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A simple and greener approach for the amide bond formation employing $FeCl_3$ as a catalyst

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Catalytic use of $FeCl_3$ in presence of glacial AcOH for the direct amidation of acid with amine in toluene has been described in this paper. The protocol worked well for the less nucleophilic aniline and its variants which gave best results under present reaction conditions. Amidation of bromoacetic acid and sterically hindered amino acid also proceed effectively to yield corresponding amides. The protocol is catalytic and circumvents the use of stoichiometric amount of reagent. The reaction led to water soluble by-products and thus makes the product isolation easier.

The amide bond is ubiquitous in nature. It constitutes the backbone of biologically significant peptides as well as in proteins.[1] It is present in many natural products and pharmaceutically interesting compounds.[2] Consequently, development of an efficient amidation method continues to be an important scientific pursuit. Despite the favourable thermodynamic stability of the resulting amide bond, the simple thermal dehydration reaction between a carboxylic acid and an amine is plagued by a large activation energy.[3] The initial formation of a stable ammonium carboxylate salt deters the dehydration step, and the intermediate salt collapses to provide the amide product only at very high temperatures (> 200 °C)[4] that are not compatible with most functionalized molecules. Consequently, there are still no general methods to access amides directly from free carboxylic acids and amines in a simple, green, and atom-economical fashion at ambient temperature. Common protocols for forming amide bonds involve the use of stoichiometric amount of expensive coupling reagents such as carbodiimides or phosphonium or uronium salts to activate and condense the carboxylic acid with amine.[5] These reagents and their associated co-reagents, including bases, and other additives, generate large amounts of wasteful by-products that complicate the isolation of the desired amide product.

A general strategy for amide bond formation is the activation of carboxylic acid as acyl halide, acylimidazole, acyl azide, anhydride or active ester followed by aminolysis.[6] Although, these methods have been developed to facilitate amide formation, they all have inherent advantages as well as limitations due to the structural diversity of substrates participating in amide formation. The direct amidation of carboxylic acid is highly attractive for industrial perspective as it would lead to be cost-effective and atom economy processes.

To overcome some of these problems associated with the above said approaches, different catalytic methods have also been designed. Amide bond formation using starting materials such as nitriles, isonitriles, oximes, aldehydes and alcohols, esters[7] as well as aminocarbonylation[8] methods employing metal catalysts are also well documented in the literature. However, ideal situation is the direct coupling of carboxylic acids with amines producing water as the only by-product. Up to now, only a few catalytic systems for the direct amide coupling of carboxylic acids and amines have been developed.[9] Organocatalytic methods employing enzymes have been used to some extent,[10] albeit with a limited substrate scope. Due to the significance of the amide bond in a vast array of applications, we were intrigued by the challenge and started to investigate the possibility of generating a direct catalytic amidation method starting from carboxylic acid.

Catalysis is a key technology, since approximately 80% of all chemical and pharmaceutical products on an industrial scale are made in presence of catalysts. During the last decades, manifold transition-metal catalysts especially based on precious metals such as palladium, rhodium, iridium, and ruthenium have been proven to be efficient for a large number of applications in organic synthesis. However, their high price as well as toxicity makes it desirable to search for more economical and environmentally benign protocol. A possible solution of this problem could be the increased use of catalysts

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based on first row transition metals, such as iron, copper, zinc, and manganese. Especially iron offers significant advantages compared with precious metals, since it is the second most abundant metal in the earth crust. The facile change of oxidation state and the distinct Lewis acid character, iron catalysts allow in principle a broad range of synthetic transformations, for example, addition reactions, substitution reactions, cycloaddition, hydrogenation, reduction, oxidation, coupling reactions, isomerizations, rearrangements, and polymerizations.[11] Das et al., reported Fe^{+3}-K10 montmorillonite clay catalysed preparation of esters and amides.[12] Rao and co-workers described a facile N-formylation of amines using Lewis acid catalysts including $AlCl_3$, $FeCl_3$, $NiCl_2$, $ZnCl_2$.[13] Williams et al., also reported an iron catalysed coupling of nitriles and amines to form amides.[14]

