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Catalytic Acylation of Amines with Aldehydes or Aldoximes

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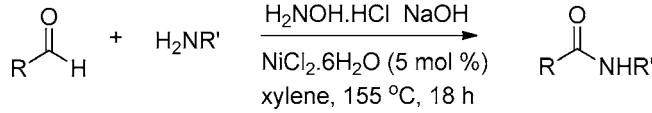
ABSTRACT



The simple nickel salt $NiCl_2{\cdot}6H_2O$ catalyzes the coupling of aldoximes with amines to give secondary or tertiary amide products. The aldoxime can be prepared in situ from the corresponding aldehyde. The use of ^{18}O-labeled oximes has allowed insight into the mechanism of this reaction.

The amide bond is one of the most important in contemporary chemistry, with applications in pharmaceutical, agrochemical, and polymer synthesis.[1,2] Currently, the most popular methods of amide synthesis rely on activation of a carboxylic acid with a coupling agent and reaction with an amine. However, this methodology suffers from the inherent drawback of producing a stoichiometric amount of waste product.[3] Enzymatic methods are also available, although high isolation costs and somewhat limited substrate ranges can be problematic.[4] Increasing attention is now being devoted to developing catalytic amide bond syntheses.[5] Employing metal catalysis in amide syntheses also creates the possibility to start from substrates other than carboxylic acids.[6] Several methods for oxidation of an aldehyde via an aminol intermediate to the amide have been developed, all using a stoichiometric amount of oxidant.[7] More recently, lanthanide catalysts have been shown to be active for the amidation of aldehydes by amines.[8]

There have been several recent reports of the metal-catalyzed rearrangement of oximes into primary amides from our research group[9] and from others.[10] The majority of reports has used precious metal complexes to catalyze the reaction, although our recent work has demonstrated that zinc and indium salts are also effective. The involvement of a nitrile intermediate in these reactions seems likely since for reactions run in the presence of acetonitrile acetamide is formed and the oxime is converted into a nitrile. There are also reports of the metal-catalyzed coupling of nitriles with

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(7) For examples, see; (a) Ishihara, K.; Yano, T. *Org. Lett.* **2004**, *6*, 1983–1986. (b) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065. (c) Ekoue - Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429–3432. (d) Chan, J.; Baucom, K. D.; Murry, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14106–14107. (e) Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, *49*, 5732–5735. (f) Gao, J.; Wang, G. W. *J. Org. Chem.* **2008**, *73*, 2955–2958. (g) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (h) Tillack, A.; Rubloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523–528.

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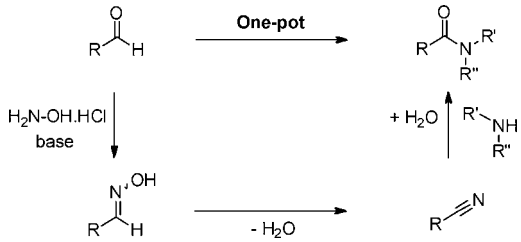
amines leading to secondary and tertiary amides.[11] We therefore reasoned that by performing the oxime to amide rearrangement in the presence of an amine that it may be possible to form secondary and tertiary amides. By generating the oxime in situ from the aldehyde, this would lead to a one-pot conversion of aldehydes into amides (Scheme 1).

Scheme 1. Proposed Scheme for Amide Formation

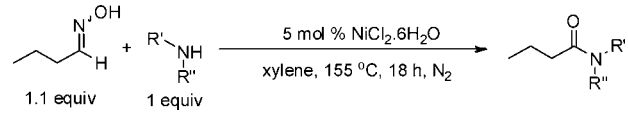


Initially, we focused on identifying a suitable catalyst for the conversion of an oxime into a secondary amide, and we used the coupling of butyraldehyde oxime with benzylamine as a model reaction. The use of indium nitrate or $Ru(PPh_3)_4H_2$ led mainly to the formation of undesired primary amide. Zinc triflate was more successful, giving the secondary amide as the major product, although further reactions to improve the selectivity were unsuccessful. However, $NiCl_2{\cdot}6H_2O$ gave a very high conversion to the secondary amide, and further optimization studies allowed us to reduce the catalyst loading and reaction time to 5 mol % and 18 h with a small excess of oxime when the reaction was run at a temperature of 155 °C, although reasonable reactivity was also observed at 110 °C. The use of a 1:1 ratio of oxime to amine gave marginally lower yields in some cases. We then examined the reaction for a range of amines with butyraldehyde oxime and a range of oximes with benzylamine, which are presented in Tables 1 and 2.

