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ARTICLE

Transamidation catalysed by magnetically separable Fe_3O_4 nano catalyst under solvent-free condition

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An environmentally benign protocol for transamidation of carboxamides with different amines under solvent free condition using magnetically separable nano Fe_3O_4 as a heterogeneous catalyst is developed. The series of aryl and alkyl amines with long chain alkyl substituents have been selectively converted into transamide products. The current protocol offers diverse substrate scope with good yield of the product. Fe_3O_4 nano catalyst have also been used for formylation of amines via transamidation of dimethyl formamide. Efficient transamidation, ease of work up, simple separation and reusability of catalyst up to six runs are the important highlights of this process.

1. Introduction:

There is an increasing need of a sustainable, efficient and greener route for the development of high quality products[1]. In this respect, nanoparticles have emerged as an important tool in many organic reactions[2–4]. The use of nano catalysts for different organic reactions is ever increasing. But, the major problem in the use of nano catalysts is its tedious recycling procedure and loss of the catalyst in the handling process. Superparamagnetic Fe_3O_4 nanoparticles have attracted considerable attention all over the world due to wide biological[5–7] and technological applications[8,9]. It has significant characteristics such as ease of separation from the reaction media by use of a simple magnet and facile recycling process[10-12]. Therefore, there is growing interest for the use of Fe_3O_4 nanoparticles as a catalyst in many organic transformations[13,14].

Amide functionality is one of the fundamental building block found in nature[15,16]. It is commonly present in natural products and synthetic compounds[17]. It is useful as a versatile building block in the preparation of bioactive products such as peptides, peptidomimetics and in proteins to make up the peptide bonds. It is also used in drugs or drug intermediates, polymers, agrochemicals and in organic materials[18–21]. There are several synthetic routes available for their synthesis. Generally, synthesis of amide involves reaction of activated carboxylic acid derivatives such as chloride, anhydride or ester with amines[22,23]. Other reactions include hydroamination of alkynes[24–26], hydration of nitriles[27–29], Schmidt reaction[30], Beckmann rearrangement[31,32], amidation of thio acids with azides[33]and aminocarbonylation process. Most of these methods suffer from limitations such as harsh reaction conditions, tedious work up procedure and low reactivity. Therefore, transamidation has gained considerable interest as the most convenient route for the synthesis of secondary or tertiary amines through tandom process. Unfortunately, transamidation is a fairly unusual reaction because of high stability and inert nature of amides. Usually, high temperature and long reaction time is required to cleave the amide bond. There are several reports for transamidation using new homogeneous and heterogeneous catalysts[34–38]. Stahl et al. have reported Al (III), Sc(III) and group 4 metal complex as a homogeneous catalyst which works under milder conditions. Despite the advances achieved by all these methods, there is difficulty in the separation, recycle and reuse of these catalysts from the product. Copper diacetate[39] and boric acid[40] have also been reported as homogeneous catalysts for effective transamidation. Nevertheless, their major shortcomings are long reaction time and difficulty in recycling. To overcome the issue of separation, Shi et al[41] have reported $HfCl_4$ supported heterogeneous catalyst. This method also has limitations like need of the strong base and limited substrate scope as it has been reported that reactions were unproductive with aliphatic amines.

Although, there are efficient reports to dictate transamidation, little attention has been given for the development of heterogeneous, recyclable catalysts. In continuation of our efforts on the development of green and sustainable methods[42] herein, we report a simple and efficient protocol for transamidation of carboxamides and phthalimide with various amines in the presence of Fe_3O_4 nano catalyst. We have also described the application of Fe_3O_4 nano catalyst for the direct formylation of various amines using *N,N*- dimethyl formamide (DMF) as a formylation agent.

