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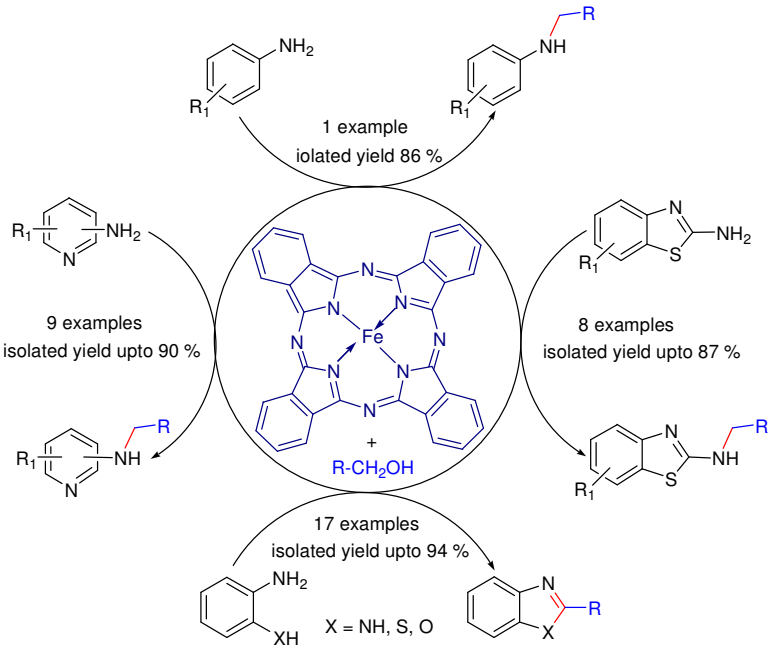
Iron Phthalocyanine as an Efficient and Versatile Catalyst for *N*-alkylation of Heterocyclic Amines with Alcohols: One-pot Synthesis of 2-Substituted Benzimidazoles, Benzothiazoles and Benzoxazoles

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



An efficient and versatile method was developed for *N*-alkylation of various amines with alcohols by utilizing aboundently available iron phthalocyanine as catalyst. Readily available alcohols were used as alkylating agents for direct *N*-alkylation of aminobenzothiazoles, aminopyridines and aminopyrimidines. *N*-alkylation of *ortho*-substituted anilines (-NH_2, -SH and –OH) led to the synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazoles in one-pot.

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PAPER

Iron Phthalocyanine as an Efficient and Versatile Catalyst for *N*-alkylation of Heterocyclic Amines with Alcohols: One-pot Synthesis of 2-Substituted Benzimidazoles, Benzothiazoles and Benzoxazoles†

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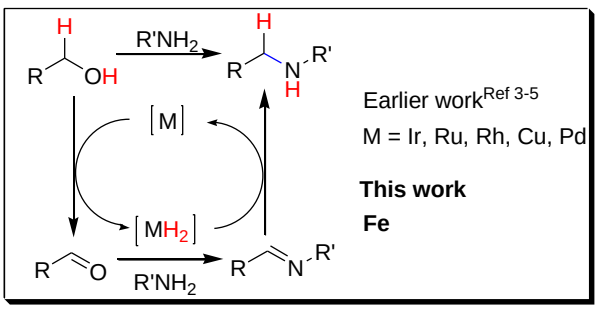
An efficient and versatile iron phthalocyanine catalyzed method has been developed for *N*-alkylation of various amines with alcohols. Readily available alcohols were used as alkylating agents for direct *N*-alkylation of aminobenzothiazoles, aminopyridines and aminopyrimidines. *N*-alkylation of *ortho*-substituted anilines (-NH_2, -SH and –OH) led to the synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazoles in one-pot.