In a typical experiment, phenylacetic acid and aniline were chosen as model substrates. Our catalytic system consisted on commercially available iron salt, $FeCl_3$. A synthetic study was first undertaken to define the best reaction conditions. The table lists the representative data obtained for the synthesis of amide in presence of iron salts including $FeCl_2$, $FeCl_3$, $FeCl_3.6H_2O$. Among the catalysts used $FeCl_2$ afforded 38% yield, where as the use of $FeCl_3$ and $FeCl_3.6H_2O$ lead to 76 and 65% yields of product respectively. When the similar reaction was carried out using $FeCl_3$ in presence of 0.5 eq of glacial AcOH afforded the product in 89% yield. Increase in the yield of product is possibly due to the increased leaving group ability of hydroxy group of an acid in presence of AcOH.

A solvent screening was carried out and among the solvents screened such as, CH_2Cl_2, THF, CH_3CN, toluene, DMF and EtOAc, toluene yielded satisfactory result. As illustrated in the earlier reports, formation of charged species is disfavoured in non polar solvent i.e., toluene and thus avoids the formation of salt during the amidation. A 20 mol% of the catalyst proved enough for the desired transformation.

Since quantitative conversions can be obtained at 160 ^oC with simple substrates and to make sure that the system would be sufficiently catalytic, a control experiment was conducted. In which, an amide formed by the treatment of acid with an amine in toluene at reflux temperature can be assumed to be the result of a background reaction (i.e., amide formation due to the thermal treatment of acid and amine). To verify that the amidation reaction is indeed catalysed by the $FeCl_3$, experiments were performed without the catalyst. These reactions resulted in 10-13% yields of the amide depending on the stoichiometry between the amine and acid components. The poor outcome of the uncatalyzed reactions clearly confirms catalytic efficiency of iron (III).

Although the mechanism of the present reaction has not been studied in detail and if any mechanistic discussion is speculative, we believe that the catalyzed transformation proceeds *via* $FeCl_3$ catalysed activation of the carbonyl group of the acid. Therefore, iron-coordinated carbonyl increases its electrophilicity to trigger the nucleophilic attack by an amine component and AcOH serve as source of H^+ ions (Fig. 1). In addition, according to the literature preceding as in case of triflic acid,[15] $FeCl_3$ may combine with AcOH to form $Fe(OCOCH_3)_3$ which may behave as active catalyst species and may involve in the reaction and meanwhile the H+ ion liberated will assist in the protonation of the –OH group of an acid. Hence in the above case no coupling product of AcOH was observed, since the AcOH employed was only 0.5 eq. However, in the absence of an acid component, usage of 1.0 and 1.5 eq. AcOH led to the corresponding coupling product with benzylamine in 6 and 16 % yields respectively.

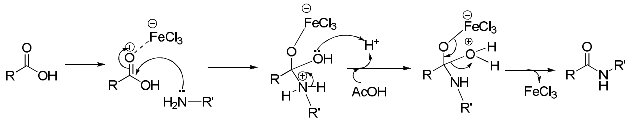
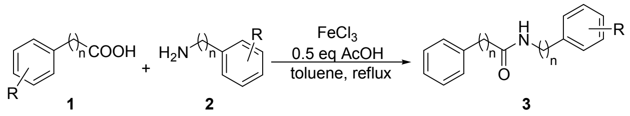


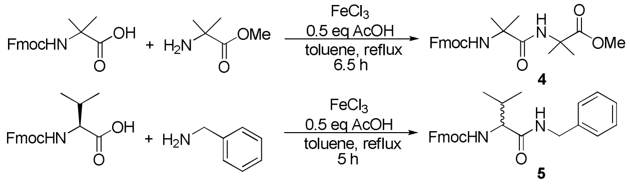
Fig. 1 Possible mechanism of amide bond formation.



Scheme 1 Synthesis of amides **3**.

To check the feasibility of this optimized process, amidation of variety of acids with various amines was carried out (Scheme 1). To our delight, the corresponding amides were obtained in good to excellent yields (Table 1). The products were characterized by mass, ^1H and ^{13}C NMR analyses.

