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Heterogeneous PS-Fe-NHC Catalysed *N*-alkylation of Amide and Amine with Alcohol as Alkylating Agent through Dehydrative C-N bond Formation Reaction

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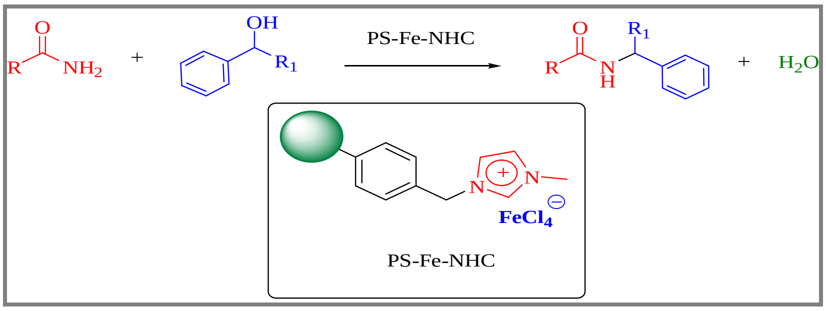
ABSTRACT

An efficient, high-yielding and rapid protocol has been developed the N-alkylation reactions of amides and amines through dehydrative C-N bond formation processes by using PS-Fe-NHC as green reusable heterogeneous catalyst. Absence of unwanted products, general applicability, reusability of the catalyst, green synthesis avoiding toxic reagents and improved and operational simplicity make this protocol a useful, greener, cost effective and practical for both academic as well as industrial purposes.

Graphical Abstract



Keywords: C-N bond formation reaction, Amide, Green Chemistry, Heterogeneous catalyst.

INTRODUCTION

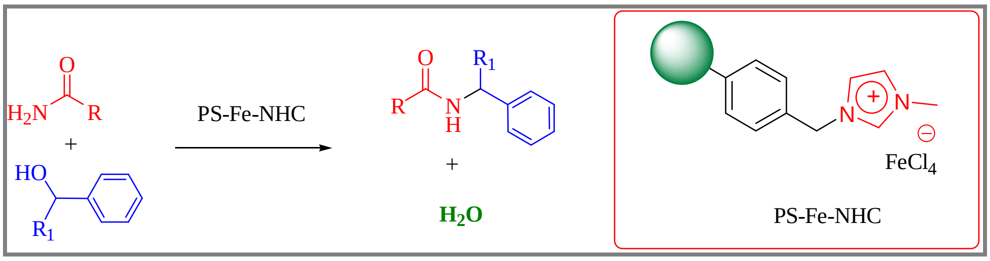
N-substituted amides and amines are important building blocks for many natural products, synthetic materials, agrochemicals, peptides and the pharmaceutical industry [1]. The environmentally benign synthesis of C-N bonds is a central, but still challenging, area of organic synthesis [2]. Traditionally, various protocols for C–N bond formation were developed by using different coupling reactions like Buchwald, Hartwig and Ullmann–Goldberg coupling, these reactions were efficient for the C–N bond formations, they suffer from one or more drawbacks such as requirement for functionalized starting materials, use of palladium or copper metals, moisture sensitive ligands, lower atom efficiency and production of toxic waste materials. In this context, N-alkylation reactions of amides and amines through dehydrative C-N bond formation processes have attracted significant attention in recent years. The application of inexpensive and abundantly available alcohols (C–OH) as alkylating agents with unactivated N-nucleophilic coupling partners, leading to the construction of the C–N bond, has the advantages of environmentally benign and high atom efficiency with the formation of water as the only side product [**3**]. Over the years, the use of oxophilic Lewis acids as catalysts grows rapidly, despite the great progress in C−N bond formation. As a consequence, amide bond formation is one of the most valuable transformations in present synthetic organic chemistry. The development of efficient procedures for construction of amide bonds is a long-standing task for chemists. ACS Green Chemistry Institute Pharmaceutical Roundtable have expressed that amide bond formation is one of the most important chemical reactions used in industry [**4**].