Introduction

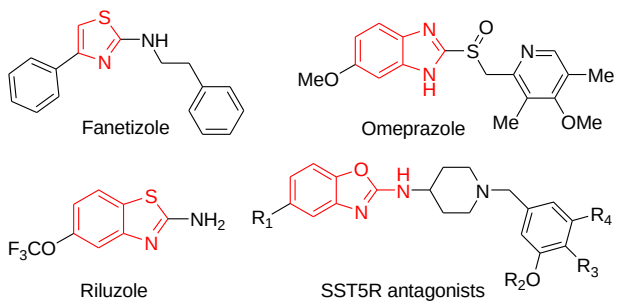
The *N*-alkylation of primary amines to higher amines is of fundamental importance to academics as well as chemical industries for the synthesis of dyes, additives, agrochemicals, functional materials and pharmacophores in various bioactive molecules.[1] The conventional approaches for the synthesis of secondary and tertiary amines involve alkylation of primary amines with an alkylating agent having a good leaving group such as alkyl halides, triflates, tosylates, and mesylates.[2] These conventional approaches are problematic due to the toxic nature of reagents used, over alkylation and generation of stoichiometric amount of waste. The alternative environmentally benign approach is metal catalyzed borrowing-hydrogen methodology by employing inexpensive and readily available alcohols as alkylating agents (Scheme 1). This approach is atom economic, thermodynamically favoured and waste free as water is the only byproduct and follow a cascade redox type pathway involving *in-situ* alcohol oxidation/imine formation/imine hydrogenation steps.



Scheme 1 Transition metal catalyzed borrowing hydrogen methodology for *N*-alkylation of amines.

Since the use of alcohols for *N*-alkylation reaction by Grigg[3] and Watanabe,[4] different transition metals based methods have been reported.[5] Harsh reaction conditions, expensive metals, toxic and capricious ligands limit the scope of these methods. Inexpensive metals based environmentally benign catalytic method are extremely desirable for the *N*-alkylation reactions with alcohols.

Benzazoles such as benzimidazoles, benzothiazoles and benzoxazoles are considered as privileged motifs in the field of medicinal chemistry.[6] The benzazole nucleus is pharmacophore present in various modern drugs including omeprazole (proton-pump inhibitor), candesartan and telmisartan (AT1 receptor antagonist), dabigatran (direct thrombin inhibitor), flunoxaprofen (NSAID), and riluzole (sodium channel blocker).[7] 2-(*N*-alkylamino)benzothiazole is also present as important structural unit in many biologically active compounds such as fanetizole (anti-inflammatory agent), UDP-galactopyranose mutase inhibitor, κ and μ opoid receptors, and small molecule somatostatin receptor subtype 5 (SST5R) antagonists (Scheme 2).[8]



Scheme 2 Bioactive molecules with benzazole and 2-*N*-(alkylamino)azole moieties.

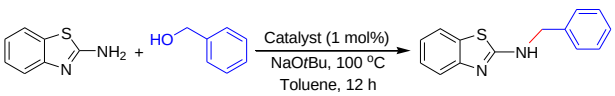
Recently, our group has developed metal phthalocyanines based inexpensive, ligand free, environmentally benign methods for nitro reduction,[9a-9c] carbonyl reduction[9d] and reductive amination.[9e] Herein, we report iron(II)phthalocyanine as an efficient, inexpensive and versatile catalyst for *N*-alkylation of heterocyclic amines and synthesis of 2-substituted benzazoles.

Results and Discussion

Optimization of reaction conditions

The reaction of 2-aminobenzothiazole with benzyl alcohol was selected as the model reaction for establishing the best reaction conditions. Initially, the effect of various iron based catalysts was investigated (Table 1). Reaction did not proceed without any catalyst in the presence of NaO*t*Bu, which excluded the contribution of base itself as a catalyst (Table 1, entry 1). The highest activity was observed with Fe(II)Pc followed by $FeCl_3$ (Table 1, entries 5 and 6). Other iron salts as well as Fe(III)Pc were found ineffective (Table 1 entries 2-4, 7).

Table 1 Catalyst screening for *N*-alkylation of 2-aminobenzothiazole[a]

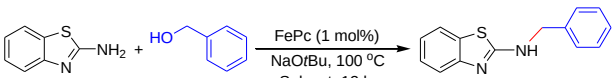


Entry	Catalyst	Yield (%)[b]
1	-	-
2	Iron metal	3
3	Fe_2O_3	2
4	$FeSO_4$	12
5	$FeCl_3$	64
6	Fe(II)Pc	92
7	Fe(III)Pc	4

[a] Reaction conditions: 2-aminobenzothiazole (1 mmol), benzyl alcohol (1 mmol), catalyst (1 mol%), NaO*t*Bu (2 mmol), toluene (5 mL) at 100 °C for 12 h. [b] GC-MS yield.

