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Copper-catalyzed rearrangement of oximes into primary amides

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The atom-efficient and cost-effective rearrangement of oximes into primary amides is catalyzed by simple copper salts. The use of homogeneous $Cu(OAc)_2$ was found to be effective for this transformation at 80 °C using 1-2 mol% of this catalyst. The reaction was successful with either conventional or microwave heating. CuO and CuO/ZnO on activated carbon provided a competent reuseable heterogeneous catalyst which could be used in a batch process or in flow. Copper salts are much cheaper than the precious metals previously used for this rearrangement, and the reaction conditions are milder than those previously reported.
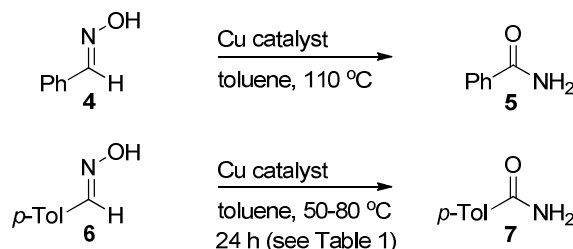
The rearrangement of oximes **1** into amides is usually associated with the Beckmann rearrangement (Scheme 1) where the R group migrates to give the formamide **2**.[1] The metal-catalyzed rearrangement of oximes provides an alternative synthetic outcome with the formation of a primary amide **3**.[2] Recently, there have been several reports of the use of precious metals for this reaction, including Rh,[3] Ir,[4] Ru,[5] Pd[6] and Ag/Au[7] catalysts. Given the importance of amides, and the conventional approach requiring the use of a stoichiometric coupling agent to activate carboxylic acids,[8] catalytic approaches to amide formation are highly desirable.[9] The rearrangement of oximes provides an alternative catalytic approach which is completely atom-efficient. We recently reported that zinc salts could be used as cheaper alternatives to precious metals as catalysts for this reaction, although catalyst loadings of 10-15 mol% were required.[10] We therefore wanted to identify a catalyst which was cheap, effective at lower catalyst loading and could be used under milder conditions than those previously reported. In this paper, we report that simple copper salts can fulfil these objectives.
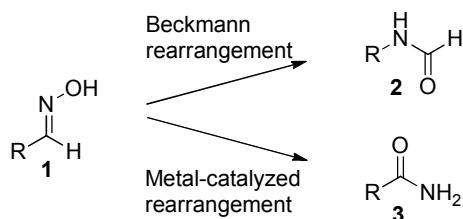
Scheme 1. Rearrangement of oximes to amides

During the course of screening reactions for the conversion of benzaldehyde oxime (**4**) into benzamide (**5**) (Scheme 2), we found that some simple copper(I) and copper(II) salts were successful for this transformation. Using 5 mol% of $Cu(NO_3)_2$, $Cu(OAc)_2$ or Cu_2O all gave 100% conversion after 24 hours. CuO and CuBr gave 80 and 90% conversion respectively, whereas $CuBr \cdot SMe_2$, $CuSO_4$, $CuCO_3$, $CuCl_2$, $CuBr_2$ and $Cu(OTf)_2$ did not work to any useful level. We further investigated $Cu(NO_3)_2$, $Cu(OAc)_2$ and Cu_2O catalysts using the p-tolyl substituted oxime **6** as the analysis of the ^{1}H NMR spectrum to distinguish starting material from product **7** was more straightforward. A series of optimization reactions was performed (Table 1) in order to reduce the catalyst loading and reaction temperature. Pleasingly, with 5 mol% of catalyst, the conversion of oxime **6** into amide **7** was still complete when the reaction was performed at 80 °C (Table 1, entries 1-3), which is the lowest temperature reported for the metal-catalyzed rearrangement of oximes to amides. In fact, reasonable activity was observed even at 50 °C (Table 1, entries 4-6). We chose to investigate the use of $Cu(OAc)_2$ further due to the lower reactivity of $Cu(NO_3)_2$ and the higher effective loading of Cu_2O (5 mol% corresponds to 10 mol% in Cu). The use of additives was briefly investigated but found to offer no advantage (Table 1, entries 7-9). Lower catalyst loadings were effective, especially when the reactions were run at higher concentration.

