



An iron-catalysed synthesis of amides from nitriles and amines

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ABSTRACT

The cheap, commercially available iron complex, Fe(NO₃)₃·9H₂O, has been used to catalyse the formation of amides by the addition of amines to nitriles.

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Amides are an important functional group in a wide range of biologically relevant molecules. Current popular syntheses of amides include the coupling reaction of an acid chloride¹ or a carboxylic acid^{1,2} and an amine, the rearrangement of an oxime³ and the recently reported ruthenium-catalysed reaction between an alcohol and an amine known as dehydrogenative acylation.⁴

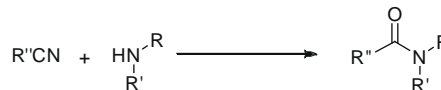
A less frequently reported amide synthesis is the coupling of a nitrile and an amine (Scheme 1).⁵

This reaction has been performed using a ruthenium⁶ or a platinum⁷ catalyst. With concerns regarding the toxicity, expense and diminishing availability of precious metals such as ruthenium and platinum,⁸ we wanted to identify economical and readily available catalysts which would perform the same reactions with comparable yields.

With its environmentally friendly character, considerable natural abundance and low price (FeCl₃ is over 500 times cheaper than RuCl₃ and over 2000 times cheaper than PtCl₂ per mol),⁹ iron was an obvious choice to investigate. Iron complexes are already known to catalyse reactions such as hydroxylations,¹⁰ conjugate additions,¹¹ epoxidations of alkenes¹² and even Grignard reactions.¹³ Recently, work has been published describing the iron-catalysed coupling of phenyl iodides with amides,¹⁴ and a Ritter reaction of alcohols with nitriles to form amides.¹⁵ However, to our knowledge, this is the first example of an iron-catalysed coupling of nitriles and amines to form amides.

Initially, we chose to compare the performance of various iron complexes in the reaction of benzylamine **1** and propionitrile **2**, which leads to the formation of amide **3** after 24 h at 125 °C (Scheme 2).

The results of this initial catalyst screening are summarised in Table 1. In the absence of any catalyst there was no conversion to amide **3** (entry 1). FeCl₂·4H₂O was identified as a catalyst for



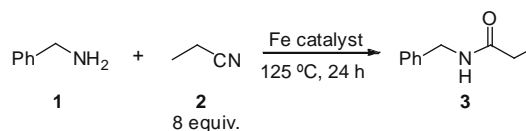
Scheme 1. Formation of amides from nitriles and amines.

amide formation (entries 2–4), although a relatively high catalyst loading was required in order to obtain a good conversion into product. The addition of water did not lead to higher conversions, and we believe that there is sufficient adventitious water present in the undried nitrile to allow full conversion into product.

The use of the ferric salt, FeCl₃·6H₂O was less successful, even though it presumably has a more Lewis acidic character. Iron(II) bromide (entry 6) and iron(II) iodide (entry 7) afforded similar levels of catalytic activity to iron(II) chloride, although iron(III) acetylacetonate (entry 8) gave none of the desired amide, even with a high catalyst loading.

However, iron(III) nitrate nonahydrate (entries 9–11) was found to be an effective catalyst when used at 10 mol % loading.

Formation of imine **4** was observed as a by-product in this reaction, especially for catalysts other than iron(III) nitrate. This transformation has previously been reported using photochemical¹⁶ or electrochemical¹⁷ conditions, and using ruthenium or iron catalysts [pentacyanonitrosyl ferrate(II)].¹⁸ Indeed, in the absence of the nitrile substrate, the imine was formed in 88% conversion with 10 mol % FeCl₂·4H₂O, and in 90% conversion with 10 mol % Fe(NO₃)₃·9H₂O (Scheme 3), even in the absence of an additional oxidant.



Scheme 2. Formation of amide **3** by the reaction of benzylamine **1** and propionitrile **2** in the presence of an iron catalyst.

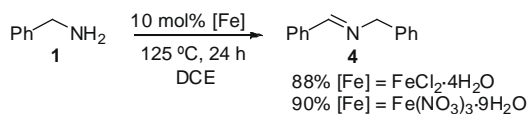
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Table 1
Effect of different iron catalysts and loading on amide formation

Entry	Catalyst	Mol %	Conversion into amide 3 ^a
1	None	—	0
2	FeCl ₂ ·4H ₂ O	5	47
3	FeCl ₂ ·4H ₂ O	10	55
4	FeCl ₂ ·4H ₂ O	25	80
5	FeCl ₃ ·6H ₂ O	15	36
6	FeBr ₂ ·xH ₂ O	10	50
7	FeI ₂ ·xH ₂ O	10	60
8	Fe(acac) ₃	25	0
9	Fe(NO ₃) ₃ ·9H ₂ O	2.5	42
10	Fe(NO ₃) ₃ ·9H ₂ O	10	87
11	Fe(NO ₃) ₃ ·9H ₂ O	20	88

^a Conversion was determined by analysis of the ¹H NMR spectra.

