Highly efficient iron phthalocyanine catalysed oxidative synthesis of imines from alcohols and amines

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Abstract: An efficient iron phthalocyanine catalyzed method was developed for direct oxidative coupling of alcohols with amines to afford corresponding imines. The present protocol is applicable to various substituted aromatic and aliphatic alcohols and amines. The reaction is believed to proceed via activation of alcohols by iron phthalocyanines through Lewis-acid base interaction to form aldehydes, which by nucleophilic attack of amines converted into the corresponding imines.

Keywords: iron phthalocyanine, imine synthesis, oxidative coupling, alcohols, amines.

Introduction

Imines are versatile intermediates in organic synthesis involving pharmaceuticals, agricultural chemicals, natural products, dyes and as elecrtophiles in many important transformations including addition, condensation and cycloaddition.[1] Traditionally, imines were synthesized from the condensation of amines and aldehydes or ketones with the azeotropic distillation of water.[2] Imines have also been synthesized by self-condensation of amines upon oxidation.[3] In contrast to these methods, one pot approaches for imine formation directly from oxidative coupling of alcohols with amines constitute more environmentally benign approach. Different catalytic systems such as ruthenium hydroxide supported on TiO_2,[4] manganese octahedral molecular sieves,[5] palladium catalyst,[6] ruthenium pincer complex,[7] POP type osmium complexes,[8] Pt/TiO_2 nanoparticles under UV irradiation,[9] copper catalyst,[10] and bimetallic Pt/Al_2O_3 catalyst[11] have been reported for this type of reaction. However, use of costly metals, additives and long reaction time limits their scope. Hence, the development of an efficient inexpensive method is highly desirable.

In recent years, iron-based complexes allowed for considerable inventions in organometallic catalysis.[12] Apart from the abundant availability, the low toxicity and biomimetic pre-catalysts make iron an ideal metal for catalysis.[13]

In continuation of our work on metallophthalocyanines based catalysis[14] recently, we have successfully applied iron(II)phthalocyanine (FePc) for reduction of nitroarenes to corresponding amines[14d] and thought to apply for the oxidative coupling of alcohols with primary amines to form corresponding imines.

Results and discussion

Initially, to optimize the best reaction conditions for the oxidative coupling of alcohols and amines to form corresponding imines, the reaction of aniline with benzyl alcohol was selected as model system (Table 1). Without catalyst very low yield was obtained (Table 1, entry 18). Among various tested iron catalysts best yield was recorded with FePc (Table 1, entries 1-5). Although, $FeCl_3$ also catalyze the reaction to good extent, yield of the product was less as compared to FePc in each studied case (Table 1, entry 1; Table 2, entry 7; Table 3, entry 6). Hence, FePc was selected as a catalyst of choice for the reaction. Different bases such as K_2CO_3, Cs_2CO_3, DABCO and $NaHCO_3$ provided very low yield, while, moderate yield was observed with KO*t*Bu (Table 1, entries 7-11). Best results were achieved with NaO*t*Bu (Table 1, entry 5). As expected without base desired product was not observed (Table 1, entry 6). Reaction conditions were further optimized by changing the reaction media. Reaction was not preceded in case of water, DMSO and PEG-400 (Table 1, entries 13, 15 and 17). In case of ethanol and DMF low yield of desired product was recorded (Table 1, entries 14 and 16). Good yield was obtained in 1,4-dioxane but best results were observed in toluene (93%) (Table 1, entries 12 and 5).

After optimizing the best reaction conditions, various combinations of alcohols and amines were examined to form the corresponding imines (Table 2-3). The reaction of benzyl alcohol with aniline resulted in high yield of corresponding imine (93%, Table 2, entry 1). The halide substituted amines were successfully coupled with benzyl alcohol to form corresponding imines without any dehalogenation (Table 2, entries 2-4). Excellent yield was obtained with *p*-bromoaniline and *p*-flouroaniline whereas very low yield was observed with m-bromoanilne (Table 2, entries 2-4). *p*-Nitroaniline and tetrahydroamino naphthalene afforded corresponding imine in very low yield even after 24 h (Table 2, entries 5 and 7). Moderate yield of imine was observed in case of 2,3-dimethylaniline (Table 2, entry 6), which may be due to the steric effect. Also, yield was not affected much on increasing the duration of reaction up to 24 h (Table 2, entry 6). Good to excellent yields were observed for various benzyl and phenylethyl amines (Table 2, entries 8-12).

