Catalytic Transamidation

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Transamidation of Primary Amides with Amines Using Hydroxylamine Hydrochloride as an Inorganic Catalyst**

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Amide bonds are among the most important linkages in industrial and medicinal chemistry today.[1] While the most common way to make an amide bond is still by using a stoichiometric amount of a coupling reagent, with growing focus on green chemistry, this method is becoming increasingly impractical.[2] Recently, in our group and others, there has been high interest in developing catalytic methods of amide bond formation which avoid using these coupling reagents.[3]

Transamidation is potentially a synthetically useful reaction, but is hindered by the high stability of the carboxamide group. Due to this stability they are rarely used as acylating agents. There are several reports of thermal transamidation reactions,[4] typically requiring very high temperatures (> 180 °C), thus having a very limited substrate range. The use of the yeast *Candidia cylindracea lipase* has been reported by Gotor et al. to promote transamidations between *N*-trifluoroethyl-2-chloropropionamide and various amines[5] and intramolecular transamidations have been reported by Langlois and Buchwald et al.[6]

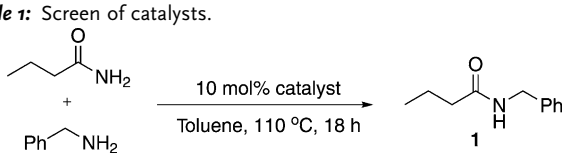
Several metal complexes have been reported to promote transamidation reactions in the last two decades, including $AlCl_3$,[7] $Sc(OTf)_3$,[8] $Ti(NMe_2)_4$[9] and polymer-bound $HfCl_4$.[10] Lanthanide catalysts have been reported to promote transamidation between Fmoc protected lactams and various amines.[11] A report by Myers et al. in 2006 described the in situ activation of primary amides using *N*,*N*-dialkylformamide dimethyl acetals, however 1.3 equivalents of the activating reagent were required, along with a lanthanide catalyst to effect the full transformation.[12] Borate esters have recently been reported to be effective reagents for transamidation reactions between primary amides and amines, however two equivalents of the boron reagent are required for the reaction.[13] Stahl et al. have found some metal complexes will facilitate the equilibration between a secondary amide and an amine when the reaction is thermoneutral.[14]

Clearly, there is a lack of an efficient, catalytic procedure for transamidation reactions between simple primary amides and amines to form secondary and tertiary amides irreversibly. Herein, we report such a procedure utilizing catalytic quantities of hydroxylamine hydrochloride to activate the primary carboxamide and promote a transamidation reaction.

During the course of our on-going efforts into developing catalytic syntheses of amide bonds,[15] we envisioned that a catalytic method of primary amide activation and subsequent irreversible transamidation with an amine would be not only an exceptionally atom efficient and clean reaction (with the only by product being ammonia) but also highly synthetically useful due to the primary carboxamide groups inertness in the presence of many other catalysts and common organic reagents. We initially screened a number of catalysts we reasoned may activate the primary amide towards nucleophilic attack (Table 1).

Pleasingly, simple hydroxylamine salts gave the best conversion into secondary amide after 18 h. Although several other hydroxylamine derivatives showed promise as catalysts, we were intrigued by the possibility of using hydroxylamine hydrochloride as a purely inorganic, metal-free catalyst. The free base of hydroxylamine is only available in water or ethanol, so a direct comparison between the hydrochloride salt and free base is not possible (Table 1, entries 4 and 5). The

Table 1: Screen of catalysts.



Entry	Catalyst	Conversion into **1** [%][a]
1	*n*-butyraldoxime	36
2	benzaldoxime	30
3	hydroxylamine sulfate	100
4	hydroxylamine hydrochloride	100
5[b]	hydroxylamine	0
6	*N*-methylhydroxylamine hydrochloride	96
7	*O*-methylhydroxylamine hydrochloride	91
8	*N*,*N*-diethylhydroxylamine hydrochloride	71
9	*O*-benzylhydroxylamine	13
10	*O*-benzylhydroxylamine hydrochloride	73
11	hydrazine monohydrate	23
12	*N*,*N*′-diphenylthiourea	13
13[c]	benzylamine hydrochloride	46
14	hydrochloric acid	51
15	nitric acid	43
16	triethylamine hydrochloride	43
17	ammonium chloride	37
18	no catalyst	10

[a] Conversions determined by ^{1}H NMR spectroscopy. [b] Reaction run in ethanol, H_2NOH cannot be extracted into toluene. [c] Added as additional 10 mol% benzylamine hydrochloride salt.

