced to PhCH=NCH$_2$Ph with the active hydrogen species from HCOOH. And the released PhCH=NH participates in the next reaction cycle.

Subsequently, we turned our attention to synthesize the functionalized imines under the standard reaction conditions, and the results were shown in Table 3. In all cases, the substituted benzaldehydes can give good yields of imines. The 4-fluorobenzaldehyde can get 70.7% yield of imine due to the presence of the electron-withdrawing fluorine (Table 3, entry 1). For the substrates with an electron-donating group, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, and 2-methylbenzaldehyde gave the imine yields more than 80% respectively (Table 3, entries 2, 3, and 4). However, 3,4-dimethoxy benzaldehyde has the greater steric hindrance, which led to a 76.3% yield of imine (Table 3, entry 5).

Conclusion

In summary, we developed a novel method to synthesize imine with aromatic aldehyde and HCOONH$_4$. The system does not need the addition of catalysts or extra additives. And the reaction process is environmentally friendly and efficient. In addition, the continuous condensation-reduction (CCCR) mechanism with the (PhCH=N)$_2$CHPh intermediate has been proposed by control experiments, intermediate transformation experiments and NMR tests results.

Experimental Section

Chemicals and Reagents. All materials were used as received without further treatment.

Reaction test. 0.5 mmol benzaldehyde, 0.5 mmol ammonium formate and 2.0 mL solvent were added into a 15 mL reactor. The headspace air was replaced with Ar. The reactors were then put in an oil bath at the desired temperature and the reaction time was set as zero. The samples were added mesitylene as internal standard and analyzed by GC-MS (GC: Agilent 7890 A, MS: Agilent 5975 C) and GC (Agilent 7890). The reactions of substituted benzaldehydes were consistent with the above process, and the reaction results were analyzed by ^{1}H–NMR.

The (PhCH=N)$_2$CHPh synthesis. A solution of PhCHO (20 mmol) was added to a solution of ammonium acetate (12 mmol) in ethanol (50 mL). The reaction mixture was stirred at room temperature for 4 d and concentrated under reduced pressure to 1/10 of the initial volume and leave the mixture of liquids to stand overnight. The white precipitate was separated and washed twice with water and ethanol, dried and recrystallized from methanol.

The imines synthesis. In general, the preparation of imine standards are as follows: The equal amounts of substituted benzaldehydes and the corresponding substituted benzylamines were

mixed in dichloromethane and stirred at room temperature respectively. After the reactions were completed, the solvent was removed by rotary evaporation.

The dibenzylamine synthesis. Various imines were dissolved in ethanol respectively, adding appropriate amount of sodium borohydride, and then stirring at room temperature. After the reactions were completed, using deionized water to remove inorganic salts, then the solvent was removed by rotary evaporation.

Supporting Information Summary

The characterization data of specific compounds and the NMR spectra of reactions.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aromatic aldehyde · ammonium formate · condensation-reduction · DMSO · imine

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