Toluene was found as the best solvent for *N*-alkylation reaction (Table 2, entry 4). No reaction occurred in case of water (Table 2 entry 2), while, DMF, 1,4-dioxane, PEG-400 and ethanol resulted in much lower yields (Table 2, entries 1, 3 5 and 6).

Table 2 Solvent screening for *N*-alkylation of 2-aminobenzothiazole[a]

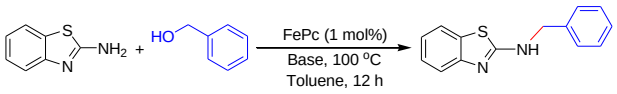


Entry	Solvent	Yield (%)[b]
1	DMF	1
2	H_2O	no reaction
3	EtOH	20
4	Toluene	92
5	1,4-dioxane	5
6	PEG-400	7

[a] Reaction conditions: 2-aminobenzothiazole (1 mmol), benzyl alcohol (1 mmol), Fe(II)Pc (1 mol%), NaO*t*Bu (2 mmol), solvent (5 mL) at 100 °C for 12 h. [b] GC-MS yield.

The reaction conditions were further optimized through variation of different bases (Table 3). Bases such as NaOH, K_2CO_3 and DABCO were found ineffective whereas K_3PO_4 afforded only 32 % yield of the desired product (Table 3, entries 1, 2 and 5, 6). Both Cs_2CO_3 and NaO*t*Bu efficiently provided the *N*-alkylation product but NaO*t*Bu was comparatively more effective (Table 3, entries 3 and 4).

Table 3 Screening of bases for *N*-alkylation of 2-aminobenzothiazole[a]



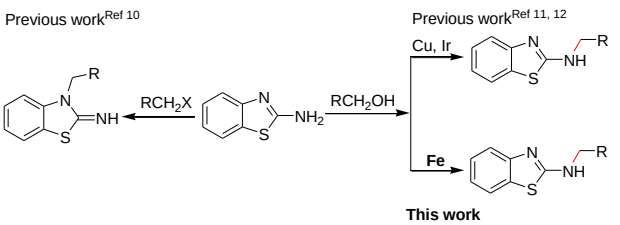
Entry	Base	Yield (%)[b]
1	NaOH	3
2	K_2CO_3	No Reaction
3	Cs_2CO_3	72
4	NaO*t*Bu	92
5	K_3PO_4	32
6	DABCO	1

[a] Reaction conditions: 2-aminobenzothiazole (1 mmol), benzyl alcohol (1 mmol), Fe(II)Pc (1 mol%), base (2 mmol), toluene (5 mL), at 100 °C for 12 h. [b] GC-MS yield.

Once the best reaction conditions were achieved, the scope of the method was investigated for the *N*-alkylation of various aminobenzothiazoles, aminopyridines and aminopyrimidines.

Regioselective *N*-alkylation of aminobenzothiazoles

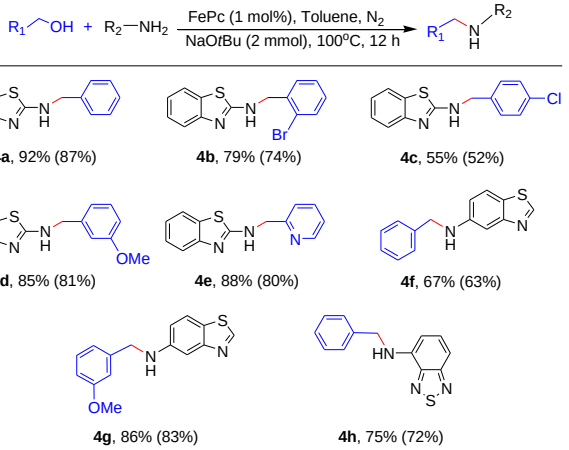
The *N*-alkylation of 2-aminobenzothiazoles with alkyl halides occurs on the most basic endocyclic nitrogen, affording *N*-endosubstituted 3-alkyl-2-iminobenzothiazolines as products (Scheme 3).[10] Various transition metal based catalytic methods have been developed for the preparation of 2-(*N*-alkylamino)benzothiazoles.[11] However, use of expensive metals and requirement of multiple steps, limit the scope of these methods. Recently, Li *et al.* have applied copper based catalyst for direct *N*-alkylation of 2-aminobenzothiazole with benzyl alcohols to synthesize 2-(*N*-alkylamino)benzothiazoles at high temperature.[12]