The scope of catalytic method was further explored for various substituted alcohols (Table 3). Excellent yields were obtained in case of methoxy, ethoxy and bromo substituted benzyl alcohols (Table 3, entries 1-3). The present protocol also successfully catalyzes the oxidative coupling of aliphatic alcohols with amines to form corresponding imines, which is one of the challenging tasks for chemists. The coupling of phenyl propyl alcohol with aniline afforded imine in excellent yield, whereas, moderate yield was observed in case of phenyl ethyl alcohol (Table 3, entries 4 and 5). Isoamyl alcohol also afforded corresponding imine in moderate yield (Table 3, entry 6).

In addition to the oxidative coupling of alcohols with amines the present catalytic system was also applicable to the self coupling of benzyl amine to form corresponding imine. Also, no base was required for the self coupling reaction; FePc alone was able to catalyse the reaction, as high yield of imine product was observed without using base (Scheme 1).

The present catalytic system also efficiently catalysed the oxidation of benzyl alcohol to benzaldehyde under the same reaction conditions (Scheme 2).

Although, the exact role of FePc was not clear, however, based on the fact that transition metal phthalocyanines act as Lewis acids[14b,14c] we propose that, Lewis acid-base interaction between FePc and oxygen of alcohol promoted the NaO*t*Bu mediated oxidation of alcohols to corresponding aldehydes, which undergo condensation with amines to form imines (Fig. 1). This is supported by the fact that in the presence of triethylamine (1 equiv.), no product was observed due to strong Lewis acid-base interaction of triethylamine with FePc (Scheme 3).

Conclusions

The use of abundantly available and low toxic iron based catalyst is an attractive catalytic alternative to other costly and toxic transition metals. In present study, an efficient iron phthalocyanine catalyzed method has been developed for the oxidative coupling of alcohols with amines to form corresponding imines. Present catalytic system was also able to catalyze the self coupling of benzyl amine to corresponding imine and oxidation of benzyl alcohol to benzaldehyde.

Experimental

Materials and Instrumentation

Metal salts used were purchased from Merck, Germany. Iron phthalocyanine was purchased from Sigma-Aldrich, USA. Silica gel (60-120 mesh) used for column chromatography was purchased from Sisco Research Laboratories Pvt. Ltd. India and all other chemicals were purchased from Spectrochem, India,; Merck, Germany, and Sigma-Aldrich, USA and were used without further purification. NMR spectra were recorded on a Bruker Avance-300 spectrometer. The GC-MS analysis was carried out on a Shimadzu (QP 2010) series Gas Chromatogram-Mass Spectrometer (Tokyo, Japan), AOC-20i auto-sampler coupled, and a DB-5MS capillary column, (30 m x 0.25 mm i.d., 0.25μm). The initial temperature of column was 70 °C held for 4 min. and was programmed to 230 °C at 4°C/min., then held for 15 min. at 230 °C; the sample injection volume was 2 μl in GC grade dichloromethane. Helium was used as carrier gas at a flow rate of 1.1 ml min-1 on split mode (1: 50).

General procedure for the oxidative coupling of alcohols with amines

To a stirred suspension of FePc (1 mol%) and NaO*t*Bu (2 equiv.) in toluene (3 mL) were added alcohol (1.0 mmol), amine (1.0 mmol) at room temperature and then the temperature was raised to 80 ^{o}C for 12 h under N_2 atmosphere. On completion of the reaction (as monitored by TLC), reaction mixture was filtered and passed through anhydrous Na_2SO_4 and dried under vacuum. The crude product was analyzed by GC-MS or purified by column chromatography over silica-gel (60-120 mesh) with appropriate mixture of *n*-hexane and ethyl acetate. The GC-MS yields of products were calculated on the basis of amine reactants. The following compounds were characterized on the basis of NMR and GC-MS data given below:

N-Benzylideneaniline (Table 2, entry 1): Yellowish powder, Yield = 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.21-7.49 (m, 7H), 7.74-7.83 (m, 3H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 128.1, 129.6, 130.0, 130.2, 133.0, 133.8, 144.3; GC-MS (EI): *m/z* 181 $[M]^+$, 152, 104, 89, 77, 63, 51.

N-Benzylidene-4-fluoroaniline (Table 2, entry 2): Colourless oil, Yield = 83%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.07-7.13 (m, 2H), 7.20-7.28 (m, 2H), 7.49-7.58 (m, 3H), 7.90-7.93 (m, 2H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 116.1, 116.4, 122.6, 122.7, 129.1, 131.8, 136.4, 148.4, 160.5; GC-MS (EI): *m/z* 199 $[M]^+$, 151, 122, 95, 75, 63, 51.

