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Iron-Catalyzed Efficient Synthesis of Amides from Aldehydes and Amine Hydrochloride Salts

Subhash Chandra Ghosh,[a] Joyce S. Y. Ngiam,[a] Christina L. L. Chai,[a,b] Abdul M. Seayad,[a] Tuan Thanh Dang,[a] and Anqi Chen[a,*]

[a] Institute of Chemical and Engineering Sciences, 8 Biomedical Grove, Neuros #07-01, Singapore 138665
Fax: (+65)-6464-2102; e-mail: chen_anqi@ices.a-star.edu.sg
[b] Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543

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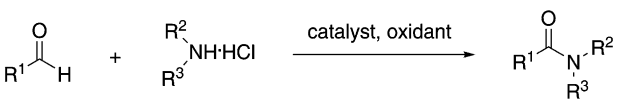
Abstract: A practical and efficient method for the synthesis of amides has been developed by iron-catalysed oxidative amidation of aldehydes with amine hydrochloride salts. A wide range of amides have been obtained in good to excellent yields under mild conditions. The application of this novel amide formation reaction to the synthesis of pharmaceutical compounds has been successfully demonstrated.

Keywords: aldehydes; amidation; amides; amine salts; catalysis; iron(II) sulphate

The amide bond is one of the most abundant functional groups found in natural products, polymers and pharmaceuticals.[1] A comprehensive survey revealed that more than 25% of known drugs contain an amide group.[2] Conventionally, amides are prepared by the reaction of an amine with a carboxylic acid derivative (acyl halide or anhydride) or by using a coupling reagent.[3] However, these methods suffer from poor atom-efficiency and/or the use of highly hazardous reagents. Consequently one of the major challenges in chemical synthesis is to develop alternative methods of amide bond formation that circumvent these problems.[4] This has led to the development of alternative methods for amide synthesis,[5] such as the Staudinger reaction,[6] the Schmidt reaction,[7] the Beckmann rearrangement,[8] aminocarbonylation of haloarenes,[9] iodonium-promoted α-halo nitroalkane amine coupling,[10] direct amide synthesis from alcohols with amines or nitroarenes,[11] aminolysis of esters,[12] coupling of nitriles with amines or alcohols,[13] hydroamidation of alkynes,[14] amidation of thioacids with azides,[15] transamidation of primary amides[16] and oxidative amidation of aldehydes.[17] Despite this, most of the methods outlined above have not been applied in industry due to drawbacks such as the use of expensive transition metal catalysts, limited substrate scope, harsh reaction conditions, etc.

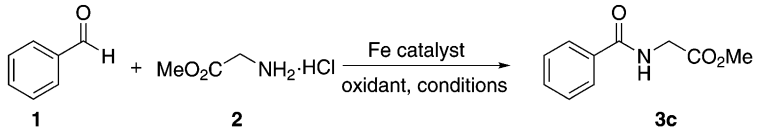
Hence, the development of efficient and practical amide formation reactions remains a great challenge. Among the emerging amide formation methods, the direct oxidative amidation of aldehydes with amine salts[17d] (Scheme 1) is an attractive method with practicality and potential industrial applications. This is because the reaction can be highly efficient and both aldehydes and amine salts are widely available. A key challenge to enable the industrial use of this reaction is to develop inexpensive catalysts that could effectively catalyse the reaction under practical and mild conditions. Herein, we report the use of inexpensive and easily accessible iron compounds as catalysts for the oxidative amidation of aldehydes with amine hydrochloride salts.

Our investigation began with the identification of an inexpensive catalyst system using the reaction of benzaldehyde and glycine methyl ester hydrochloride to form methyl-2-benzamidoacetate as the test reaction (Table 1). As iron salts are inexpensive, environmentally benign and have been shown to catalyse peroxide reagent-mediated oxidation reactions,[18] we sought to screen commercially available iron salts as catalysts for the reaction. The initial reaction performed with $FeCl_3 \cdot 6H_2O$ as a catalyst, $CaCO_3$ as a base, hydrogen peroxide (30% in water) as an oxidant in acetonitrile at 60 °C was unsuccessful. GC analysis of the reaction mixture showed that <5% of the desired amide was formed (entry 1) together with



Scheme 1. Oxidative amidation of aldehydes with amine hydrochloride salts.