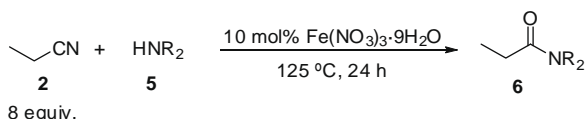
**Scheme 3.** Reaction of benzylamine in the absence of nitrile. DCE = 1,2-dichloroethane.

Fortunately, minimal imine side product was observed when the reaction was performed in the presence of nitrile, using 10 mol % Fe(NO₃)₃·9H₂O as catalyst. The use of additional ligands was examined briefly for the conversion of nitrile **2** into amide **3**. When iron(II) chloride was used as the catalyst, the addition of DPEphos [bis(2-diphenylphosphinophenyl)ether] or ethylenediamine led to no product formation. When 2,2-bipyridyl was used in conjunction with either the iron(II) chloride catalyst or iron(III) nitrate catalyst, the reactions were successful, but afforded no beneficial effect.

When the reaction using 10 mol % iron(III) nitrate (Table 1, entry 10) was repeated in the presence of solvent, the conversion was somewhat reduced using polar solvents (THF, 60%; EtOAc, 66%; and DCE, 77%), and usage of non-polar solvents led to a more significant reduction (toluene, 18%; pentane, 30%).

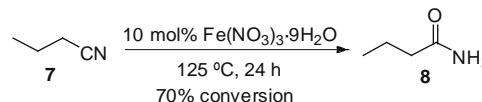
Having concluded from these results that the optimal catalyst system was 10 mol % Fe(NO₃)₃·9H₂O, we then turned our attention to expanding the scope of this reaction, initially investigating the reaction of propionitrile **2** with a range of amines **5** to form amides **6** (Scheme 4 and Table 2).

In general, unbranched primary amines were successful for the formation of secondary amines from nitriles. Benzylamine (entry 1) and substituted variants (entries 2 and 3) were suitable, although anilines (entries 4 and 5) afforded low conversion into product, presumably due to their low nucleophilicity. The simple amines, *n*-butylamine (entry 6) and allylamine (entry 7), afforded the corresponding amides with quantitative conversion. The presence of α -substituents on the amine can have a detrimental effect on reactivity; whilst isopropylamine (entry 10) could be converted into amides efficiently, the more hindered 1-phenylethylamine (entry 11) gave a lower conversion and *t*-butylamine was sufficiently bulky that no secondary amide product was formed. The use of a secondary amine also led to a lower conversion (entry

**Scheme 4.** Optimised reaction with a range of amines.**Table 2**
Reactions of a range of amines with propionitrile to give the corresponding amides **6**

Entry	Amine	Conversion to amide ^a (%)
1	Benzylamine	87 (65)
2	<i>p</i> -Methoxybenzylamine	88 (79)
3	<i>p</i> -Methylbenzylamine	90 (82)
4	Aniline	8
5	<i>p</i> -Fluoroaniline	15
6	<i>n</i> -Butylamine	100
7	Allylamine	100
8	2-Phenylethylamine	89
9	(<i>N</i> -2-Aminoethyl)morpholine	78
10	Isopropylamine	86
11	1-Phenylethylamine	31
12	<i>t</i> -Butylamine	0
13	<i>N</i> -Methylbenzylamine	10
14	Morpholine	88
15	1,3-Diaminopropane	50 (diamide), 42 (monoamide)

^a Conversion was determined by analysis of the ¹H NMR spectra. Figures in brackets indicate isolated yields (%).

**Scheme 5.** Reaction in the absence of amine.

13), although when the less sterically demanding cyclic secondary amine, morpholine (entry 14), was used, the reaction was successful.

In the cases where the amine was unreactive, for either steric or electronic reasons, significant amounts of the primary amide, CH₃CH₂CONH₂, were formed by hydrolysis. The reaction was repeated on butyronitrile **7** in the absence of an amine substrate and this led to the formation of butyramide **8** in 70% conversion (Scheme 5). Although many reactions in which a nitrile is hydrolysed to a primary amide already exist,¹⁹ to our knowledge, this is the first example of an iron-catalysed synthesis of a primary amide via hydrolysis of a nitrile.

We also wanted to explore a range of nitriles as substrates for amide formation. We chose to use allylamine **9** with a range of nitriles **10**, which led to the formation of allylamides **11** (Scheme 6 and Table 3). Aliphatic (entries 1–3) and aromatic nitriles were successfully converted into amides, except for *p*-aminobenzonitrile (entry 8), which afforded none of the expected amide, presumably due to electronic deactivation.

The amide product from entry 6, Table 3 is a precursor to a drug molecule which has diuretic and anti-inflammatory properties.²⁰ In order to demonstrate further the use of this reaction in the synthesis of another biologically active molecule, a simple preparation of the anti-depressant Moclobemide **14** (marketed as Manerix[®])²¹ from commercially available starting materials **12** and **13** was performed (Scheme 7) in a moderate 54% isolated yield.