Acknowledgments

Authors are grateful to the Director of the institute for providing necessary facility and encouragement. P.K.V. and U.S. are also thankful to CSIR for fellowship.

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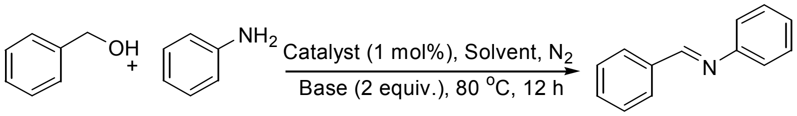
N.; Singh, B. *Adv. Synth. Catal.* **2012**, *354 (5),* 870. doi: 10.1002/adsc.201100645. (d) Sharma, U.; Verma, P. K.; Kumar, N.; Kumar, V.; Bala, M.; Singh, B. *Chem. Eur. J.* **2011**, *17 (21)*, 5903. doi: 10.1002/chem.201003621. (e) Sharma, U.; Verma, P.; Kumar, N.; Kumar, V.; Singh, B. *Adv. Synth. Catal.* **2010**, *352 (11-12),* 1834. doi: 10.1002/adsc.201000191.

Table 1. Optimization of reaction conditions for imine synthesis from benzyl alcohol and aniline.[a]

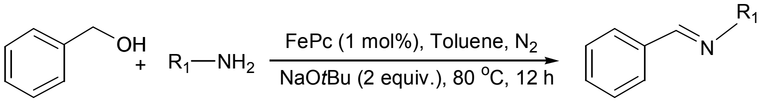


Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	$FeCl_3$	NaO*t*Bu	Toluene	72
2	Fe_2O_3	NaO*t*Bu	Toluene	54
3	$FeSO_4$	NaO*t*Bu	Toluene	60
4	Iron metal	NaO*t*Bu	Toluene	53
5	**FePc**	**NaO*t*Bu**	**Toluene**	**93**
6	FePc	-	Toluene	No Reaction
7	FePc	K_2CO_3	Toluene	19
8	FePc	KO*t*Bu	Toluene	55
9	FePc	Cs_2CO_3	Toluene	16
10	FePc	DABCO	Toluene	26
11	FePc	$NaHCO_3$	Toluene	16
12	FePc	NaO*t*Bu	1,4 Dioxane	77
13	FePc	NaO*t*Bu	H_2O	No Reaction
14	FePc	NaO*t*Bu	EtOH	39
15	FePc	NaO*t*Bu	DMSO	No Reaction
16	FePc	NaO*t*Bu	DMF	57
17	FePc	NaO*t*Bu	PEG-400	No Reaction
18	-	NaO*t*Bu	Toluene	35

[a] Reaction conditions: aniline (1 mmol), benzyl alcohol (1 mmol), FePc (1 mol%), base (2 equiv.), toluene (3 mL), 80 °C, 12 h, N_2.

[b] Yield was calculated on the basis of GC-MS analysis.

Table 2. One pot imine synthesis from benzyl alcohol with various amines.[a]



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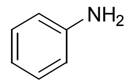
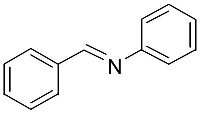
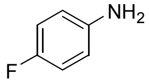
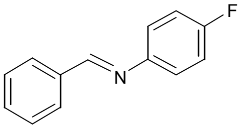
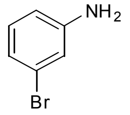
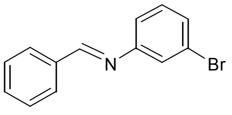
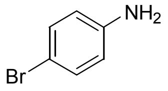
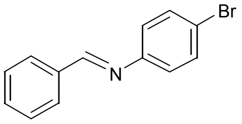
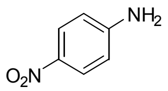
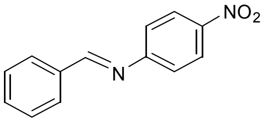
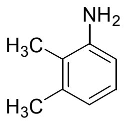
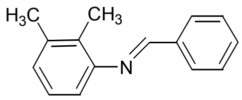
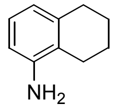
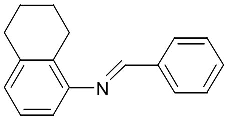
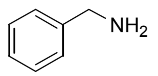
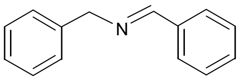
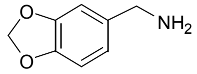
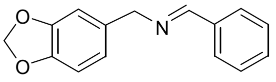
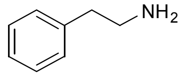
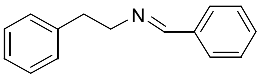
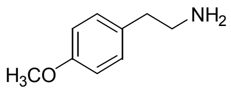
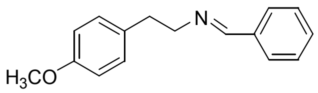
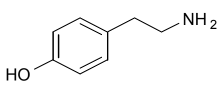
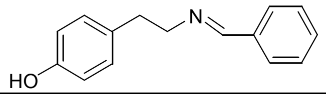
1			93 (87)
2			89 (83)
3			22
4			93
5			18^{c}
6			60 69^{c}
7			13 27^{d} $11^{d,e}$
8			98
9			94
10			98
11			76
12			99