Most substrates gave a very high conversion into amide, indicating that the reaction tolerates a wide range of functional groups on either substrate, including halogens, alkenes, and heterocycles, as well as some secondary and α-branched amines. Although the amine in entry 9 was used successfully, more hindered secondary amines were poor substrates (see Supporting Information). Enantiopurity was completely preserved when an amine containing a chiral center was used in the reaction (Table 1, entry 12). Using particularly sterically hindered amines resulted in lowered conversions into the secondary amide, as did using less nucleophilic amines. The presence of a second nucleophilic nitrogen atom in the molecule also lowered conversions, possibly due to coordination of this nitrogen to the catalyst. As has been found with other metal-catalyzed rearrangements of oximes, ketoximes and oxime ethers were unreactive in these reaction conditions.

(11) (a) Murahashi, S. I.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* **1986**, *108*, 7846–7847. (b) Cobley, C. J.; van den Heuvel, M.; Addabi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467–2470. (c) Allen, C. L.; Lapkin, A. A.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 4262–4264.

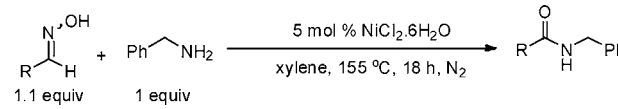
Table 1. Range of Amine Substrates[a]



entry	amine	conversion[b] (%)	isolated yield (%)
1	4-chlorobenzylamine	100	83
2	piperonylamine	100	89
3	5-methylfurfurylamine	100	90
4	*n*-butylamine	100	96
5	allylamine	100	79
6	tryptamine	67	-
7[c]	aniline	100	91
8[c]	4-fluoroaniline	68	-
9	*N*-methylbenzylamine	100	89
10	morpholine	100	83
11	pyrrolidine	81	70
12	(*R*)-1-methylbenzylamine	100	91 (>95% ee)

[a] Additional examples in Supporting Information. [b] Determined by NMR. [c] Run with 1.2 equiv of oxime.

Table 2. Range of Oxime Substrates[a]



entry	oxime	conversion[b] (%)	isolated yield (%)
1	acetaldoxime	100	88
2	heptaldoxime	100	89
3	3-phenylpropaldoxime	100	90
4[c]	benzaldoxime	70	62
5[c]	4-fluorobenzaldoxime	100	83
6	4-methoxybenzaldoxime	36	-
7	3-chlorobenzaldoxime	71	66
8	piperonaldoxime	100	76
9	2-naphthaldoxime	92	76

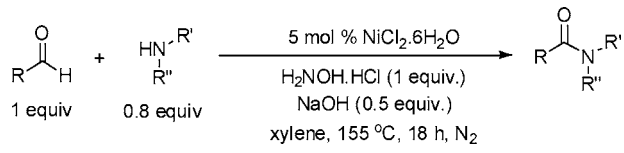
[a] Additional examples in Supporting Information. [b] Determined by NMR. [c] Run with 1.2 equiv of oxime.

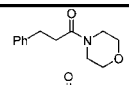
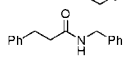
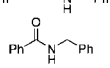
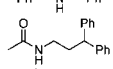
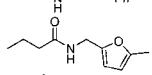
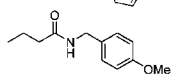
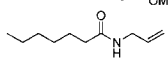
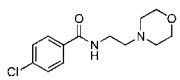
We decided to develop a one-pot conversion of aldehydes into secondary and tertiary amides by forming the aldoxime in situ. This required the addition of hydroxylamine hydrochloride (and a base; see Supporting Information) to the reaction mixture of an aldehyde, an amine, and the nickel catalyst. A range of different aldehydes and amines were coupled to form the respective amides using these reaction conditions (Table 3).

A broad range of amides were successfully synthesized with good isolated yields using this new methodology. As with the reaction using the preformed oxime, several functional groups have been shown to be tolerated.

During the course of our studies on the rearrangement of oximes and our expansion of this reaction to allow formation

Table 3. Use of Aldehyde Substrates



entry	amide	conversion[a] (%)	isolated yield (%)
1		92	80
2		100	81
3		100	91
4		100	81
5		100	83
6		95	78
7		100	92
8		86	73

[a] Determined by NMR.