Table 1. Optimisation of the reaction conditions.[a]



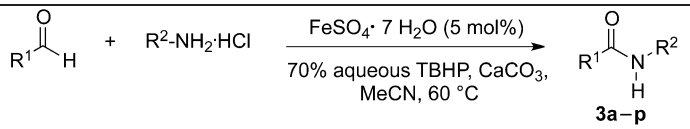
1 2 3c

Entry	Catalyst	Oxidant	Base	Solvent	Yield [%][b]
1	$FeCl_3·6H_2O$	H_2O_2	$CaCO_3$	CH_3CN	<5
2	$FeCl_3·6H_2O$	T-Hydro	$CaCO_3$	CH_3CN	85
3	$FeCl_2·4H_2O$	T-Hydro	$CaCO_3$	CH_3CN	70
4	$FeCl_2$	T-Hydro	$CaCO_3$	CH_3CN	75
5	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	CH_3CN	89
6	$Fe(acac)_3$	T-Hydro	$CaCO_3$	CH_3CN	81
7	Fe_3O_4	T-Hydro	$CaCO_3$	CH_3CN	<5
8	$FeSO_4·7H_2O$	–	$CaCO_3$	CH_3CN	0
9	–	T-Hydro	$CaCO_3$	CH_3CN	5
10	$FeSO_4·7H_2O$	T-Hydro	–	CH_3CN	10
11	$FeSO_4·7H_2O$	T-Hydro	Na_2CO_3	CH_3CN	21
12	$FeSO_4·7H_2O$	T-Hydro	K_2CO_3	CH_3CN	<5
13	$FeSO_4·7H_2O$	T-Hydro	$NaHCO_3$	CH_3CN	<5
14	$FeSO_4·7H_2O$	T-Hydro	Cs_2CO_3	CH_3CN	<5
15	$FeSO_4·7H_2O$	T-Hydro	LiOH	CH_3CN	<5
16	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	THF	7
17	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	dioxane	60
18	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	*t*-BuOH	19
19	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	toluene	<5
20	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	CH_3CN	75[c]
21	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	CH_3CN	68[d]
22	$FeSO_4·7H_2O$	T-Hydro	$CaCO_3$	CH_3CN	88[e]

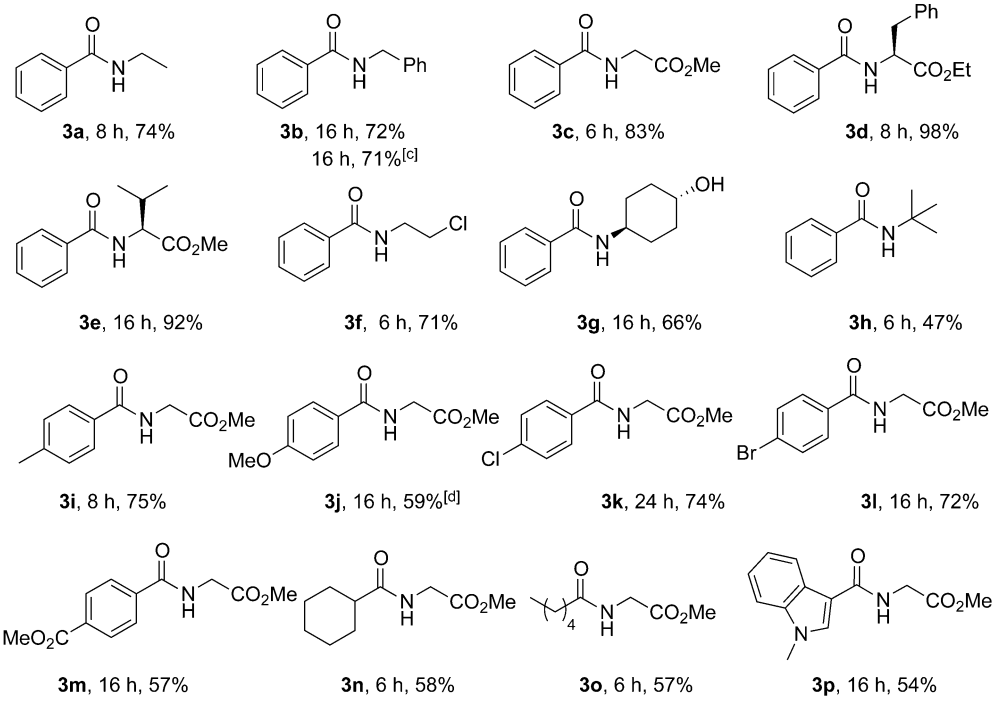
[a] Reactions were carried out with benzaldehyde (1.0 mmol), glycine methyl ester HCl salt (1.2 mmol), base (1.1 mmol), oxidant (1.1 mmol), Fe catalyst (5 mol% unless otherwise indicated), solvent (0.2 mL) at 60 °C for 16 h.
[b] Yields were determined by quantitative GC analysis using dodecane as an internal standard.
[c] 2 mol% catalyst was used.
[d] 1 mol% catalyst was used.
[e] Reaction time was 6 h.

