



Cost efficient synthesis of amides from oximes with indium or zinc catalysts

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ABSTRACT

Simple indium and zinc salts have been successfully used as catalysts for the rearrangement of oximes into primary amides. The direct synthesis of nitriles or primary amides from aldehydes has also been demonstrated using these inexpensive catalysts.

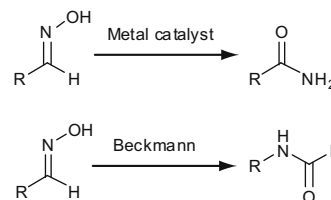
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Amides are one of the most important and prolific functional groups found in biologically relevant molecules. In a recent industry-led survey, the need for catalytic atom efficient amide formation was highlighted.¹ The ACS Green Chemistry Institute Pharmaceutical Roundtable has also identified amide formation avoiding poor atom economy reagents as the highest priority area.² Currently, the most popular methods for amide production are from an acid chloride/carboxylic acid and an amine, or involve the use of stoichiometric coupling reagents such as carbodiimides, but neither of these methods is without drawbacks.³ Enzymatic methods are also available, although isolation costs and somewhat limited substrate ranges can present challenges.⁴

The metal-catalyzed rearrangement of aldoximes into primary amides is a completely atom efficient method for forming primary amides (Scheme 1) and recently, rhodium,⁵ iridium⁶ and ruthenium⁷ catalysts have been shown to be effective for this reaction. During the preparation of this Letter, reports of a gold/silver co-catalyzed⁸ and palladium-catalyzed⁹ variant appeared, along with the use of InCl_3 (5 mol %) for nitrile hydrolysis and oxime rearrangement.¹⁰ The synthetic outcome contrasts with the traditional Beckmann rearrangement where the hydrogen rarely migrates.^{11,12}

However, the currently reported catalysts all share the problem of high cost. Herein, we report simple, lower cost metal salts that catalyze the rearrangement of aldoximes into primary amides as efficiently as the precious metal catalysts currently used for this transformation and demonstrate the potential for the direct conversion of aldehydes into primary amides or nitriles using these new catalysts.

Initially, we screened a number of simple catalysts to compare their reactivity with the reported ruthenium, iridium and rhodium catalysts. While the majority of the catalysts tested showed no activity towards the aldoximes or gave high conversions to the dehydration product, we found that $\text{In}(\text{OTf})_3$, ZnI_2 , CuBr and $\text{Ca}(\text{OH})_2$ all catalyzed the rearrangement of butyraldoxime into

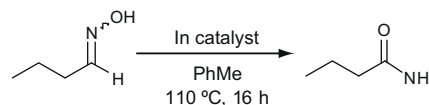


Scheme 1. Comparison of oxime rearrangements.

butyramide with over 60% conversion. Indium triflate provided essentially complete conversion, and we investigated the use of other $\text{In}(\text{III})$ catalysts for the isomerization reaction (Table 1). The cheaper chloride and nitrate salts afforded a similar reactivity to the more expensive triflate, and reasonable conversions were obtained even with 0.1 mol % of catalyst (entries 2, 4 and 7). The use of 0.4 mol % of $\text{In}(\text{NO}_3)_3$ (entry 6) was chosen as a lower limit to catalyze the rearrangement.

Table 1

Use of indium catalysts



Entry	Catalyst	Catalyst loading (mol %)	Conversion ^a (%)
1	$\text{In}(\text{OTf})_3$	1	99
2	$\text{In}(\text{OTf})_3$	0.1	67
3	InCl_3	1	98
4	InCl_3	0.1	65
5	$\text{In}(\text{NO}_3)_3$	1	98
6	$\text{In}(\text{NO}_3)_3$	0.4	98
7	$\text{In}(\text{NO}_3)_3$	0.1	88
8 ^b	$\text{In}(\text{NO}_3)_3$	0.01	32

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

^b Run in xylene, 150 °C, 16 h.