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complete lack of activity when hydroxylamine free base was used could be explained by the use of ethanol as a solvent, as when hydroxylamine hydrochloride was used as catalyst in ethanol no activity was observed. The use of *O*-benzylhydroxylamine free base in toluene compared with *O*-benzylhydroxylamine hydrochloride in toluene shows the presence of the acid salt has a positive effect on the conversion into secondary amide (Table 1, entries 9 and 10). Interestingly, the use of just acid as a catalyst (Table 1, entries 13–15) showed some activity in all cases, although they were not as effective as hydroxylamine hydrochloride.

Next, different solvents and temperatures were screened using hydroxylamine hydrochloride as the catalyst. Toluene at 105 °C with a varying amount of $H_2NOH{\cdot}HCl$ (depending on the substrates used) was found to be the optimal combination, so a range of primary amides and amines was screened under these conditions to test the tolerance of this new reaction (Table 2).

A wide range of functional groups has been shown to be tolerated by the reaction conditions, including halogens (Table 2, entries 3, 11, 22), free phenolic hydroxy groups (entry 9), heterocycles (entries 5, 7, 13), alkenes (entry 2), and alkynes (entry 18). Aliphatic amides generally gave the highest conversions, with some substrates requiring only 10 mol% hydroxylamine hydrochloride to reach complete conversion in 16 h (entries 1, 2, 17).

Other notable observations from this substrate screening are that Boc protecting groups are unaffected in the reaction (entries 7 and 14), allowing for selective acylation of one nitrogen atom in a mono-protected diamine, or selective coupling of a Boc-protected amino amide to an amine. Ester protected amino acids can also be *N*-acylated without any loss of the ester functionality. Monosubstituted ureas can be selectively acylated, yielding unsymmetrical ureas (entry 15).

Formamide can be used as a formylating agent in this reaction, giving *N*-formyl products, including [*N*-formyl(*O*-benzyl)]glycinate (entries 16–19). Slight racemization at the α-position to the carbonyl was observed when 1-Boc-L-prolinamide was used as a starting material (entry 7).

In the interest of atom efficiency, we have run these reactions at a temperature of 105 °C, allowing for the use of a catalytic amount of hydroxylamine hydrochloride to activate the primary amide group. However, several aliphatic amide substrates gave good conversions into secondary amide at lower temperatures when an increased amount of hydroxylamine hydrochloride was used (Table 3). The benzoic primary amide, however, was very slow to react at 80 °C, even with 1 equivalent of hydroxylamine hydrochloride present (Table 3, entry 8).

Most notable in Table 3 are the examples using formamide. At room temperature (20 °C), the uncatalyzed reaction gave <1% conversion. Addition of just 30 mol% hydroxylamine hydrochloride increased this to 100% (entries 2 and 3). This is a remarkable result when compared with other catalytic formylation reactions which generally use much more active formylating agents (formic acid, formaldehyde) and are run at higher temperatures.[3]

To understand this chemistry further, we conducted a series of experiments to gain an insight into possible

Table 2: Range of primary amides or primary amide equivalents and amines used in the transamidation reaction.[a]