~25% of benzoic acid formed *via* oxidation of the aldehyde and large amounts of unreacted aldehyde. Subsequently, a variety of oxidants including NaOCl, NaO_2Cl, $PhI(OAc)_2$, TEMPO, Oxone® and air was screened but in all cases only 0–5% amide product formation was observed (not shown in Table 1). When the inexpensive peroxide oxidant T-Hydro (70% aqueous *tert*-butyl hydroperoxide) was used as the oxidant, the yield of amide increased to 85% (entry 2). With T-Hydro being identified as an appropriate oxidant, a wide range of commercially available iron salts was screened with varying success (entries 3–7). $FeSO_4·7H_2O$ performed better as compared to other iron catalysts and as it is also non-corrosive and less expensive, this catalyst was selected for further optimissation. Control experiments revealed that all three components, that is, iron catalyst, base and oxidant, are essential for this transformation. In the absence of *tert*-butyl hydroperoxide (TBHP), no amide formation was observed (entry 8) whereas without the iron catalyst and/or the base, only <10% of the product was formed (entries 9 and 10). The effect of bases was also examined and our study showed that replacement of $CaCO_3$ with other bases such as K_2CO_3, $NaHCO_3$ drastically reduced the yield of the amide product (entries 11–15) due to ester hydrolysis under the reaction conditions (60 °C, 16 h) and imine formation.[19] The advantage of $CaCO_3$ could be attributed to its weak basicity and insoluble nature which enables the slow formation of amine and thus avoids the hydrolysis of the ester and imine formation. Screening of solvents was also carried out and it was found that acetonitrile was the best solvent among several others screened (entries 16–19). A catalyst loading of 5 mol% was found to be optimal as decreasing catalyst loading to 2 mol% or 1 mol% reduced the yield to 75% and 68%, respectively (entries 20 and 21). Optimisation of the reaction times showed that the reaction was completed within 6 h at 60 °C (entry 22) as comparable yields were obtained when the reaction was carried out for 16 h at the same temperature (entry 5).

Table 2. Oxidative amidation of aldehydes with primary amine hydrochloride salts.[a,b]



3a–p



[a] Reactions were carried out with an aldehyde (1.0 mmol), primary amine hydrochloride salt (1.2 mmol), calcium carbonate (1.1 mmol), TBHP (70 wt% in water, 1.1 mmol) in acetonitrile (0.2 mL) at 60 °C under an inert atmosphere.

[b] Isolated yields.

[c] Reaction was carried out by *in-situ* HCl salt formation.

[d] 4-Methoxybenzoic acid (20%) was isolated as a by-product.

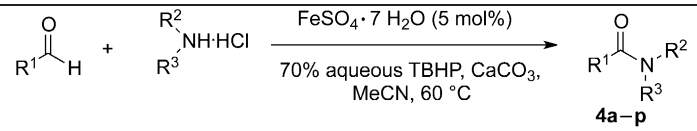
With the optimised conditions in hand, the substrate scope of this reaction was explored with various aldehydes and primary amine hydrochloride salts (Table 2). In general, secondary amides were obtained in good to excellent yields for aldehydes with both electron-donating and electron-withdrawing substituents. The reaction is compatible with various functional groups such as ester (**3c–3e** and **3i–3p**), alkyl chloride (**3f**) and alcohol (**3g**). However, the reaction is sensitive to steric hindrance as the reaction with *tert*-butylamine hydrochloride salt afforded the corresponding amide in moderate yield (**3h**). Aliphatic or heteroaromatic aldehydes were converted into their corresponding amides in moderate to good yields (**3n–3p**).

With the promising results for secondary amide formation, we further explored the possibility of extending the reaction to the more challenging tertiary amides which were not accessible under CuI-$AgIO_3$-catalysed conditions.[17d] Gratifyingly, the reaction worked well with various secondary amine hydrochloride salts, providing tertiary amides in good to excellent yields (Table 3).