We assume that the iron catalyst acts as a Lewis acid making the nitrile more susceptible to nucleophilic addition. Two possible routes to the amide product can be considered, either proceeding

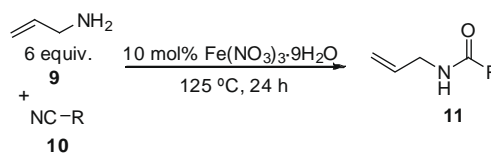
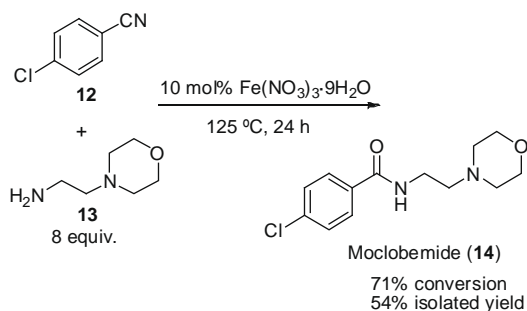
**Scheme 6.** Optimised reaction with a range of nitriles.

Table 3
Reactions of a range of nitriles with allylamine to give the corresponding amides **11**

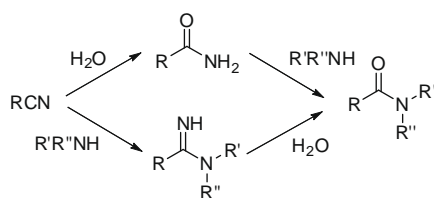
Entry	Nitrile 10	Conversion to amide ^a (%)
1	Acetonitrile	100
2	Butyronitrile	100
3	Octonitrile	87
4	Benzonitrile	50
5 ^b	<i>p</i> -Chlorobenzonitrile	100 (69)
6	<i>p</i> -(Trifluoromethyl)benzonitrile	100 (72)
7	3-Cyanopyridine	100 (98)
8	<i>p</i> -Aminobenzonitrile	0

^a Conversion was determined by analysis of the ¹H NMR spectra. Figures in brackets indicate isolated yields (%).

^b In this example, *n*-butylamine was used in the place of allylamine.



Scheme 7. Synthesis of the anti-depressant Moclobemide using iron catalysis.

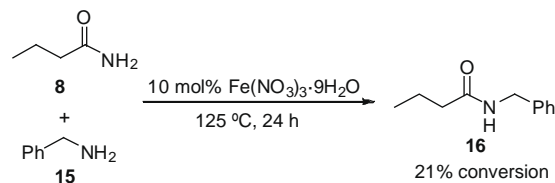


Scheme 8. Proposed pathways for amide formation.

via the primary amide which then reacts with the amine, or alternatively via an amidine intermediate which is then hydrolysed to the amide (Scheme 8).

The metal-catalysed formation of amidines from nitriles and amines has previously been reported.²² Evidence specifically supporting the amidine mechanism, at least for the Pt-catalysed reaction, has been put forward by de Vries and co-workers⁷ who found that when *n*-propylamine was reacted with acetonitrile in the absence of water, the major products formed were mono- and bis-amidines. In addition, for the reaction between propionitrile and 2-aminoethanol, the first product formed is an amidine, which then reacts further, forming the final product, 2-ethyl-2-oxazoline.

We treated primary amide **8** with amine **15** (Scheme 9), which led to a low conversion into secondary amide **16** after 24 h when exposed to the iron catalyst under the same reaction conditions as previously used. Since the conversion is lower than that observed in the overall transformation of nitrile into amide, this suggests that initial primary amide formation is a minor pathway. We, therefore, propose that the amine adds to the iron-complexed nitrile to give an amidine, and that this is then hydrolysed to the amide.



Scheme 9. Low conversion for the reaction of a primary amide with an amine suggests that this is not the major reaction pathway.

The fact that *t*-butylamine is not an effective substrate for amidation indicates that a Ritter-type pathway involving the formation of a carbocation is unlikely to be operating.

In summary, Fe(NO₃)₃·9H₂O acts as a cost-efficient catalyst for the experimentally straightforward synthesis of amides from nitriles and amines.²³ The reaction is most favourable for primary unbranched amines reacting with nitriles which are not too electron rich. Efforts to improve the catalyst, confirm the scope and limitations of these reactions and further mechanistic studies are currently underway in our laboratory.

Acknowledgement

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- Representative experimental procedure*: Fe(NO₃)₃·9H₂O (80 mg, 0.2 mmol, 10 mol %) was added to an oven-dried Schlenk tube. Propionitrile (1.14 mL, 16 mmol) and benzylamine (0.21 mL, 2 mmol) were added dropwise to the Schlenk tube, which was then sealed and the reaction mixture was allowed to stir at room temperature for 10 min before being heated (125 °C) for 24 h. The resulting reaction mixture was filtered through a short plug of silica, eluting with CH₂Cl₂-MeOH (98:2), and then concentrated in vacuo to give a brown oil. The product was recrystallised from CH₂Cl₂-hexane and allowed to stand in a freezer overnight before being filtered. The resulting amides were analysed by ¹H NMR spectroscopy and mass spectrometry and their data were compared with the literature values.