Scheme 2. Use of copper catalysts for the rearrangement of oximes into amides

Table 1. Optimization of catalyst and conditions.[a]

Entry	Catalyst	Loading (mol%)	Temp (°C)	Additive (5 mol%)	Conversion (%)
1	$Cu(NO_3)_2$	5	80	-	100
2	$Cu(OAc)_2$	5	80	-	100
3	Cu_2O	5	80	-	100
4	$Cu(NO_3)_2$	5	50	-	10
5	$Cu(OAc)_2$	5	50	-	37
6	Cu_2O	5	50	-	40
7	$Cu(OAc)_2$	5	50	AcOH	40
8	$Cu(OAc)_2$	5	50	K_2CO_3	25
9	$Cu(OAc)_2$	5	50	Bipy	17
10	$Cu(OAc)_2$	2	80	-	100[b]
11	$Cu(OAc)_2$	2	80	-	100
12	**$Cu(OAc)_2$**	**1**	**80**	**-**	**100[b]**
13	$Cu(OAc)_2$	1	80	-	64
14	None	-	110	-	<1

[a]Reactions were performed on oxime **6** (2 mmol) in toluene (3 mL) with additive (2.4 mmol) and copper catalyst for 24 h at the temperature indicated. [b]Reactions performed under more concentrated conditions, toluene (0.5 mL).

We applied the conditions shown in Table 1, entries 10 and 12 to the conversion of other oximes to give the corresponding amides shown in Table 2.[11] Oximes containing aryl groups with either electron-withdrawing moieties (Table 2, entry 3), halides (Table 2, entries 4 and 5), or electron-rich groups (Table 2, entries 6 and 7) were all successful. The least reactive substrate when using 1 mol% $Cu(OAc)_2$ was the aliphatic butyraldehyde oxime, although at the higher catalyst loading, complete conversion into butyramide was observed.

Table 2. Conversion of oximes into amides with $Cu(OAc)_2$.[a]

Entry	Amide product	Catalyst loading (mol%)	Conversion (%)[b]
1	Ph—C(O)NH$_2$	2	100 (82)
2	4-MeC$_6$H$_4$—C(O)NH$_2$	2	100 (81)
3	4-O$_2$NC$_6$H$_4$—C(O)NH$_2$	2	100 (67)
4	4-ClC$_6$H$_4$—C(O)NH$_2$	2	100 (76)
5	4-FC$_6$H$_4$—C(O)NH$_2$	2	100 (75)
6	4-Et$_2$NC$_6$H$_4$—C(O)NH$_2$	2	100 (65)
7	(methylenedioxyphenyl)—C(O)NH$_2$	1	90 (84)
8	(2-naphthyl)—C(O)NH$_2$	2	88 (78)
9	(2-thienyl)—C(O)NH$_2$	1	90 (58)
10	CH$_3$CH$_2$CH$_2$—C(O)NH$_2$	2	100 (91)
11	CH$_3$(CH$_2$)$_6$—C(O)NH$_2$	2	100 (82)
12	PhCH=CH—C(O)NH$_2$	3	79 (70)

[a]Reactions were performed on oxime (3 mmol) in toluene (0.75 mL) with $Cu(OAc)_2$ (1 or 2 mol%) for 24 h at 80 °C. [b]Values in parentheses are isolated yields.

As expected for a metal-catalyzed oxime rearrangement, the ketoxime derived from acetophenone was inert to reaction under these conditions, perhaps due to the mechanism of reaction in the case of aldoximes, which can proceed via dehydration of the oxime to give a nitrile intermediate followed by further reaction to give the amide product.[10]

We found that the rearrangement reactions could conveniently be performed using microwave irradiation. Thus, benzaldehyde oxime (**4**) and butyraldehyde oxime (**8**) were converted into the corresponding amides **5** and **9** after 1 hour at 80 °C using microwave conditions (Scheme 3). Using a lower catalyst loading of 4 mol%, complete conversion of oxime **8** into amide **9** was achieved after 2 hours at 80 °C under microwave conditions. The reaction was performed on other substrates under microwave conditions (Table 3).

We were pleased to find that shorter reaction times could also be used when using conventional heating, at least for the conversion of oxime **6** into amide **7**. Performing the reaction at 110 °C with 2 mol% $Cu(OAc)_2$, 17% conversion was observed after 10 minutes, but complete conversion was obtained after 30 minutes. Performing the reaction at 80 °C, 85% conversion was observed after 60 minutes.