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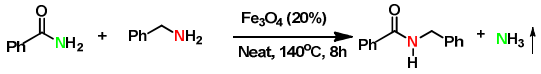
2. Result and discussion:

In the present study, we have reported an efficient and industrially viable method for transamidation. Initially, we began our study with benzamide and benzyl amine as a model substrate using nano-Fe_3O_4 as a catalyst in toluene at 120°C but no product formation was observed after 24 h (Table 1, entry 1). Reactions were performed in different solvents such as xylene, DMSO, diglyme, water and chlorobenzene but, no improvement in the yield was observed (Table 1, entry 2-6). To our delight, when we performed the reaction under neat condition at 120°C, 29% yield of the product was observed (Table 1, entry 7). On increasing the temperature to 140°C, increase in the yield to 91% was noted (Table 1, entry 8). We have also performed the catalyst loading study, but decrease in the yield was observed on decreasing the catalyst loading (Table 1, entry 9, 10). Whereas, on increasing the amount of the catalyst to more than 20 wt. %, no improvement in the yield was observed (Table 1, entry 11). Hence, the optimised reaction conditions include 20 wt. % catalyst, at 140°C for 8 h under neat condition. Furthermore for comparison, the model reactions were carried out in presence of different catalysts such as Al_2O_3, MgO, ZnO under similar reaction conditions but no appreciable yield was observed (Table 1, entry 12-14). When the reaction was performed without catalyst at 140°C, only 28% of the desired product was obtained. This suggests that the catalyst plays a major role in the reaction. The rate of reaction was faster due to the nano form of the catalyst. When the reaction is performed under a neat condition, better diffusion of nano Fe_3O_4 catalyst in the reaction mixture was observed. Due to which substrate are directly adsorbed on the surface of the catalyst resulting in increased rate of the reaction and higher yield of the product. However, in presence of different solvents, comparatively less active sites are available because of which traces yield of the product were obtained.

Table 1: Optimisation of reaction condition[a].

Scheme-1



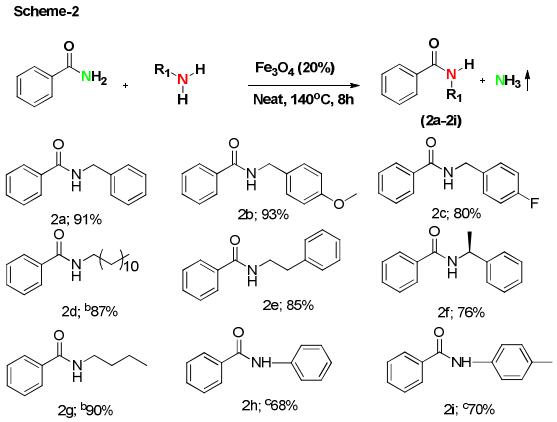
Entry	Catalyst	Temperature	Solvent	Isolated Yield[b]
1[c]	Fe_3O_4	120	Toluene	Nil
2	Fe_3O_4	120	Xylene	Nil
3	Fe_3O_4	130	DMSO	traces
4	Fe_3O_4	130	Diglyme	traces
5	Fe_3O_4	110	Water	Nil
6	Fe_3O_4	120	Chlorobenzene	Traces
7	Fe_3O_4	120	-	29%
8	Fe_3O_4	140	-	91%
9[d]	Fe_3O_4	140	-	70%
10[d]	Fe_3O_4	140	-	79%
11[d]	Fe_3O_4	140	-	91%
12	Al_2O_3	140	-	78%
13	MgO	140	-	82%
14	ZnO	140	-	80%
15[e]	-	140	-	28%

[a]Reaction condition: amide (1 mmol), amine (1.2 mmol); catalyst: 20 wt. %, solvent 2ml, in a seal tube, 8h, [b]isolated yields.; [c]Reaction time 24 h for entry 1; [d]Reaction performed with 10, 15 and 25 wt. % of the catalyst in entries 9-11; [e]Reaction performed in absence of the catalyst.

With these optimised conditions in hand, the general applicability and efficiency of this protocol was demonstrated by a wide substrate study with various amines. As shown in table 2, both electron donating and withdrawing groups present on the benzyl amine provided good to excellent yield of the transamidation product (76-93%). Reaction of benzamide with dodecyl amine and butyl amine gave the desired product in 87% and 90% yield respectively in 3 h. However, the reaction rate was found to be slow between benzamide and less nucleophilic amines, giving 68 to 70% yield, in 24 h.

Table 2: Scope of transamidation of benzamide with various amines[a].