[a] Reaction conditions: amines (1 mmol), benzyl alcohol (1 mmol), FePc (1 mol%), NaO*t*Bu (2 equiv.), toluene (3 mL), 80 °C, 12 h, N_2.

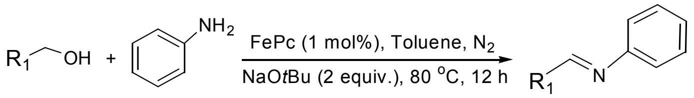
[b] Yield was calculated on the basis of GC-MS analysis. Isolated yield are given in parenthesis.

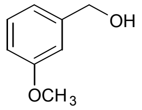
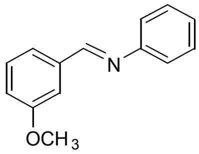
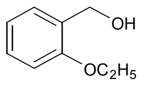
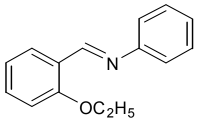
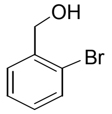
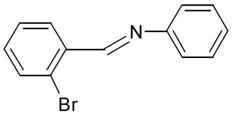
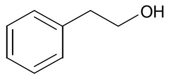
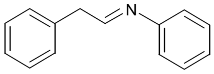
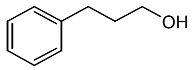
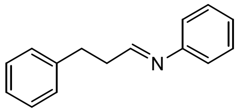
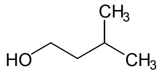
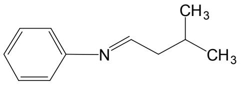
[c] Reaction time 24 h.

[d] 1.5 equiv. of alcohol was used.

[e] Reaction was carried out with $FeCl_3$.

Table 3. One pot imine synthesis from various alcohols with aniline.[a]



Entry	Alcohol	Product	Yield (%)[b]
1			94
2			98
3			91
4			56
5			93
6			56 $5^{c,d}$

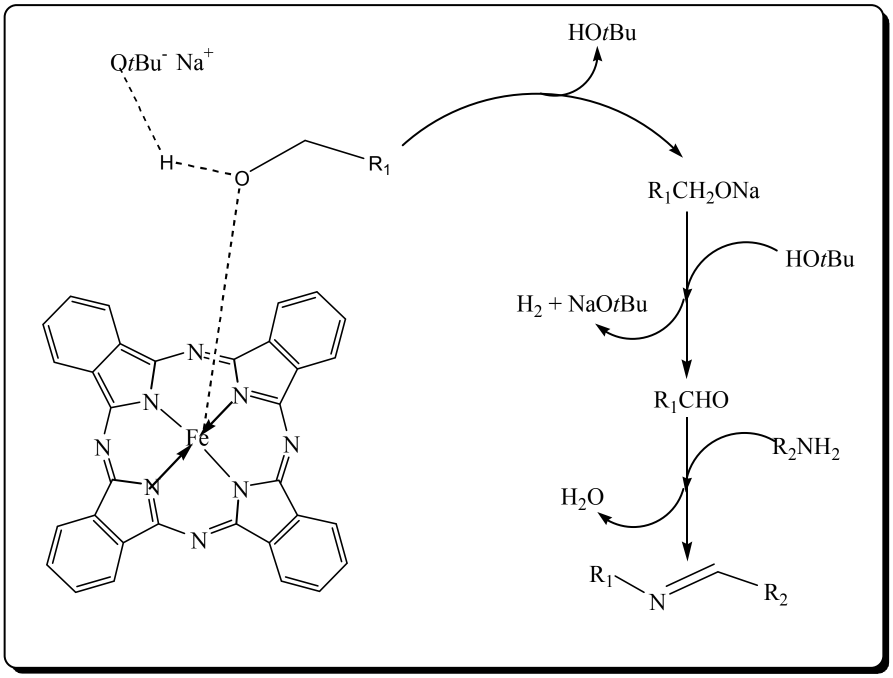
[a] Reaction conditions: aniline (1 mmol), alcohols (1 mmol), FePc (1 mol%), NaO*t*Bu (2 equiv.), toluene (3 mL), 80 °C, 12 h, N_2.