Scheme 3 Regioselective *N*-alkylation of 2-aminobenzothiazoles with alkyl halides and alcohols.

In contrast, Fe(II)Pc catalyzed regioselective *N*-alkylation of aminobenzothiazoles with alcohols afforded *N*-exosubstituted *N*-alkylaminobenzothiazoles under the optimal reaction conditions (Table 4). The *N*-alkylation of 2-aminobenzothiazole with benzyl alcohol (entry **4a**) gave the desired product in excellent yield. The halogen subsituted benzyl alcohols (entries **4b** and **4c**) afforded the corresponding products in good yields. 3-Methoxybenzyl alcohol (entry **4d**) and heteroaromatic alcohol such as 2-pyridylmethanol (entry **4e**) were efficiently utilized to obtain the corresponding desired product.

Table 4 *N*-alkylation of aminobenzothiazoles with alcohols.[a,b]



[a] Reaction conditions: amine (1 mmol), alcohol (1 mmol), Fe(II)Pc (1 mol%), NaO*t*Bu (2 mmol), toluene (5 mL) at 100 °C for 12 h. [b] Isolated yields are given in parenthesis.

The *N*-alkylation of 6-aminobenzothiazole with benzyl alcohol and 3-methoxybenzyl alcohol afforded the desired products in good yields (entries **4f** and **4g**). Furthermore, the *N*-alkylation of 4-amino-2,1,3-benzothiadiazole with benzyl alcohol also afforded the corresponding product in good yield (entry **4h**).

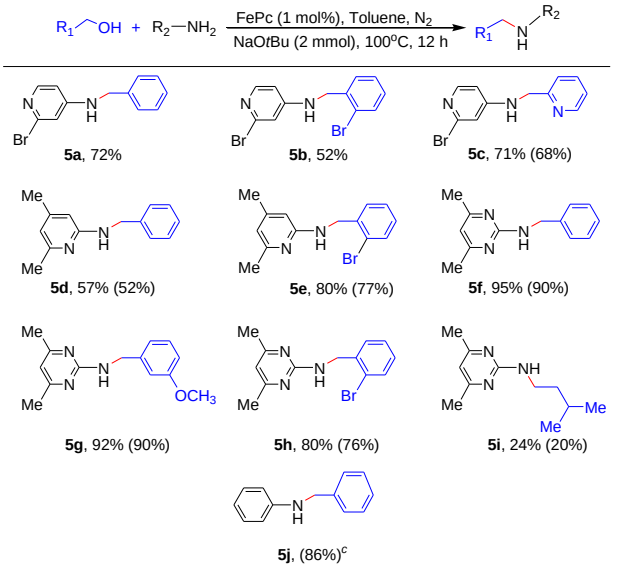
N-alkylation of aminopyridines and aminopyrimidines

The selective *N*-alkylation of aminopyridines to the corresponding secondary amines is a challenging task due to the formation of amides as byproduct.[13] Under present reaction conditions the *N*-alkylation of substituted aminopyridines and aminopyrimidines with alcohols proceeded smoothly with good to excellent yields (Table 5). The reaction of 4-bromo-2-aminopyridine with benzylic alcohols (entries **5a** and **5b**) afforded the desired products in good yields. Also, the reaction with 2-pyridylmethanol (entry **5c**) did not distress the yield of the corresponding secondary amine product. The *N*-alkylation of 4,6-dimethyl-2-aminopyridine was successfully caried out with benzylic alcohols (entries **5d** and **5e**) in good to high yields. Interestingly, the reaction of 4,6-dimethyl-2-amino-pyrimidines with benzylic alcohols (entries **5f**-**5h**) afforded the desired products in excellent yields. Low yield of the product (24 %) was observed for the *N*-alkylation of 4,6-dimethyl-2-amino-pyrimidine with isoamyl alcohol (entry **5i**). The present protocol also performed the *N*-alkylation of aniline with benzyl alcohol in high yield (entry **5j**).