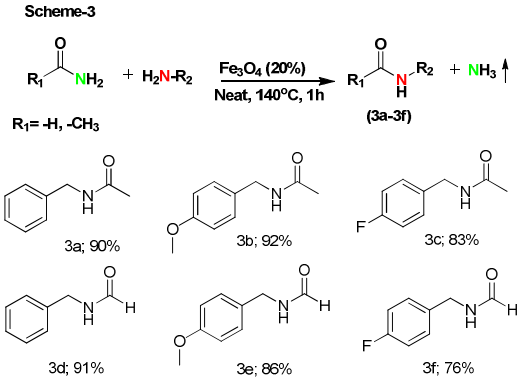
Scheme-2



[a]Reaction condition: amide (1 mmol), amine (1.2 mmol), 20 wt. % catalyst, seal tube, time: 8 h, temperature: 140°C, isolated yield; [b]temperature: 100 °C, [b]Reaction time: 3h; [c]Reaction time: 24 h.

Table 3: Scope of transamidation of aliphatic amide with various amines[a].

Scheme-3



[a]Reaction condition: aliphatic amide (1mmol), amine (1.2mmol), 20 wt. % catalyst, seal tube, time: 1 h, temperature: 100 °C, isolated yield.

To ascertain the scope of the transamidation process, we carried out the reaction of aliphatic amide namely, formamide and acetamide with different amines Table 3 (electron

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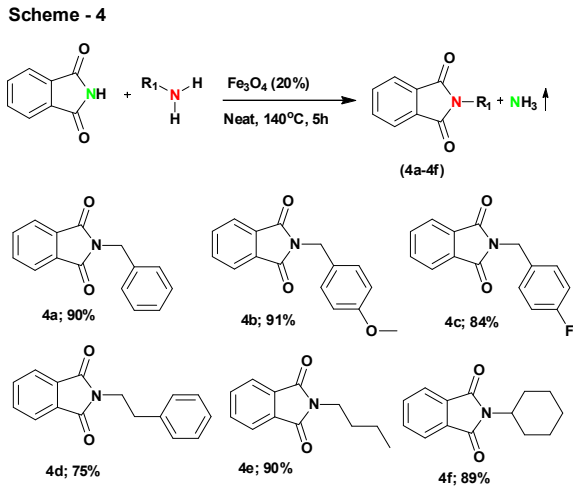
donating and electron withdrawing). The reaction proceeded smoothly under milder condition at 100°C in 1 h. Under this condition, aliphatic amides like acetamide and formamide were reacted with various amines to obtain the desired products in good to excellent yields (76-92%).

Phthalimide is a potential precursor in pesticide, medicine and many dye intermediates. Thus, after successful transamidation of benzamide, we attempted transamidation of phthalimide with different amines (benzyl, aliphatic and cyclic amines) (Table 4). All the amines reacted smoothly and gave the corresponding *N*-substituted derivative in good yield (75-91%). Thus, this methodology has broad applicability.

Table 4: Transamidation of phthalimide with various amines[a].



[a]Reaction condition: phthalimide (1 mmol), amine (1.2 mmol), 20 wt. % catalyst, seal tube, time: 5 h, temperature: 140°C, isolated yield.

After efficacious transamidation of benzamide under neat condition, we were keen to know whether *N,N*-dimethyl formamide (DMF) could be used for direct formylation of amines. Recent literature reports include $HCONH_2/NH_2OH.HCl$[43], $HCONH_2/Cp_2ZrCl_2$[44] and use of carboxylic acid in presence of protic ionic liquids[45]. However, these methods require longer reaction time, high catalyst loading or anhydrous condition for the reaction. Hence, we prophesied that Fe_3O_4 mediated transamidation using DMF may be advantageous for direct formylation of amines. Therefore, we have performed the reaction of benzyl amine in presence of DMF with 20 wt. % of the Fe_3O_4 catalyst. The reaction was completed in 18 h. In this reaction, DMF plays a dual role of solvent as well as formylation agent. The reaction was performed with various aliphatic, aromatic amines in presence of DMF and Fe_3O_4 as a catalyst (Table 5). In the formylation of benzyl amine derivatives, the electronic effect of the substituent had no effect on the yield of product. It offered good to excellent yield of the targeted product (72-93%).