In past, few synthetic strategies have been developed for the preparation of amides. The most common method for the synthesis of amide is the condensation reaction of carboxylic acid or activated carboxylic acid derivatives (ester, acyl chloride and anhydride) with amine or amine surrogates (nitroarenes or aryl azide) at high temperature and in presence of stoichiometric amount of catalyst [**5**]. Limitations are mostly due to the reactions with esters require strongly basic or acidic catalysts, limited stability of many acid chlorides and anhydrides, resulting in poor atom-efficiency and formation of a significant amount of chemical waste are major drawbacks of this approach. To avoid these drawbacks, various alternative methods for the synthesis of amides have been developed. Presently, the more popular and highly attractive methods for *N*-substituted amide synthesis is the Ritter reaction of nitriles with alcohols under Brønsted acid catalytic conditions has been reported [**6**] and the dehydrative amination of alcohols with amides have good alternative approach as the nucleophilic substitution of the hydroxy groups in alcohols with various *N*-nucleophiles [**3**]. Cross-dehydrative coupling reaction is one of the most powerful tools for covalent bond direct construction and has been extensively studied over the past decade. The popularity of these methods is because they are more cost-effective and greener processes than the other approaches, and they have extremely high atom economy.

Very recently, more research groups have turned their attention towards the direct *N*-alkylation with alcohols by using acid-catalyst such as $Ca(NTf_2)_2$ with additive Bu_4NPF_6 [**7**], Re_2O_7[**8**], $RhCl(PPh_3)_3$ [**9**], $IrCl_3$[**9**],$FeCl_3$ [**10**], $Fe_2(SO_4)_3.xH_2O$ on silica [**11**], $Bi(OTf)_3/KPF_6$[**12**]. Heterogeneous solid acids catalysts such as, proton-exchanged montmorillonite (H-mont) [**13**], $HClO_4$-SiO_2 [**14**] and *N*-heterocyclic carbene-phosphine iridium complexes (NHC-Ir) [**15**], [BsTdIM][OTf] [**16**], Amberlyst-15 immobilized in [Bmim][BF_4] [**17, 26**] etc. have been reported and efficiently catalyze the dehydrative C-N bond formation reaction between alcohols and amides. However, many of these approaches suffer from one or more drawbacks such as requirement of expensive and excess catalysts, atom-efficiency prolonged reaction time as well as functional group tolerance and recyclability.

In context of green chemistry, the development of an efficient, environmentally benign and air-tolerant, heterogeneous catalyst is desirable [**18**]. In modern era of organic synthesis, polymer supported recyclable catalyzed reactions has been one of the most progressive research area [**19**]. In this respect, polymer supported NHC-$FeCl_3$ catalyst have gained much attention due to their recyclability and high reactivity giving higher yields with better atom economy [**20**]. Owing to the economic appeal of heterogeneous Lewis acid catalyst, their applications in dehydration N-alkylation of amide using alcohol as alkyl group source for C-N bond formation seems to be of great importance.

Considering the advantages of the C-N bond formation, in continuation of our earlier work on the synthesis of biologically active compounds by using heterogeneous catalyst [**21-29**], we have developed a PS-Fe-NHC catalyzed dehydrative C-N coupling reaction of *N*-nucleophiles with alcohol as alkyl surrogate that is suitable for N-alkylation of primary amides and amines. (Scheme 1). However, to the best of our knowledge, heterogeneous PS-Fe-NHC catalyzed N-alkylation reactions of amides have not been explored.



Scheme 1. PS-Fe-NHC catalyzed N-alkylation of amides.

MATERIALS AND METHODS

Chemicals required for the synthesis were obtained from Aldrich, Spectrochem, Loba- Company. All melting points were taken in one end sealed capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR using KBr. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker at 300 and 75 MHz respectively in DMSO-d_6 with TMS as an internal standard. Mass spectra (ES-MS) were recorded on Water-Micro (QUATTRO-II) mass spectrometer in *m/z*.

General experimental procedurefor *N*-arylation of amide: A 10 mL round bottom flask containing *N*-nucleophile (**1**) (1.2 mmol), alcohol (**2**) (1.0 mmol) in nitromethane (3 mL),then PS-Fe-NHC (4.0 mol %) and PTSA (0.1 mmol) were added. The reaction mixture was sturred at reflux temperature for 12 h. The reaction progress was monitored by TLC. After the reaction was completed, the mixture cooled to room temperature and diluted by ethyl acetate (10 mL). Separate the catalyst by simple filtration, washed the residue (catalyst) with hot ethyl acetate (2×5 mL). The organic layer was washed with water (3×5 mL), the organic layers were combined, dried over anhydrous Na_2SO_4, followed by concentrated under reduced pressure. The crude product was then purified by column chromatography eluting with (95: 5 v/v ratio of petroleum ether–ethyl acetate) to give pure products. The selected products were characterized by FTIR, PMR, CMR and Mass spectroscopy, whereas the remaining products characterized by their physical constants and are found to be in good agreement with the reported literature.