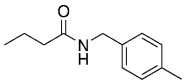
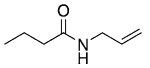
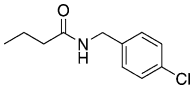
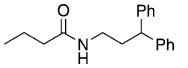
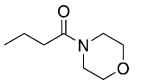
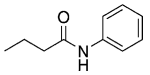
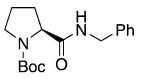
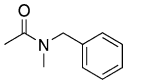
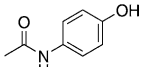
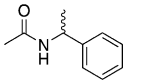
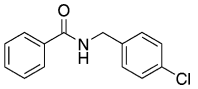
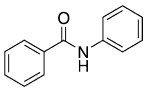
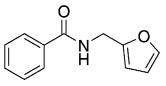
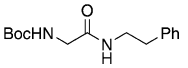
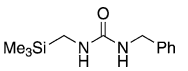
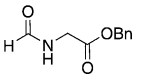
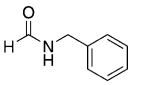
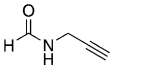
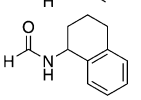
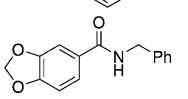
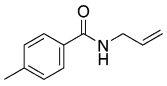
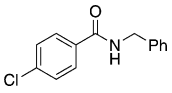
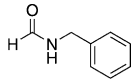
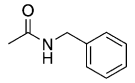
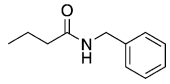
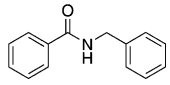
Entry	Product	Mol% $H_2NOH{\cdot}HCl$	*t* [h]	Conv. [%][b]	Yield [%]
1		10	16	100	81
2		10	16	100	86
3		10	20	100	91
4		20	20	100	83
5		20	20	95	90
6		50	20	63	–
7	 88% *ee*	50	24	98	87
8		50	24	62	–
9		50	24	83	76
10		50	24	90	81
11		50	24	88	71
12		50	24	70	59
13		50	24	63	–
14		50	22	79	71
15[c]		50	22	69	–
16		10	22	100	91
17		10	16	100	86
18		10	20	98	87
19		10	20	100	82
20		50	24	86	74

Table 2: (Continued)

Entry	Product	Mol% $H_2NOH{\cdot}HCl$	*t* [h]	Conv. [%][b]	Yield [%]
21		50	22	68	–
22[d]		50	24	79	70

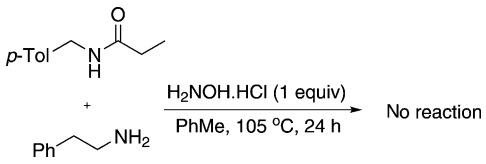
[a] All reactions 1 M in PhMe, 1:1 amide:amine, unless stated otherwise. [b] Conversions determined by ^{1}H NMR spectrsocopy. [c] Starting materials were *N*-[(trimethylsilyl)methyl]urea and benzylamine. [d] Run at 150 °C in xylenes.

Table 3: Representative examples of primary amides and amines used in the transamidation reaction at lower temperatures.

Entry	Product	*T* [°C]	Mol% $H_2NOH{\cdot}HCl$	Conv. [%][b]
1		50	10	94
2		20	30	100
3		20	0	<1
4		80	50	100
5		50	100	78
6		80	50	80
7		50	100	64
8		80	100	25

[a] All reactions run for 16 h, 1:1 amide:amine, 1 M in PhMe. [b] Conversions determined by ^{1}H NMR spectroscopy.

mechanisms by which this reaction may be operating. It became clear to us that once the reaction reaches the secondary or tertiary amide product, it is irreversible. Running a secondary amide in the presence of an amine under the same reaction conditions did not lead to a crossover (Scheme 1). Even increasing the ratio of amine to five



Scheme 1. Crossover with a secondary amide not observed under the reaction conditions.

equivalents (compared with the secondary amide) did not result in a crossover reaction. This feature of the reaction is highly synthetically useful, as even in the presence of an excess of another nucleophile, no breakdown of the secondary amide product is observed.

In the absence of catalyst, only 10% conversion into secondary amide was observed after 18 h (Table 1, entry 18), therefore the primary amide must be activated in some way by the hydroxylamine hydrochloride. In the absence of acid, a marked decrease in conversion is seen (Table 1, entries 9 and 10), suggesting the acid is participating in the reaction mechanism in some way.

^{1}H NMR experiments run in [D_8]toluene showed a clear interaction between the NH amide protons and *O*-methylhydroxylamine hydrochloride (Table 4), suggesting a hydrogen bonding interaction between the two species in the

Table 4: Chemical shift of amide protons is affected by the presence of *O*-methylhydroxylamine hydrochloride.