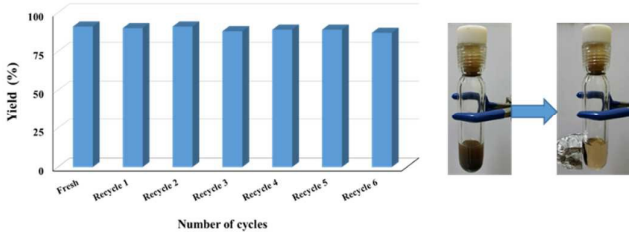
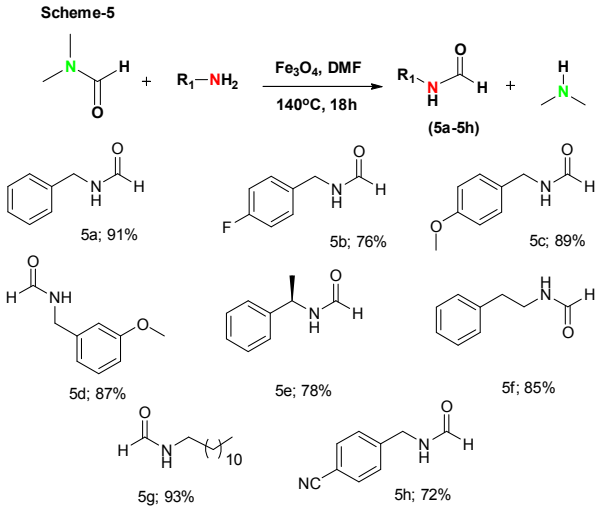


Figure 1: Recyclability study of the Fe_3O_4 nano catalyst.

Table 5: Scope of *N*-formylation of amines using *N,N*-dimethylformamide as formylation agent[a].



[a]Reaction condition: amine (1.5 mmol), DMF: 2ml, 20 wt. % catalyst, seal tube, time: 18 h, temperature: 140 °C, isolated yield.

To assess the recyclability of the catalyst, we examined the transamidation of benzamide with benzyl amine under the optimised condition. The results are summarised in figure 1. After completion of the reaction, the catalyst was separated by an external magnet, washed with methanol and dried at 60°C for 1 h. The recovered catalyst was then used for the next batch. It was observed that catalyst could be recycled efficiently up to six runs. This study indicates potential application of nano Fe_3O_4 as a heterogeneous catalyst for transamidation reaction with wide substrate scope under neat condition. Figure 2 and 3 show TEM and SEM images of the fresh and reused catalyst. Although, slight aggregation of the catalyst was observed in the SEM image due its magnetic nature, there is no change in the surface morphology and size of the catalyst after 6th recycle.

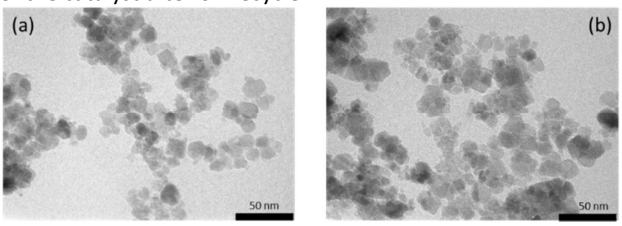


Figure 2: TEM images of Fe_3O_4 nano catalyst before use (a) and after six runs (b)

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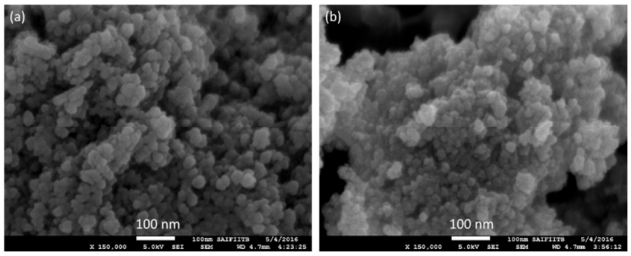

Figure 3: SEM images of Fe_3O_4 nano catalyst before use (a) and after six runs (b).