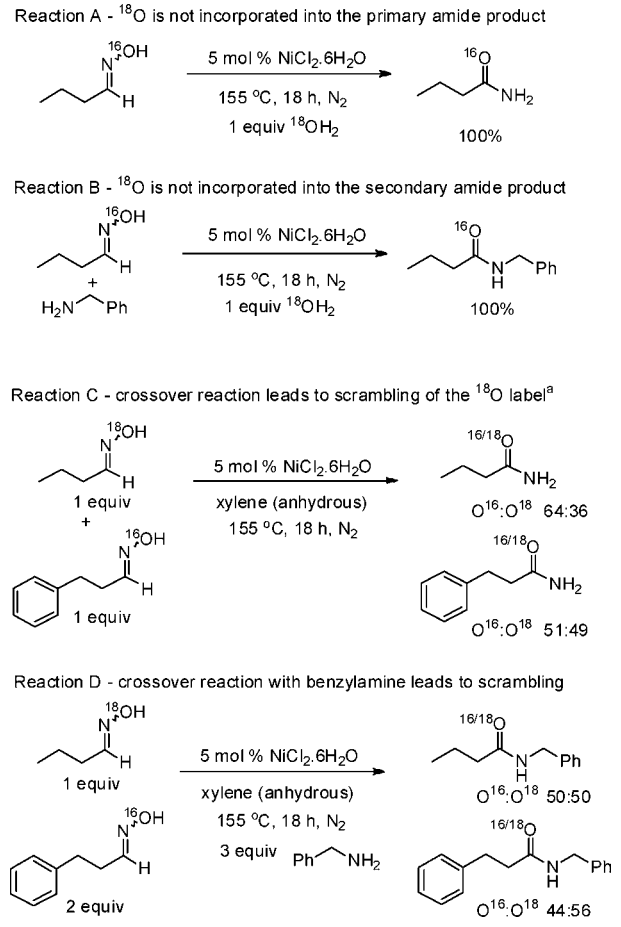
of secondary and tertiary amides, we have performed several experiments to gain further insight into the mechanisms which might be operating.

From previously reported work by Kopylovich et al., we could assume that the oxime binds to the nickel through the nitrogen.[12] Loss of water from the nickel−oxime complex would generate a nitrile.[13] We investigated isolating the nitrile intermediate by running the reaction of 2-phenylacetaldoxime in a 10-fold excess butyronitrile. This did allow the reaction to be intercepted at the nitrile stage, and the products isolated from this reaction were 2-phenylacetonitrile and butyramide.

After generation of a nitrile intermediate, one possible reaction pathway is hydration of the nitrile to the primary amide and subsequent transamidation or N-alkylation to give a secondary or tertiary amide. We found there was no reaction of butyramide with benzylamine under the reaction conditions, implying that the mechanism does not proceed via the primary amide. Alternatively, addition of the amine to the nitrile would generate an amidine intermediate, which could subsequently be hydrolyzed by water liberated in an earlier step.[14] However, we also found the reaction of benzylamine with propionitrile under these reaction conditions to be very slow and gave very low conversion into a secondary amide. These reactions supported the formation of a nitrile intermediate in the reaction but also implied that hydration to the primary amide and addition of the amine to give an amidine intermediate were not significant mechanism pathways.

We then performed a series of experiments using ^{18}O labels.[15] The rearrangement of unlabeled butyraldehyde oxime was performed in the presence of $^{18}OH_2$, which afforded the primary amide without incorporation of the ^{18}O label (Scheme 2, reaction A). When butyraldehyde oxime was reacted with benzylamine in the presence of $^{18}OH_2$, we again saw no incorporation of the ^{18}O label (Scheme 2, reaction B). These experiments suggest that loss of water from the oxime or addition to the nitrile is not occurring to any significant extent during the reaction, as it was expected that $^{16}OH_2$ exchange with $^{18}OH_2$ would have been facile and rapid, leading to incorporation of the ^{18}O into the amide product, at least to some extent. The possibility of an

Scheme 2. Reactions Using ^{18}O-Labeled Substrates[a]



[a] 92% isotopic enrichment in starting oxime.