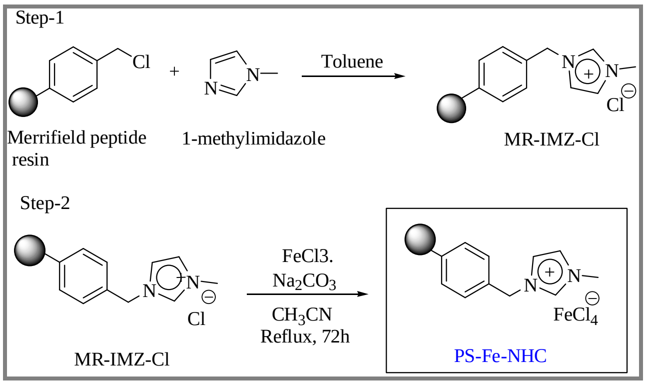
Spectral data for representative compound:

***N*-Benzhydryl benzamide(3a):** Colour: White crystalline solid, Yield: 92%, MP = 170-172 °C (Lit. 168-170°C) [**11**], **IR**(KBr, cm^{-1}):3330, 3030, 1635, 1528, 1440, 779, 617; ^{1}**H NMR** (300 MHz, DMSO-*d*$_6$) δ (ppm): 9.29 (d, *J*= 9.0Hz, 1H), 7.92 (t, *J*= 6.9 & 1.5 Hz, 2H), 7.50 (dd, *J*= 7.5 & 6.9 Hz, 3H), 7.38-7.32 (m, 8H), 7.27 (dd, *J*= 6.3 & 2.1Hz, 2H), 6.42 (d, *J*= 8.9 Hz, 1H). ^{13}**C NMR** (75 MHz, DMSO-*d*$_6$) δ (ppm): 166.56, 142.69, 134.74, 134.81, 128.82, 128.69, 128.05, 127.49, 56.83. **Mass** (ES-MS, *m/z*)**:** 286.2 **(M-1)**, 288.2 **(M+1)**.

***N*-Benzhydryl acetamide(3b):** Colour: White crystalline solid, Yield: 78%, MP = 142-144 °C (Lit. 143-144°C) [**6**], **IR** (KBr, cm^{-1}): 3340, 3030, 1655, 1528, 1440, 779, 617; ^{1}**H NMR** (300 MHz, DMSO-*d*$_6$) δ (ppm): 8.79 (d, *J*= 8.7Hz, 1H), 7.37-7.23 (m, 10H), 6.12 (d, *J*= 8.7Hz, 1H), 1.93 (s, 3H).; ^{13}**C NMR** (75 MHz, DMSO-*d*$_6$) δ (ppm): 168.93, 143.11, 142.65, 128.94, 128.80, 127.72, 127.34, 127.05, 56.32, 23.06.; **Mass** (ES-MS, *m/z*)**:** 224.2 (100%) (**M-1**); 226.2 (**M+1**), 167.1 (100%).

RESULTS AND DISCUSSION

Initially we have developed the best polymer supported catalyst, PS-Fe-NHC, which was prepared in two steps with small modification to the previously reported procedure (Scheme 2) [**20**]. In the first step imidazolium-loaded polystyrene resin supported ionic liquid (MR-IMZ-Cl) prepared from Merrifield peptide resin reacted with 1-methyl imidazole in toluene.



Scheme 2. Synthesis of PS-Fe-NHC catalyst.

This polystyrene resin supported ionic liquid was used as a support for the preparation of the Lewis acid Fe (III) ionic liquid catalyst. After carrying out the reaction of the MR-IMZ-Cl with ferric chloride, a polymer supported Lewis acid Fe (III) -*N*-heterocyclic carbene complex with the imidazolium loaded polymeric support (PS-Fe-NHC) was obtained. The obtained (PS-Fe-NHC) complex was characterized by FT-IR and amount of Fe loaded on the polymeric support was determined by using ICP-AES analysis.