3. Characterisation of the catalyst:

The Fe_3O_4 nano catalyst was prepared according to previously reported literature method[46]. The XRD pattern of the Fe_3O_4 nanoparticle is shown in Figure 4. A number of Bragg reflections by their indices (220), (311), (400), (422), (551) and (440) indicate the cubic crystal phase of Fe_3O_4[47]. TEM image of the catalyst displays dark Fe_3O_4 core with spherical surface morphology and average particle size between 13-15 nm (Figure 2a). This nano size of Fe_3O_4 provides higher surface area and active sites, resulting in faster reaction rate. The SEM image of the Fe_3O_4 nano particles is shown in Figure 3a. It shows that they have spherical morphology and it has marked tendency to form large aggregates due to magnetic characteristics.

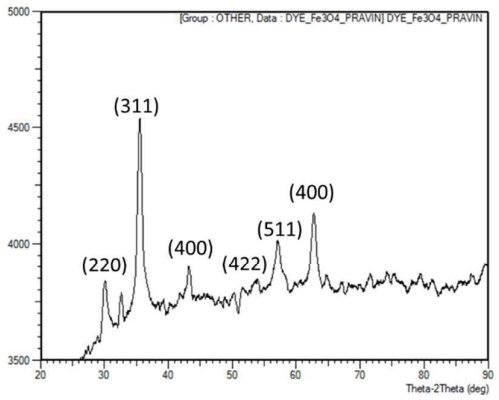

Figure 4: XRD images of Fe_3O_4 nano catalyst

4. Plausible reaction Mechanism:

Based on the present experimental results and literature reports[40,43,48], it is supposed that catalytically active site of Fe_3O_4 is Fe^{3+} which behaves as Lewis acid and coordinates to the carbonyl group of amide to form intermediate step-I. Then, nucleophilic attack by an amine at the carbonyl centre of the activated amide intermediate step-I generates intermediate step-II. It is subsequently followed by a rearrangement to give intermediate step-III, which is then followed by elimination of ammonia to yield the desired product, thus regenerating the Fe_3O_4 catalyst (Figure 5).

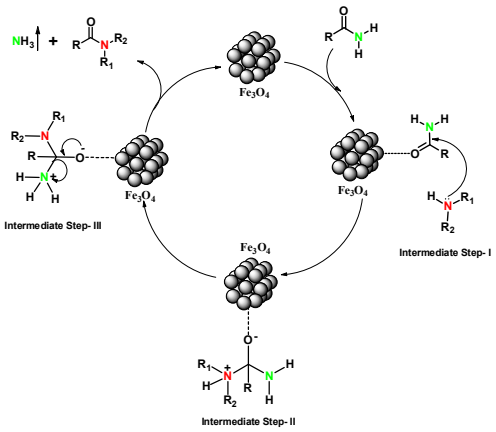

Figure 5: Plausible reaction mechanism

5. Conclusion:

In summary, we have developed an efficient protocol for transamidation of carboximide under solvent free condition using heterogeneous nano catalyst. A wide range of aliphatic, aromatic and benzylic amines could be efficiently converted into their transamidation products with good to excellent yield. Along with this, the ease of separation and reusability of the catalyst are the added advantages of this process. The developed protocol is simple, green and economically viable.

Experimental:

General procedure for transamidation:

A mixture of amide (1 mmol), amine (1.2 mmol) and Fe_3O_4 (20 wt.%) was stirred in a sealed tube at specified temperature for specified reaction time (scheme 1-4). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and dissolved in ethyl acetate. The catalyst was separated from the reaction mixture by an external magnet. The crude reaction mass was concentrated and then purified by column chromatography using hexane and ethyl acetate as eluent.

General procedure for formylation using DMF:

A mixture of benzyl amine (1.5 mmol), *N, N*- dimethyl formamide and Fe_3O_4 (20 wt. %) was stirred at 140 °C for 18 h in a sealed tube (scheme 5). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and dissolved in dichloromethane. The catalyst was separated from the reaction mass by an external magnet. Water was then added to the reaction mixture to remove excess of DMF and then reaction mass was extracted into dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to column chromatography to obtain the pure desired product (eluent hexane and ethyl acetate).

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Notes and references

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Graphical abstract