N-alkylation of *ortho*-substituted anilines: synthesis of benzimidazoles, benzothiazoles and benzoxazole

The most commonly used methods for the synthesis of benzazoles include the condensation of *ortho*-substituted (-NH_2 or -SH or -OH) anilines with aldehydes,[14] nitriles,[15] carboxylic acids,[16] or acyl chlorides.[17] Most of these methods are associated with the limitations such as poor selectivity, side reactions, tedious work-up procedures and requirement of special oxidation process. Alternatively, few reports are also

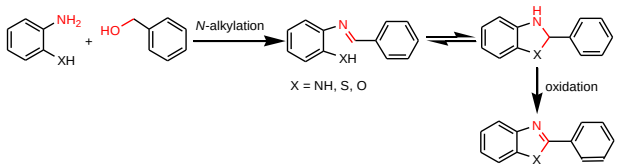
Table 5 *N*-alkylation of aminopyridines and aminopyrimidines with alcohols.[a,b]



[a] Reaction conditions: amine (1 mmol), alcohol (1 mmol), Fe(II)Pc (1 mol%), NaO*t*Bu (2 mmol), toluene (5 mL) at 100 °C for 12 h. [b] Isolated yields are given in parenthesis. [c] Reaction temperature 140 °C.

available on the synthesis of benzazoles directly from alcohols.[18] Recently, Ru/Xanthphos,[19a] Ru,[18a] IBX[19b] have been applied for the synthesis of benzimidazole. Deng *et al.* reported dppf [1,1'-bis(diphenylphosphino)ferrocene] catalyzed synthesis of 2-arylbenzoxazoles directly from *o*-nitrophenols and benzyl alcohols.[20]

The process involves *N*-alkylation of anilines to corresponding imines, followed by *in-situ* cyclization and oxidation to corresponding 2-arylbenzazoles (Scheme 4).



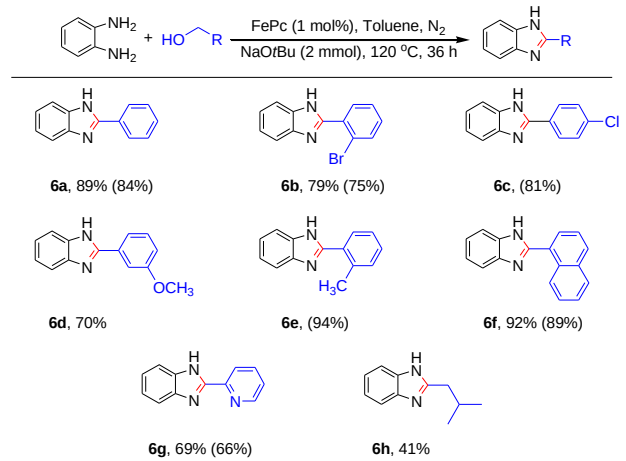
Scheme 4 *N*-alkylation of *ortho*-substituted anilines and *in-situ* cyclization to 2-arylbenzazoles.

Although, the reaction conditions were similar as for the *N*-alkylation, however, reaction took longer time for completion at slightly high temperature. Various experiments were carried out to optimize the *N*-alkylation of *ortho*-substituted anilines (see supporting information, Table S1). In order to explore the scope of the present method, the reactions of *o*-substituted (-NH_2 or -SH or -OH) anilines were successfully performed with a variety of alcohols (Table 6, 7 and scheme 5).