The FT-IR spectra of PS-Fe-NHC shows most of the typical peaks centered at 1600, 1560, 1160 and 1075 cm^{-1} could correspond to the feature band absorption of the Imidazolium ring. The spectrum of the catalyst has peaks at 1,560 cm^{-1} assigned to C–N stretching and the strong band of quaternary imidazolium on the bead appeared at 1158 cm^{-1}. The peaks in the region of 2,800–3,100 cm^{-1} are assigned to aromatic and methylene C–H stretching of the Merrifield resin (Figure 1). The ICP-AES analysis of polymer-supported NHC-Fe(III)-complex showed the Iron loading is 1.3449 mmol g^{-1} of catalyst.

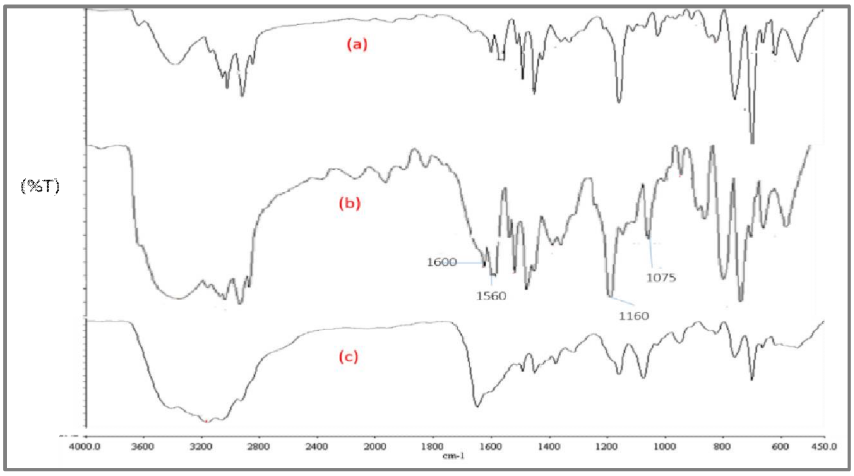
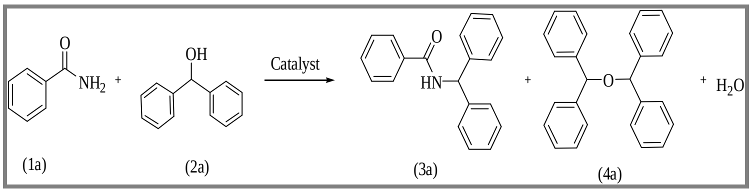


Figure1. FT-IR spectra of (a) PS- IMZ-Cl, (b) fresh PS-Fe-NHC catalyst and (c) after 3rdrecycle run.

During the preliminary studies benzamide (**1a**) (1.2 mmol) and benzhydryl alcohol (**2a**) (1.0 mmol) were chosen as model substrates for initial optimization of the reaction conditions (Table 1 and 2). A series of experiments were performed to optimize various reaction parameters, such as the catalyst, catalyst loading, additive, solvent, temperature and time. The proposed transformation was first examined by treating a mixture of **1a** and **2a** with various catalysts were tested. Among these heterogeneous catalysts examined PS-Fe-NHC was found to be the best, providing excellent yields of the desired product **3a** (Table 1, entries 1–9).

Table 1. Study of Catalyst, additive and Catalyst loading[a]



Entry	Catalyst	Catalyst loading (mol %)	Additive	Yield[b] (3a) (%)/[4a]
1	--	--	--	00
2	Fe_3O_4	4	--	36
3	$CuFe_2O_4$	4	--	32
4	CuI-Nano	4		48
5	MC-Cu(acac)$_2$	4	--	18
6	PS-IMZ-Cl	4	--	08
7	PS-Fe-NHC	4	--	78 [**12**]
8	PS-Cu-NHC	4	--	28
9	PS-Fe-NHC	4	PTSA	92 [**05**]
10	PS-Fe-NHC	4	MS 4A	78
11	PS-Fe-NHC	4	H_2SO_4	83
12	PS-Fe-NHC	4	H_3PO_4	78
13	PS-Fe-NHC	4	$AlCl_3$	83
14	PS-Fe-NHC	4	$Al_2(SO_4)_3$	81
15	PS-Fe-NHC	4	$NaHSO_4$	84
16	PS-Fe-NHC	3	PTSA	88
17	PS-Fe-NHC	5	PTSA	92
18[c]	PS-Fe-NHC	4	PTSA	84
19	--	--	PTSA	54

[a]Reaction condition: Benzamide (**1a**) (1.2 mmol) and benzhydryl alcohol (**2a**) (1.0 mmol), additive (10 mol%), nitromethane (3 mL), reflux,12h. [b]Isolated yields. [c]PTSA (5 mol%)

The self-condensation of benzydryl alcohol to give symmetrical ether **4a** is one of the side reactions observed. To coincidence, we used PTSA as the additive and we observed that product was obtained in excellent yield (Table 1, entries 9–15). We further studied catalyst loadings ranging from 3 to 5 mol%; increasing the catalyst concentration from 3 to 4 mol% increased the yield of **3a** to 92%, a further increase to 5 mol% did not improve the yield further (Table 1, entries 16, 17).We have also checked the effect of the concentration of additive PTSA on model reaction by reducing from 10 mol% to 5 mol%, decreased the yield of **3a** to 84% (Table 1, entries 9, 18).