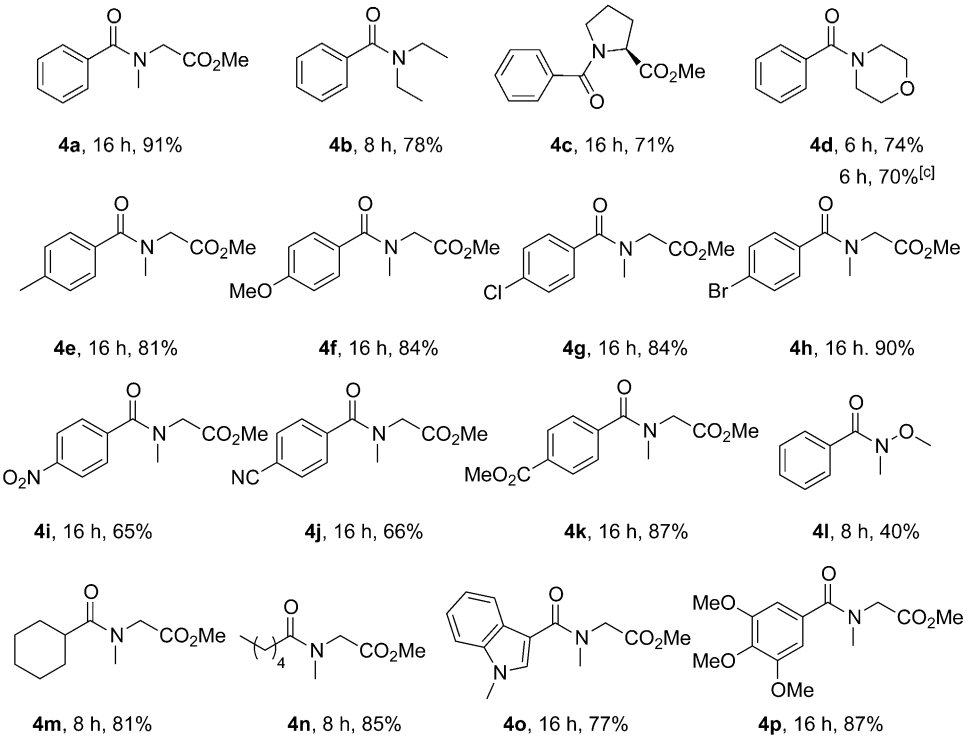
Similar to the case of primary amine salts, the reaction with secondary amine salts is not sensitive to electronic influence as both electron-rich and electron-deficient aldehydes gave good to excellent yields of the desired amides. The reaction is well tolerated with various functional groups, again indicating the broad applicability of this reaction. Surprisingly, aliphatic aldehydes and heterocyclic aldehydes gave much improved yields of the desired amides than in the case of secondary amides (**4m–4o**). Weinreb amides, which are important synthetic intermediates, can also be prepared by this amidation method in moderate yield (**4l**) under our current conditions.

Particularly noteworthy for this reaction is that hydrochloride salts derived from amino acids such as phenylalanine, valine (**3d**, **3e**) and proline (**4c**) underwent amidation to provide the corresponding amides in high yields and without detectable racemisation (see the Supporting Information). This could provide

Table 3. Oxidative amidation of aldehydes with secondary amine hydrochloride salts.[a,b]



4a–p



4a, 16 h, 91% **4b**, 8 h, 78% **4c**, 16 h, 71% **4d**, 6 h, 74%

6 h, 70%[c]

4e, 16 h, 81% **4f**, 16 h, 84% **4g**, 16 h, 84% **4h**, 16 h. 90%

4i, 16 h, 65% **4j**, 16 h, 66% **4k**, 16 h, 87% **4l**, 8 h, 40%

4m, 8 h, 81% **4n**, 8 h, 85% **4o**, 16 h, 77% **4p**, 16 h, 87%

[a] Reactions were carried out with an aldehyde (1.0 mmol), a secondary amine hydrochloride salt (1.2 mmol), calcium carbonate (1.1 mmol), TBHP (70 wt% in water, 1.1 mmol) in acetonitrile (0.2 mL) at 60 °C for the time indicated under an inert atmosphere.

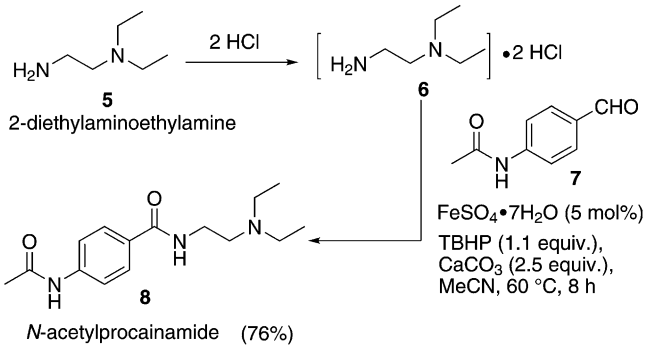
[b] Isolated yields.

[c] Reaction was carried out by *in-situ* HCl salt formation.