The reaction of *o*-phenylenediamine with benzyl alcohol (entry **6a**) afforded 2-phenylbenzimidazole in high yield. Good yields were obtained with halide bearing benzyl alcohols (entries **6b** and **6c**). The reaction of 3-methoxybenzyl alcohol, 3-methylbenzyl alcohol and 1-naphthyl alcohol proceeded smoothly to give the desired products in good to excellent yields (entries **6d**-**6f**). Heteroaromatic alcohol, 2-pyridylmethanol (entry **6g**), gave the corresponding product in

good yield (69%), however, low yield (41%) was obtained with aliphatic alcohol, isoamyl alcohol (entry **6h**).

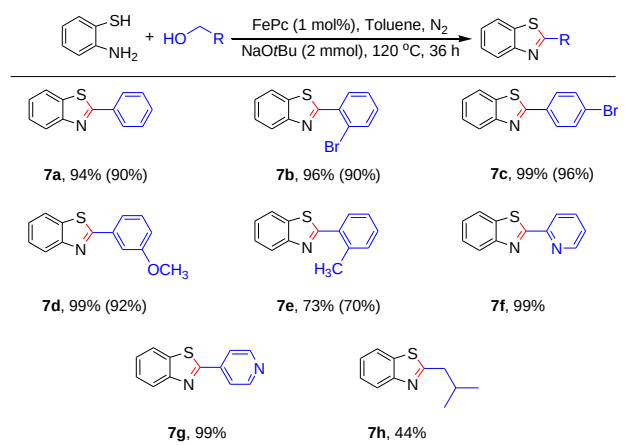
Table 6 *N*-alkylation of *o*-phenylenediamine with alcohols.[a,b]



[a] Reaction conditions: *o*-phenylenediamine (1 mmol), alcohol (1.5 mmol), Fe(II)Pc (1 mol%), NaO*t*Bu (2 mmol), toluene (5 mL) at 120 °C for 36 h. [b] Isolated yields are given in parenthesis.

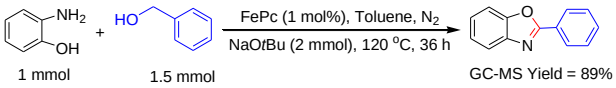
Reaction of substituted benzyl alcohols with 2-aminothiophenol afforded the desired 2-substituted benzothiazoles in excellent yields (Table 7). In case of benzyl alcohol (entry **7a**), 2-bromobenzyl alcohol (entry **7b**), 4-bromobenzyl alcohol (entry **7c**), 3-methoxybenzyl alcohol (entry **7d**), and 2-methylbenzyl alcohol (entry **7e**) good to excellent yields were observed. Heteroaromatic alcohols such as 2-pyridylmethanol (entry **7f**) and 4-pyridylmethanol (entry **7g**) also gave the corresponding benzothiazole products in excellent yields. The reaction of aliphatic isoamyl alcohol (entry **7h**) afforded the desired product in low yield.

Table 7 *N*-alkylation of 2-aminothiophenol with alcohols.[a,b]



[a] Reaction conditions: 2-aminothiophenol (1 mmol), alcohol (1.5 mmol), Fe(II)Pc (1 mol%), NaO*t*Bu (2 mmol), toluene (5 mL) at 120 °C for 36 h. [b] Isolated yields are given in parenthesis.

The present protocol was also applied for the synthesis of 2-phenylbenzoxazole by the reaction of 2-aminophenol with benzyl alcohol in good yield (Scheme 5).



Scheme 5 *N*-alkylation of 2-aminophenol with benzyl alcohol and *in-situ* cyclization to 2-phenylbenzoxazole.

Mechanistic Study

Based on the previously known hydrogen transfer methodologies,[18,21] it is expected that the present process underwent the three steps of alcohol oxidation-imine formation-imine hydrogenation. To confirm this, few experiments were carried out. In the absence of amine, oxidation of benzyl alcohol to benzaldehyde was observed under present reaction conditions confirming the first step (Fig. 1 a). When the reaction was carried out at low temperature (70 °C) or stopped in-between, imine was observed as major product which confirms the second step. The hydrogenation of imine afforded corresponding amine under the present reaction conditions, which further confirmed the second step (Fig. 1b).