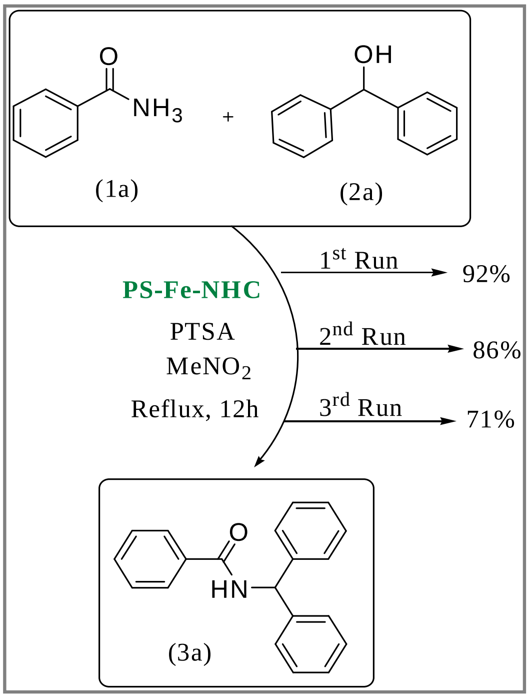
Table 2: Reaction parameter study[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] 3a/4a (%)
1	DMF	100	12	22
2	**$MeNO_2$**	**Reflux**	**12**	**92/05**
3	DCE	Reflux	12	81
4	DCM	Reflux	12	34
5	Toulene	Reflux	12	84
6	Dioxane	Reflux	12	79
7	ACN	Reflux	12	38
8	Water	Reflux	12	06
9	$MeNO_2$	Reflux	10	82/12
10	$MeNO_2$	Reflux	15	92/05
11	$MeNO_2$	80	12	78/15
12[c]	$MeNO_2$	Reflux	12	84/10

[a]Reaction condition: Benzamide (**1a**) (1.2 mmol) and benzhydryl alcohol (**2a**) (1.0 mmol), PS-Fe-NHC (4 mol%), PTSA (10 mol%), solvent (3 mL). [b]Isolated yields. [c]Benzamide (**1a**) (1.0 mmol)

Further, it screened with different solvents in order to enhance the rate of reaction. Among the solvents screened for the model reaction we observed that, the reaction performed well in nitromethane gave good yield of **3a**. (Table 2, entries 2, 1-8). We have also studied the effect of the time. Which showed that no increase in yield of the **3a** with increasing in reaction time from 12h to 15h. But affect the decrease in time up to 10h decreases the yield of **3a** and increases the **4a.** The reaction time was optimized at 12h (Table 2**,** entries 9, 10). We also studied the effect of the temperature showed that the decrease at 80°C, decreases the yield of **3a** with increasing the yield of **4a** (Table 2, entries 2, 11). We studied the effect of concentration of benzamide (**1a**), if we have decrease the concentration of benzamide, increase the yield of ether **4a** (Table 2, entries 12). After the study of all reaction parameters, the optimized reaction condition for the *N*-alkylation of amide reaction is Fe(III) Lewis acid catalyst (4.0 mol %) with PTSA(0.1 mmol) as additive, in nitromethane was the best solvent at refluxed for 12 h.

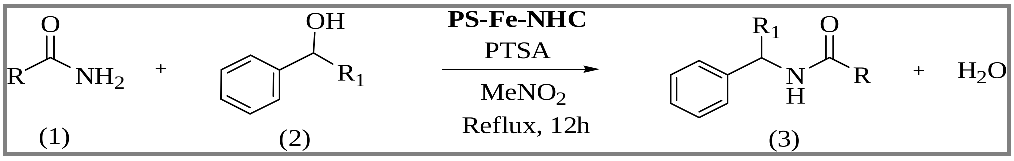
In order to make our catalytic system more economical, we focused on the reusability of the PS-Fe-NHC catalyst in this C-N bond forming reaction. As shown in Scheme 3, the catalyst exhibited remarkable activity in the first two consecutive recycles, while a decrease in conversion was observed in the third recycle. After completion of the reaction according to TLC, the reaction mixture was diluted with ethyl acetate then catalyst was filtered and the catalyst was washed with ethanol (3×5 ml), then dried it at 100°C for 2 h and used in the reusability studies.