[b] Yield was calculated on the basis of GC-MS analysis.

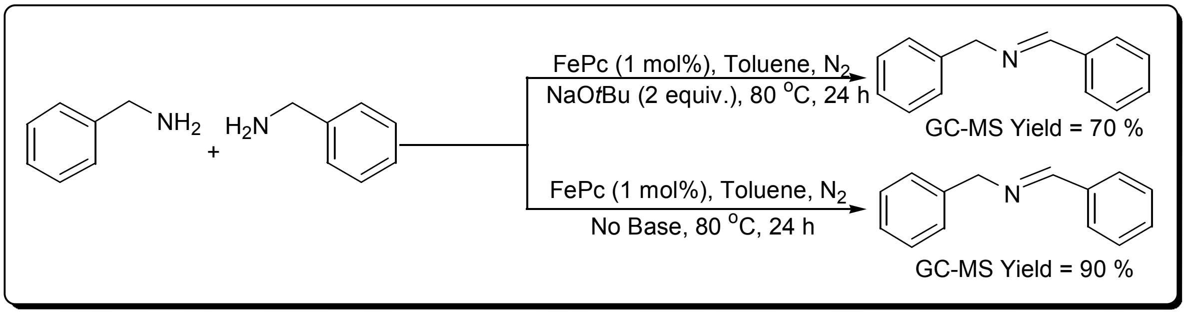
[c] Reaction was carried out with $FeCl_3$.

[d] Reaction time 24 h.

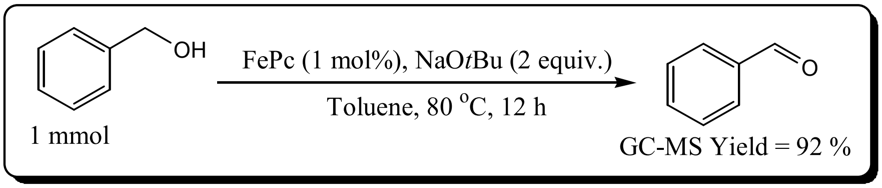
Fig. 1. Proposed pathway for oxidative coupling of alcohols with amines to form imines.



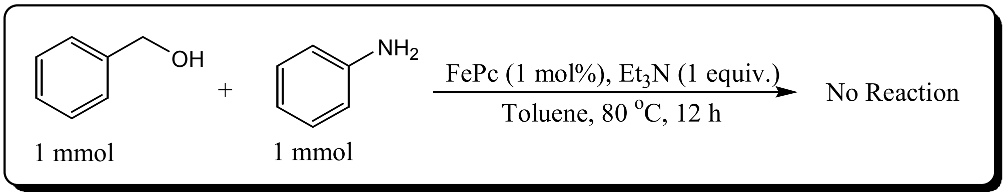
Scheme 1. Self coupling reaction of benzyl amine to form corresponding imine.



Scheme 2. Oxidation of benzyl alcohol to benzaldehyde.



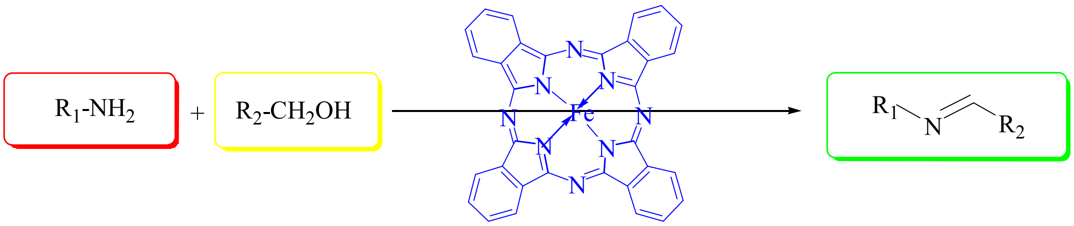
Scheme 3. Reaction of benzyl alcohol with aniline in the presence of triethylamine.



Graphical abstract:

Highly efficient iron phthalocyanine catalysed oxidative synthesis of imines from alcohols and amines

Manju Bala, Praveen Kumar Verma, Neeraj Kumar, Upendra Sharma, and Bikram Singh



FePc (1 mol%)
t-BuONa (2 equiv.), Toluene

An efficient iron phthalocyanine catalyzed method was developed for direct oxidative coupling of alcohols with amines to afford corresponding imines. The present protocol is applicable to various substituted aromatic and aliphatic alcohols and amines.