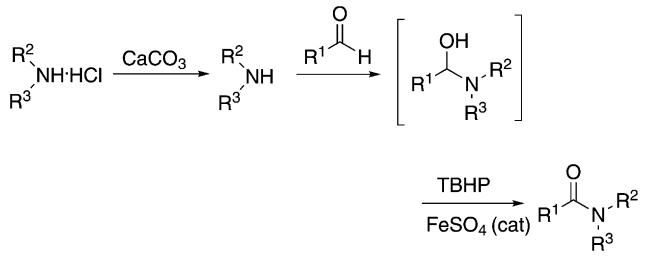
an alternative and economical method for peptide synthesis without using expensive, high molecular weight coupling reagents.[3]

It is known[20] that amines undergo *N*-oxidative decomposition or imine formation (for primary amines) in the presence of TBHP. Our present work and that reported by Li et al.[17d] showed that the use of amine salts is crucial for this oxidative amidation because it is less prone to oxidation by TBHP. The use of insoluble $CaCO_3$ as the base could also be beneficial to the reaction as it enables slow formation of the amine hence minimises the undesired amine oxidation reactions. However, numerous amines are commercially supplied in the free form, which are not suitable for this TBHP-mediated oxidative amidation, we thus sought to expand the substrate scope by *in-situ* formation of amine salts from free amines. This strategy was successfully demonstrated in the case of benzylamine (**3b**) and morpholine (**4d**) and the corresponding amides were obtained in yields comparable to those using commercial amine salts. This strategy was further applied to the synthesis of antiarrhythmic drug *N*-acetylprocainamide (**8**) in which 2-diethylaminoethylamine (**5**) was converted to its bis-hydrochloride salt by the addition of 2.05 equivalents of concentrated hydrochloric acid, followed by the usual amide formation procedures (see the Supporting Information). The desired product (**8**) was isolated in 76% yield (Scheme 2). This one-step synthesis of **8** is much more efficient than a three-step patented route in 16% overall yield.[21] This example demonstrates the potential industrial application of our iron-catalysed oxidative amidation.

The mechanism of this iron-catalysed oxidative amidation was investigated briefly. Initially, in the presence of $CaCO_3$, the amine salt is converted to the free amine which then reacts with the aldehyde. The amidation step could theoretically proceed *via* a hemiaminal,[5,17d] an imine[11g] or less likely a carboxylic acid intermediate under the reaction conditions. How-



Scheme 2. Synthesis of *N*-acetylprocainamide by the *in-situ* formation of a bis-amine HCl salt.



Scheme 3. Proposed mechanism of iron sulphate-catalysed oxidative amidation.

ever, the reaction of benzylamine with benzoic acid and the pre-formed *N*-benzylimine of benzaldehyde did not yield a significant amount of amides, this ruled out the possible involvement of an imine or a carboxylic acid. Hence a hemiaminal intermediate is most likely to be involved as has been proposed previously.[5,17d] Since the oxidation reactions with TBHP in the presence of an iron compound are known to proceed *via* a free radical process,[22] it is likely that this iron-catalysed oxidative amidation reaction could also involve a radical mechanism. This hypothesis was confirmed by the addition of a free radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol (1 equiv.), and this resulted in complete inhibition of amide formation. This supports the mechanism outlined in Scheme 3 where this amidation reaction is likely to proceed through the slow formation of free amine from the amine salt with insoluble $CaCO_3$, followed by reaction with aldehydes to form a hemiaminal intermediate which is subsequently oxidised to the amide by TBHP in the presence of the iron catalyst.

In conclusion, we have identified iron(II) sulphate as an inexpensive and effective catalyst for the oxidative amidation of aldehydes with amine hydrochloride salts. This catalyst has much wider substrate scope than a previously reported catalyst system,[17d] enabling the synthesis of both secondary and tertiary amides under mild conditions. The *in-situ* formation of amine salts further extends the substrate scope of the reaction. This practical method should find wide applications in amide synthesis.

Experimental Section

General Procedure for the Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts

To a mixture of $FeSO_4 \cdot 7H_2O$ (13.9 mg, 0.05 mmol, 5.0 mol%), amine hydrochloride salt (1.2 mmol, 1.2 equiv.) and $CaCO_3$ (110 mg, 1.1 mmol, 1.1 equiv.) in acetonitrile (0.2 mL) was added aldehyde (1 mmol, 1 equiv.) and TBHP (70 wt% in H_2O, 0.16 mL, 1.1 mmol, 1.1 equiv.) under argon atmosphere at room temperature. The reaction vessel was capped and the mixture allowed to stir for 6–24 h at 60 °C. All the volatiles were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel to obtain the amide product.

Acknowledgements

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