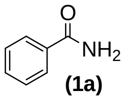
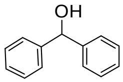
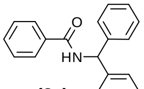
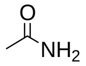
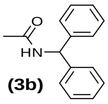
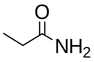
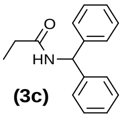
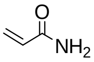
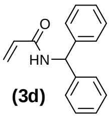
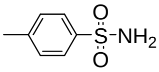
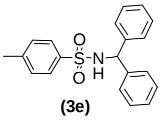
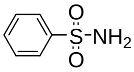
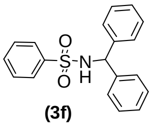
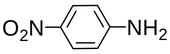
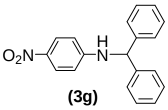
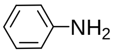
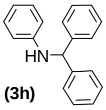
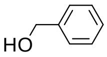
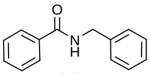
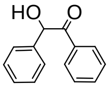
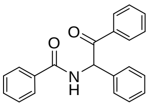


Scheme 3. Recyclability study of PS-Fe-NHC catalyst.

Having optimized the reaction conditions in hand, we next set out to explore the substrate scope of PS-Fe-NHC catalyzed dehydrative C-N bond forming reaction of alcohol with various N-nucleophiles. Various N-nucleophiles containing amide and amino groups were investigated. We observed that p-toulene sulphonamide, acetamide, acrylamide and electron withdrawing amines give good yield of corresponding products (Table 3). Next we attempted to widen the scope of PS-Fe-NHC catalyst for the less reactive benzylic alcohol and benzoin were tested with **1a**, almost reaction was failed in the optimized conditions.

Table 3. PS-Fe-NHC catalyzed synthesis of ***N***-alkyl amides[a]



Entry	N-Nucleophile (1)	Alcohol (2)	Product (3)	Yield[b] (%)	M.P.(°C) (Obt.) [ref.]
1	 **(1a)**	 **(2a)**	 **(3a)**	92	170-172 (168-170) [11]
2	 **(1b)**	(2a)	 **(3b)**	78	142-144 (143-144) [6]
3	 **(1c)**	(2a)	 **(3c)**	74	152-154
4	 **(1d)**	(2a)	 **(3d)**	85	178-180 (177-179) [14(a)]
5	 **(1e)**	(2a)	 **(3e)**	92	154-156 (156-158) [11]
6	 **(1f)**	(2a)	 **(3f)**	84	186-188 (186-187) [16]
7	 **(1g)**	(2a)	 **(3g)**	54	194-196 (194-195) [11]
8	 **(1h)**	(2a)	 **(3h)**	0[c]	--
9	(1a)	 **(2b)**	 **(3i)**	0[c]	--
10	(1a)	 **(2c)**	 **(3j)**	0[c]	--

[a]Reaction condition: N-Nucleophile (**1**) (1.2 mmol), alcohol (**2**) (1.0 mmol), PS-Fe-NHC (4 mol%), PTSA (10 mol%), $MeNO_2$(3 mL), reflux, 12h. [b]Isolated yields. [c]No reaction.

APPLICATION

The present method was environmentally benign. The procedure offers advantages in terms of better yields, short reaction times, mild reaction conditions, and reusability of the catalyst. The easy separation, high thermal stability of catalyst and an environmentally benign procedure makes this methodology useful contribution to the existing procedures available for the synthesis of N-aryl/alkyl amide through dehydrative C-N bond formation reaction.

CONCLUSION

The present study reports an efficient heterogeneous catalytic dehydrative C-N bond formation for the N-alkylation of amide and amines with alcohols by using a PS-Fe-NHC as stable, recyclable heterogeneous Lewis acid catalyst furnishing good to excellent yields of the corresponding products. Furthermore, the catalytic system was also recycled for up to three consecutive recycles with minimum loss of catalytic activity.

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