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Attempts to reduce the reaction temperature by performing the reaction at reflux in lower boiling solvents resulted in lower conversions into the primary amide (ethanol, 80 °C, 78%; hexane, 90 °C, 58%; ethyl acetate, 80 °C, 49%). When the reaction was run in the presence of 5 mol % triflic acid in the absence of any indium salt, only 3% of amide was formed, along with 6% of the corresponding nitrile. This result suggests that the metal catalyst is directly involved in the isomerization process.

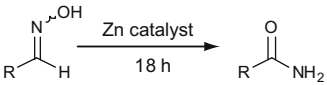
Since indium catalysts are still relatively expensive,¹³ we also chose to optimize the reaction using a zinc catalyst¹⁴ as a cheaper alternative, even though a higher catalyst loading was required (Table 2). Zinc chloride was found to be more effective for the formation of benzamide (Table 2, entry 1), with zinc nitrate being more effective for the formation of butyramide (Table 2, entry 3). These catalysts were marginally superior to the triflate and iodide catalysts. Using 10 mol % catalyst loading at 100 °C in heptane,¹⁵ ZnCl₂ again gave the best conversion into benzamide (Table 2, entry 7), and Zn(NO₃)₂ the best conversion into butyramide (Table 2, entry 8).

To assess the scope of the reaction, various oximes were subjected to the indium and zinc catalysts under the optimized conditions (Table 3). The majority of oxime substrates were transformed cleanly into the product amides with either catalyst. However, the indium catalyst was inefficient for the isomerization of the 4-methoxy substrate (Table 3, entry 7), and failed to effect isomerization of the furyl substrate (Table 3, entry 17), with unreacted starting material being present in both cases, even after longer reaction times. The electron-rich nature of these substrates may make the oxime too stable for reaction.

Fortunately, the zinc catalyst was effective for both these transformations (Table 3, entries 8 and 18). It would appear that the reaction is sensitive to steric effects, since the 2-methyl substrate (entries 21 and 22) underwent limited isomerization under the reaction conditions.

In all cases, oximes were used as a mixture of (*E*)- and (*Z*)-isomer. When reactions were stopped early, there was no change in the ratio of isomers in the unreacted starting material. We therefore assume that either both isomers react at the same rate, or that equilibration is faster than rearrangement.⁶ While oxime ethers and ketoximes were found to be unreactive in the presence of these zinc and indium catalysts, an interesting result was observed when the reaction was carried out in acetonitrile as solvent.¹⁶ Benzaldoxime was converted into benzonitrile with good isolated yield, and an equal amount of acetamide was observed (Scheme 2). This is consistent with a mechanism involving dehydration of the oxime into a nitrile followed by rehydration of the nitrile to give an amide, which in the presence of a nitrile leads to the observed crossover.

Table 2
Use of zinc catalysts

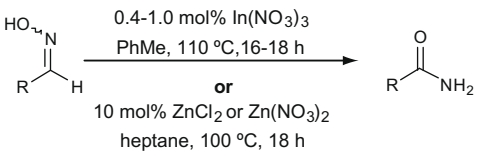


R = phenyl, *n*-butyl

Entry	Catalyst (mol %)	Solvent (temp [°C])	Conversion ^a (%) R = Ph	Conversion ^a (%) R = <i>n</i> -Bu
1	ZnCl ₂ (8)	PhMe (110)	92	68
2	ZnI ₂ (8)	PhMe (110)	58	66
3	Zn(NO ₃) ₂ (8)	PhMe (110)	75	95
4	Zn(OTf) ₂ (8)	PhMe (110)	90	80
5	ZnCl ₂ (10)	PhMe (110)	93	—
6	Zn(NO ₃) ₂ (10)	PhMe (110)	—	100
7	ZnCl ₂ (10)	Heptane (100)	97	—
8	Zn(NO ₃) ₂ (10)	Heptane (100)	—	100

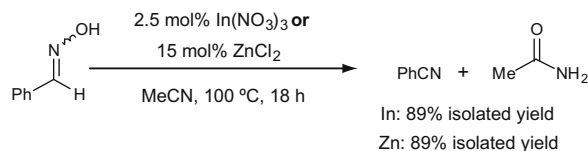
^a Conversion was determined by the analysis of the ¹H NMR spectra.