Table 3. Conversion of oximes into amides with $Cu(OAc)_2$.[a]

Entry	Amide product	Conversion (%)[b]
1	Ph—C(O)NH$_2$	95 (81)
2	4-ClC$_6$H$_4$—C(O)NH$_2$	97 (90)
3	4-Et$_2$NC$_6$H$_4$—C(O)NH$_2$	86
4	(2-naphthyl)—C(O)NH$_2$	93 (80)
5	(2-thienyl)—C(O)NH$_2$	100 (74)
6	nPr—C(O)NH$_2$	100 (93)
7	PhCH=CH—C(O)NH$_2$	93 (85)

[a]Reactions were performed on oxime (2 mmol) in toluene (0.75 mL) with $Cu(OAc)_2$ (4 mol%) for 2 h at 80 °C. [b]Values in parentheses are isolated yields.
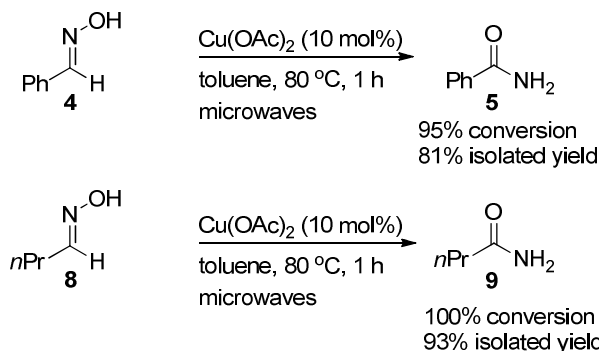
Scheme 3. Oxime rearrangement using microwave irradiation

Having established good reaction conditions for the homogeneous isomerization of oximes into amides, we wanted to explore the development of a heterogeneous variant of this process. Given the success with homogeneous copper and zinc catalysts we chose to investigate the use of CuO on activated carbon, ZnO on activated carbon and CuO/ZnO on activated carbon.[12] We were pleased to find that these heterogeneous catalysts were also active for the rearrangement reaction for the conversion of benzaldehyde oxime (**4**) into benzamide (**5**) (Scheme 4). In all of these cases, small amounts of benzonitrile (**10**) and other unidentified by-products were detected by GC analysis of the crude reaction mixtures.

		5 : 10 : other
CuO on activated C	89% conv.	90 : 7 : 3
ZnO on activated C	87% conv.	91 : 6 : 3
CuO/ZnO on activated C	98% conv.	93 : 5 : 2
activated C only	8% conv.	0 : 75 : 25
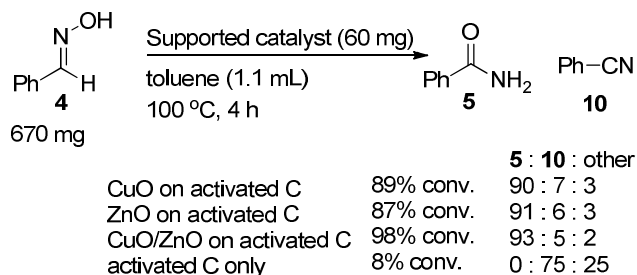
Scheme 4. Oxime rearrangement with heterogeneous catalysts

Based on these results we undertook an optimization study for the rearrangement of oxime **4** using CuO/ZnO on activated carbon, varying the time, temperature and catalyst loading, as detailed in Table 4. We chose to use a catalyst loading of 60 mg for reactions performed on a 5.5 mmol scale, which approximates to 2 mol% catalyst loading as used in the homogeneous reactions. After 1 hour at 80 °C, the products were formed in only 30% conversion and contained almost equal amounts of benzamide (**5**) and benzonitrile (**10**) (Table 4, entry 1), but as the reaction times increased, up to 98% conversion was achieved with much higher selectivity for the amide (Table 4, entry 4). This implies that benzonitrile is an intermediate in the reaction pathway.[13] At 100 °C (Table 4, entries 5-8) and 130 °C (entries 9-12), higher conversions were observed, although selectivity was not improved. We chose to use the conditions of 100 °C for 4 hours for subsequent experiments. In the absence of catalyst there was very little conversion (Table 4, entry 13) with the majority of the product being the nitrile. Higher catalyst loadings did help to drive the reaction to completion and the selectivity was also improved when a catalyst loading of 200 mg was used (entry 17).

Table 4. Conversion of oxime **4** into products **5** and **10** using CuO/ZnO on C.

Entry	Time (h)	Loading (mg)	Temp (°C)	Conversion (%)	Selectivity[a] **5 : 10** : other
1	1	60	80	30	47 : 44 : 9
2	2	60	80	58	74 : 19 : 7
3	4	60	80	88	91 : 4 : 6
4	6	60	80	98	94 : 4.5 : 1.5
5	1	60	100	39	53 : 36 : 11
6	2	60	100	67	80 : 12 : 8
7	4	60	100	98	93 : 5 : 2
8	6	60	100	>99	93 : 5 : 2
9	1	60	130	75	73 : 13 : 14
10	2	60	130	97	83 : 6 : 11
11	4	60	130	>99	89 : 3 : 8
12	6	60	130	100	87 : 3 :10
13	4	0	100	5	2 : 97 :1
14	4	7.5	100	52	71 : 22 : 7
15	4	30	100	93	87 : 8 : 5
16	4	100	100	99	93 : 5 : 2
17	4	200	100	100	96 : 3 : 1

[a]Selectivity and conversion were determined by GC.