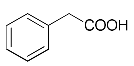
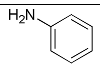
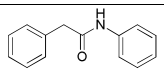
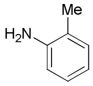
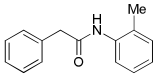
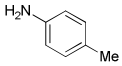
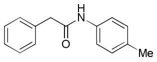
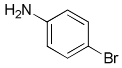
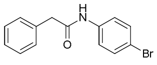
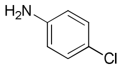
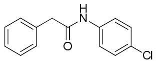
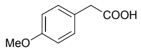
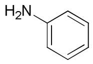
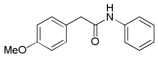
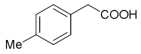
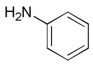
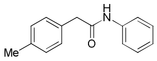
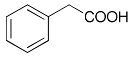
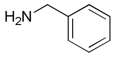
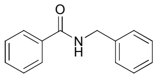
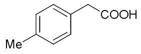
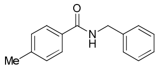
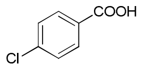
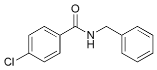
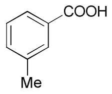
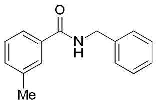
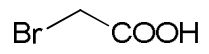
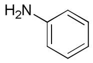
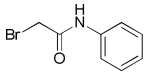
Bromoacetic acid whose coupling is troublesome *via* acid chloride method also gave the corresponding amide with aniline in fairly good yields (Table 1, entry 12). It is also interesting to see if racemisation could occur when a chiral amino acid is used under present reaction conditions. Thus we carried out the amidation of Fmoc-Val-OH with benzyl amine and the product **5** was obtained in 74% yield, but with noticeable racemisation as observed through HPLC analysis (method: ACN:H_2O-70:30, run time = 30 min). However, we undertook the coupling of sterically hindered Aib amino acid, which doesn't possess the chiral centre as well. Satisfactorily, corresponding Fmoc-protected Aib-Aib dipeptide **4** was obtained in 67% yield (Scheme 2).



Scheme 2 Synthesis of amino acid derived amides **4** and **5**.

Overall, the protocol employing $FeCl_3$ in presence of glacial AcOH worked well for the less nucleophilic aniline and its variants, bromoacetic acid and sterically hindered amino acid which gave best results when subjected to amidation under present reaction conditions. The protocol discussed in the present work is catalytic and thus circumvents the use of stoichiometric amount of reagents for the amide formation. The reaction led to water soluble by-products and thus makes the product isolation simple as well as easier.

Table 1. List of amides prepared employing $FeCl_3$.

entry	Acid (1)	Amine (2)	Amide (3)	Yield (%)
1			 (6 h) 3a	89
2			 (5.5 h) 3b	80
3			 (5 h) 3c	84
4			 (6 h) 3d	81
5			 (5.5 h) 3e	74
6			 (4.5 h) 3f	83
7			 (5 h) 3g	80
8			 (6 h) 3h	83
9			 3i	82
10			 (5.5 h) 3j	85
11			 (5.5 h) 3k	81
12			 (6 h) 3l	68

Experimental Section

To a solution of acid (1.0 mmol) in toluene (6 mL) was added 20 mol% $FeCl_3$ [98% purity, procured from Merck] and an additional 0.5 eq of AcOH and the reaction mixture was allowed stir at 50 ^{o}C for 10-15 min. Then an amine (1.0 mmol) in toluene (4 mL) was added to the above reaction mixture. The reaction mixture was refluxed at 70-75 ^{o}C temperature till the completion of the reaction as monitored by TLC. Upon complete consumption of the starting materials, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The crude product was extracted into EtOAc (15 mL). The EtOAc layer was then washed with 5% Na_2CO_3 (5 mL), dil. HCl (5 mL), water (2 x 5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to afford the crude which was then purified through silica gel column chromatography (EtOAc/hexane).

The NMR spectra provided in the ESI† are of the as-isolated products.

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Graphical abstract:

A simple and greener approach for the amide bond formation employing $FeCl_3$ as a catalyst

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Protocol employing $FeCl_3$ in presence of glacial AcOH is described for the less nucleophilic aniline and its variants, bromoacetic acid and sterically hindered amino acids.