Table 3
Scope of the reaction



Entry	R	Catalyst (mol %)	Time (h)	Conversion ^a (yield) (%)
1	C ₃ H ₇	In(NO ₃) ₃ (0.4)	16	98 (87)
2	C ₃ H ₇	Zn(NO ₃) ₂ (10)	16	100 (93)
3	C ₆ H ₅	In(NO ₃) ₃ (1.0)	18	85 (79)
4	C ₆ H ₅	ZnCl ₂ (10)	18	97 (88)
5	C ₆ H ₅ CH=CH	In(NO ₃) ₃ (0.4)	16	100 (90)
6	C ₆ H ₅ CH=CH	Zn(NO ₃) ₂ (10)	16	100 (93)
7	4-MeOC ₆ H ₄	In(NO ₃) ₃ (1.0)	18	30
8	4-MeOC ₆ H ₄	ZnCl ₂ (10)	18	96 (89)
9	4-MeC ₆ H ₄	In(NO ₃) ₃ (0.8)	16	97 (88)
10	4-MeC ₆ H ₄	ZnCl ₂ (10)	16	96 (84)
11	4-ClC ₆ H ₄	In(NO ₃) ₃ (0.8)	16	96 (88)
12	4-ClC ₆ H ₄	ZnCl ₂ (10)	16	100 (90)
13	C ₆ H ₅ CH ₂	In(NO ₃) ₃ (0.8)	16	97 (86)
14	C ₆ H ₅ CH ₂	Zn(NO ₃) ₂ (10)	18	100 (94)
15	4-Et ₂ NC ₆ H ₄	In(NO ₃) ₃ (1.0)	18	98 (96)
16	4-Et ₂ NC ₆ H ₄	ZnCl ₂ (10)	18	98 (91)
17	2-Furyl	In(NO ₃) ₃ (1.0)	18	0
18	2-Furyl	ZnCl ₂ (10)	18	100 (93)
19	3-ClC ₆ H ₄	In(NO ₃) ₃ (1.0)	18	96 (87)
20	3-ClC ₆ H ₄	ZnCl ₂ (10)	18	97 (91)
21	2-MeC ₆ H ₄	In(NO ₃) ₃ (1.0)	18	14
22	2-MeC ₆ H ₄	ZnCl ₂ (10)	18	31

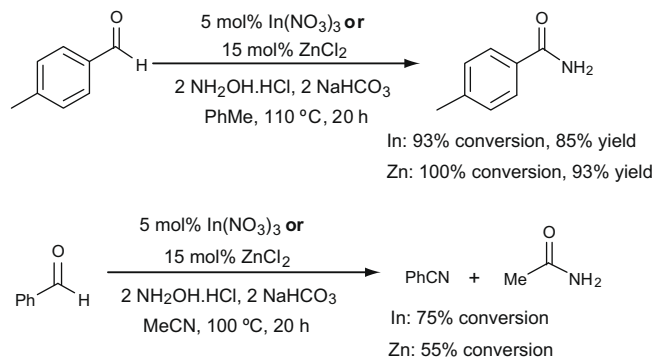
^a Conversion was determined by the analysis of the ¹H NMR spectra.



Scheme 2. Conversion of aldehydes into amides or nitriles.

We have also found that it is possible to convert aldehydes into either amides¹⁷ or nitriles¹⁸ using an in situ process where hydroxylamine hydrochloride is present. A moderate conversion into benzonitrile was observed with In(NO₃)₃ (the remaining 25% being the aldoxime and not benzamide) however, it was necessary to use higher catalyst loadings in order to obtain reasonable conversion into product (Scheme 3).

In summary, we have identified new, efficient, low cost catalysts which rearrange aldoximes into primary amides with good



Scheme 3. Conversion of aldehydes into amides or nitriles.

to excellent isolated yields. The switch from an expensive metal catalyst provides another example of using a 'cheap metal for a noble task'.¹⁹

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.048.

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