(12) Makarycheva-Mikhailova, A. V.; Gushchin, P. V.; Kopylovich, M. N.; Ganebnykh, I. N.; Charushin, V. N.; Haukka, M.; Pombeiro, A. J. L.; Kukushkin, V. Y. *Inorg. Chem. Commun.* **2006**, *9*, 869–871.

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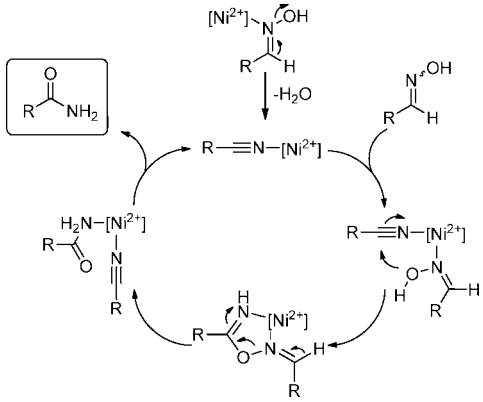
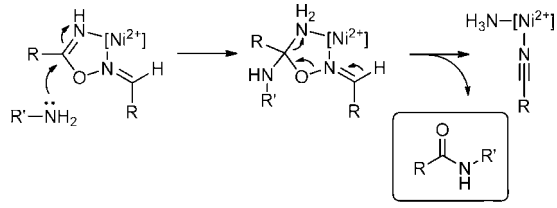
intramolecular oxygen transfer was also deemed to be unlikely, as the reaction involving ^{18}O-labeled butyraldehyde oxime and nonlabeled 3-phenylpropanaldoxime led to scrambling of the label in the amide products (Scheme 2, reactions C and D).

On the basis of the results of these experiments, we now propose the following bimolecular reaction mechanism (Scheme 3). Intramolecular attack on the nitrile by a coordinated oxime[16] leads to a five-membered cyclic intermediate. Decomposition of this intermediate gives the primary amide product and another coordinated nitrile to continue the catalytic cycle. In the presence of an amine, the same cyclic intermediate could be intercepted, and decomposition would then give a secondary or tertiary amide product (Scheme 4).

Scheme 3. Proposed Mechanism of Oxime Rearrangement



Scheme 4. Proposed Interception of the Cyclic Intermediate



Evidence of a bimolecular mechanism operating in the metal-catalyzed rearrangement of aldoximes into primary amides has been reported by Johnson and Miller[17] who found that the reaction can be described by two consecutive pseudofirst-order rate constants.

Chang and co-workers have reported their investigation into the mechanism of rearrangement of an aldoxime into a primary amide using a rhodium catalyst.[18] They also suggest a bimolecular process, whereby a coordinated nitrile is attacked by the hydroxy group of a molecule of oxime, which itself is associated with the metal center through the nitrogen atom. Their mechanism is supported by the significant rate increase seen when a catalytic amount of nitrile is added to the reaction.

Although we have seen evidence to support our proposed mechanism, other possible pathways cannot be completely excluded at this stage. In the reaction involving one labeled and one unlabeled oxime (Scheme 2, reaction C), the label was not completely scrambled, leaving the butyramide product with a higher proportion of ^{18}O than the other amide. This leads to questioning whether an intramolecular mechanism is also operating alongside our proposed intermolecular one, as a minor reaction pathway. Additionally, in the course of their work on novel ligand syntheses, Kukushkin et al. have shown when platinum−nitrile complexes are treated with an oxime, addition of the hydroxy group across the carbon−nitrogen triple bond proceeds with the nitrile remaining coordinated to the metal and the oxime uncoordinated.[19] It should be noted however that the platinum−nitrile complexes were preformed before addition of the oxime. Nonetheless, this observation indicates the possibility of another reaction pathway in which a coordinated nitrile is attacked by a free oxime in the reaction.

Herein, we have reported a novel synthesis of secondary and tertiary amides from the coupling of an oxime (which can be generated in situ from an aldehyde and hydroxylamine hydrochloride) and an amine. This current method shows clear advantages over other amide syntheses due to its low cost, readily available catalyst, and simple experimental procedure. We have also reported our efforts to elucidate the mechanism of this reaction via a labeling study. Work to improve the catalyst efficiency and expand the substrate range as well as further experiments to investigate the mechanism of this reaction are now in progress in our laboratory.

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Supporting Information Available: Experimental procedures, characterization of amides, and copies of ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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