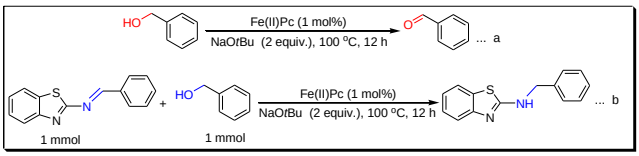
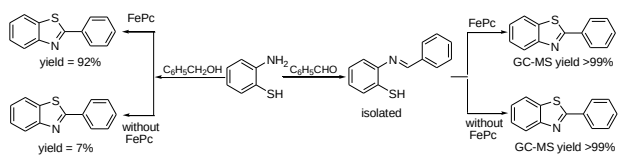


Figure 1 Oxidation of alcohol (a) and hydrogenation of imine (b).

The synthesis of 2-arylbenzazoles from *ortho*-substituted anilines and alcohols involves *in-situ* alcohol oxidation to aldehyde/imine formation/cyclization and finally oxidation of cyclized product (Scheme 4)[18]. We propose that FePc promote the oxidation of alcohols to aldehydes. Aldehydes react with 2-arylbenzazoles to form imine, which remain in equilibrium with cyclized product. The cyclized product is then oxidized either by base or oxygen[22] to final product. To confirm this, controlled experiments were carried out with and without FePc (entries 1 and 6 respectively, Scheme 6 left, Table S1). Yield of desired product decreased drastically without FePc. On the other hand reaction of 2-aminothiophenol with benzaldehyde instead of alcohol in the absence of catalyst gave 83% of 2-phenylbenzothiazole (entry 18, Table S1). This confirmed that FePc is mainly involved in oxidation of alcohols to aldehydes.



Scheme 6 Controlled experiments for elucidation of mechanism.

As, no effect of FePc was observed when controlled experiments were performed with isolated imine intermediate (Scheme 6, right), further confirmed the involvement of FePc in the oxidation of alcohols to aldehydes.

Experimental

General Information

Metal salts used were purchased from Merck, Germany. Iron phthalocyanines, amines, alcohols, and benzothiazoles were 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. Mass spectra were recorded on QTOF-Micro of Waters Micromass. The GC-MS analysis was carried out on 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). Melting points were determined on a Barnstead Electrothermal 9100.

General experimental procedure for *N*-alkylation of aminobenzothiazoles

To a stirred suspension of FePc (1 mol%) and NaO*t*Bu (2 mmol) in toluene (5 mL) were added alcohol (1.0 mmol), aminobenzothiazole (1.0 mmol) at room temperature and then temperature was raised to 100 ^{o}C for 12 h. 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 analysed 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 aminobenzothiazole reactants.

General experimental procedure for *N*-alkylation of aminopyridines and aminopyrimidines

To a stirred suspension of FePc (1 mol%) and NaO*t*Bu (2 mmol) in toluene (5 mL) were added alcohol (1.0 mmol), pyridine or pyrimidine (1.0 mmol) at room temperature and then temperature was raised to 100 ^{o}C for 12 h. 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 analysed 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.

General experimental procedure for the synthesis of *ortho*-substituted benzazoles

To a stirred suspension of FePc (1 mol%) and NaO*t*Bu (2 mmol) in toluene (5 mL) were added alcohol (1.5 mmol), *o*-substituted aniline (1.0 mmol) at room temperature and then temperature was raised to 120 ^{o}C for 36 h. 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 analysed 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.

Conclusion

The use of abundantly available and low toxic iron based catalyst is an attractive catalytic alternative to other costly and toxic transition metals. In the present study, an efficient iron phthalocyanine catalyzed method has been developed for the *N*-alkylation of aminobenzothiazoles, aminopyridines and aminopyrimidines. The present process is also applicable for the efficient synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazole by the *N*-alkylation of *ortho*-substituted anilines with readily available alcohols.

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[†]Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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22 The possibility of oxygen acting as oxidant for the conversion of cyclized product into final product can not be ruled out at this stage. However, all reactions were carried out under nitrogen atmosphere so there is less possibilities of oxygen acting as the sole oxidant.