It was possible to re-use the supported catalyst, which was recovered by the addition of ethanol to cool the reaction mixture followed by filtration to isolate the catalyst. The solids were then washed with acetone followed by ethanol to remove adsorbed reactant or products. The washed catalyst was first dried at 80 °C for 4 hours then at 250 °C for 8 hours in a flow of nitrogen. The dried catalyst was used for the rearrangement of benzaldehyde oxime (**4**) under reaction conditions similar to that of fresh catalyst. Fresh catalyst gave 98% conversion with 93% selectivity (Table 4, entry 7), and the first re-use led to essentially identical results (98% conversion, 92% selectivity). Subsequent runs afforded 93% conversion with 89% selectivity and then 80% conversion with 85% selectivity on the fourth run.

Using the optimized conditions, we employed the CuO/ZnO supported catalyst for the rearrangement of other oximes into amides, as shown in Table 5. This catalyst was found to be effective for the transformation of a range of substituted aryl oximes, although the presence of electron-withdrawing substituents led to somewhat lower conversions (Table 5, entries 2 and 3). Alkenyl (Table 5, entry 10) and alkyl (Table 5, entries 11 and 12) oximes underwent the rearrangement successfully, although the conversions and selectivities were lower than those observed for aryl oximes.

Table 5. Conversion of oximes into amides with CuO/ZnO

$$R-CH=N-OH \quad (1) \xrightarrow[\text{toluene, 100 }^{\circ}\text{C, 4 h}]{\text{CuO/ZnO (10 wt\%)}} \quad R-C(=O)-NH_2 \quad (3)$$

Entry	Amide product	Conversion (%)	Selectivity 3 : nitrile : other
1	$Ph-C(=O)-NH_2$	98	93 : 5 : 2
2	$4\text{-}O_2NC_6H_4-C(=O)-NH_2$	86	91 : 8 : 1
3	$4\text{-}NCC_6H_4-C(=O)-NH_2$	89	88 : 10 : 2
4	$4\text{-}MeC_6H_4-C(=O)-NH_2$	98	89 : 8 : 3
5	$4\text{-}MeOC_6H_4-C(=O)-NH_2$	98	91 : 8 : 1
6	$4\text{-}F_3COC_6H_4-C(=O)-NH_2$	97	89 : 9 : 2
7	$4\text{-}ClC_6H_4-C(=O)-NH_2$	99	91 : 8 : 1
8	$3\text{-}ClC_6H_4-C(=O)-NH_2$	99	90 : 7 : 3
9	naphthalene-2-$C(=O)-NH_2$	99	86 : 12 : 2
10	$Ph-CH=C(CH_3)-C(=O)-NH_2$	88	77 : 20 : 3
11	$Ph-CH_2CH_2-C(=O)-NH_2$	75	78 : 14 : 8
12	$C_6H_{13}-C(=O)-NH_2$	75	60 : 18 : 22

The activity of CuO-ZnO/C catalyst for rearrangement of benzaldehyde oxime (**4**) in batch encouraged us to perform the same reaction in a flow reactor (X-Cube, ThaleNano, Hungary). Complete conversion of **4** with 88% selectivity for benzamide was observed in the flow reactor using a 4.86 mol/L concentration of benzaldehyde oxime at 150 °C.

In conclusion, effective homogeneous and heterogeneous catalysts have been identified for the rearrangement of oximes into amides. The reaction is atom-efficient and uses relatively mild reaction conditions and catalyst loading. Copper salts are significantly cheaper than the precious metal complexes which have previously been reported for this reaction. In addition, the reactions

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11. Representative experimental procedure; Benzaldehyde oxime (**4**) and Cu(OAc)$_2$·H$_2$O (12.0 mg, 3 mol%) were dissolved in toluene (0.5 mL) in an oven-dried Schlenk tube and heated at 80 °C for 24 h. After cooling, the solvent was removed under vacuum and the product isolated by column chromatography (silica, EtOAc/hexane, 3:1) to give benzamide (**5**) (298 mg, 82%) as a colourless solid. Products were analyzed by comparison of their ^{1}H and ^{13}C NMR spectra with authentic

samples. Further experimental details are provided in the supporting information

12. Kindly donated by Mast Carbon Technology Ltd, Henley Park, Normandy, Guildford, Surrey, GU3 2AF, UK.

13. Based on the mechanism with other catalysts, it seems likely that the intermediate nitrile is converted into amide by oxygen transfer from another oxime molecule. Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096-5099.