Entry	Conditions[a]	NH shifts [ppm]
1	0.05 M butyramide	4.37, 4.70
2	0.1 M butyramide	4.40, 5.25
3	0.2 M butyramide	4.37, 5.23
4	0.05 M butyramide-$MeONH_2{\cdot}HCl$	4.40, 4.68
5	0.1 M butyramide-$MeONH_2{\cdot}HCl$	4.37, 5.53
6	0.2 M butyramide-$MeONH_2{\cdot}HCl$	4.53, 5.86

[a] In [D_8]toluene, 55 °C.

reaction solvent (Figure 1). In the presence and absence of *O*-methylhydroxylamine hydrochloride, different effects on chemical shift are observed as the concentration is increased.[16]

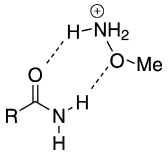
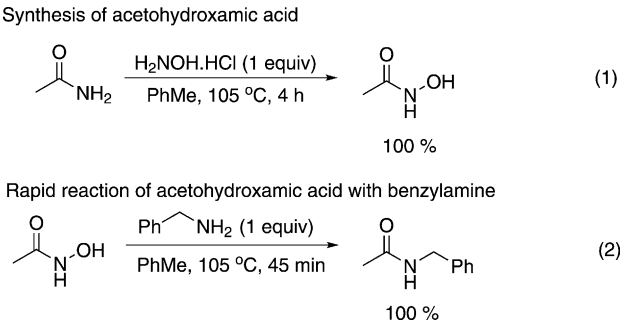


Figure 1. Proposed method of primary amide activation through hydrogen bonding.

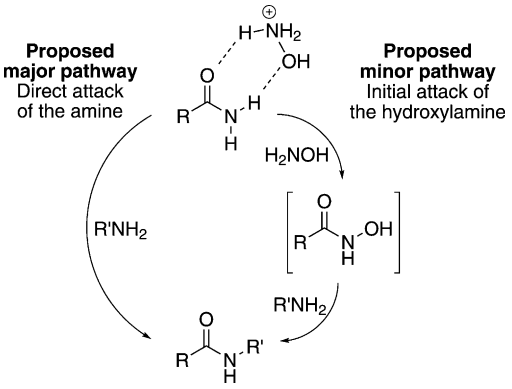
It is also possible that the hydroxylamine attacks the "activated" primary amide, generating an intermediate hydroxamic acid. Indeed, when hydroxylamine hydrochloride and acetamide (in a 1:1 ratio) were subjected to the reaction conditions, complete conversion into the hydroxamic acid was observed within 4 h. Furthermore, when acetohydroxamic acid and benzylamine were subjected to the reaction conditions, complete conversion into the secondary amide was observed within 45 min, suggesting that, if the hydroxamic acid is formed, transformation into the product (and thus regeneration of the catalyst) is very rapid (Scheme 2).

Kinetic studies were then performed by following the reaction of butyramide and benzylamine (with varying amounts of hydroxylamine hydrochloride present) over time (see Supporting Information). The results show an approx-



Scheme 2. Hydroxamic acid reactions.

imate first-order relationship between concentration of hydroxylamine hydrochloride and the initial rate of reaction. Therefore, as one equivalent of hydroxylamine is involved in the rate-determining step of the reaction, the slow step of the mechanism could be either initial activation of the primary amide (formation of the hydrogen-bonded complex) or attack of this complex (Scheme 3). The relative pK_a of the amine and



Scheme 3. Proposed reaction pathways.

hydroxylamine dictate that the amine is more basic and thus more nucleophilic towards the carbonyl—the opposite order of reactivity seen in S_N2 reactions at saturated centers. Therefore we propose the major pathway to be attack of the amine onto the hydrogen bonded primary amide–hydroxylamine complex and that this is the rate-determining step.[17]

In conclusion, we have reported a novel method for the transamidation of primary carboxamides with primary or secondary amines to give secondary or tertiary amides, utilizing catalytic quantities of hydroxylamine hydrochloride to activate the usually chemically robust primary amide group. A proposed mechanism of primary amide activation through a hydrogen-bonding complex is also presented with initial ^{1}H NMR and kinetics studies. Further investigations into improving the efficiency of the catalyst and the room temperature formylations are on-going in our laboratory.

Experimental Section

The primary amide species (2 mmol) was added to an oven-dried Radleys carousel tube, followed by toluene (2 mL) and the amine species (2 mmol, see Table 2). Hydroxylamine hydrochloride was then added and the carousel tube was sealed before the reaction mixture was heated at 105 °C. After being allowed to cool to room temperature, the solvent was removed in vacuo on a rotary evaporator and 20 mL dichloromethane added. The reaction mixture was then washed with water (2 × 30 mL) to remove the hydroxylamine hydrochloride, and the resulting organic layer was dried over $MgSO_4$. The solution was concentrated in vacuo and then analyzed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. Purification by column chromatography and recrystallization was carried out as necessary.

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