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A simple Ru catalyst for the conversion of aldehydes or oximes to primary amides

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ABSTRACT

$Ru(DMSO)_4Cl_2$ is catalytically active for converting aldehydes to primary amides via oxime intermediates. This catalyst is readily available, and requires no additional ligands, a great simplification compared to previous work. A Ru(II)/(IV) mechanism is proposed.

1. Introduction

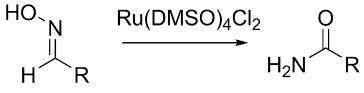
Amides, which are valuable intermediates in organic synthesis and in industrial applications such as detergents, lubricants and pharmaceuticals [1], are commonly prepared from the stoichiometric reaction of amines with acyl chlorides, acid anhydrides, and esters [2]. However, the toxicity and waste formation involved in these methods has made the atom-economical synthesis of amides a high priority, especially in the pharmaceutical industry.

(1)

One approach is the Beckmann rearrangement, in which an acid assists in migration of the R group anti to N–OH to give the rearranged amide (Eq. (1)) [3]. Alkyl and aryl groups readily migrate while H generally does not, making ketoximes favored over aldoximes [4]. Traditionally, acids such as PCl_5 are used in the Beckmann rearrangement, but transition metal catalysts containing nickel [5], palladium [6], iridium [7] and rhodium [8] have also been reported. In a recent advance, Williams and coworkers reported a ruthenium catalyst for this reaction with high selectivity, yield and low catalyst loading [9]. However, additives like *p*-toluenesulfonic acid (*p*-TsOH) and other ligands are required, and nitriles are frequently found in addition to the amide (abnormal Beckmann rearrangement). Gnanamgari and Crabtree [10] found that additives and product mixtures can be avoided with a ruthenium terpyridine catalyst to achieve equally high yields. In a further simplification of this reaction, we now report that $Ru(DMSO)_4Cl_2$, having only dimethylsulfoxide (DMSO) and Cl^- as ligands, provides a much simpler precatalyst for the conversion of aldehydes and aldoximes to amides. $Ru(DMSO)_4Cl_2$ is known to be active for β-alkylation and coupling of ketones to alcohols [11–13]; we now find that Ru(II) can indeed also rearrange oximes to amides via H migration. The metal precatalyst can easily be synthesized in high yield by refluxing $RuCl_3$ hydrate in DMSO for a short time [14]. Our catalyst does not require additives, and gives high yields with no nitrile formation.

2. Results and discussion

In the initial screening phase, we looked only at the conversion of preformed oximes to amides in toluene (Eq. (2)). As shown in Table 1, aromatic aldoxime substrates such as (E)- and (Z)-benzaldehyde oxime (Table 1, Entries 1 and 2), and a heterocyclic aldoxime (R = furaldehyde, Table 1, Entry 7) are quantitatively converted to benzaldamide within 8 h in refluxing toluene.



(2)

Because acid and basic additives have been reported to increase the yield in prior systems [7, 9], we also ran reactions with 1 equivalent of *p*-TsOH, (Table 1, Entry 3), and 1 equivalent of sodium bicarbonate (Table 1, Entry 4). The addition of acid resulted in complete conversion but to an uncharacterizable mixture of products, while added base had no influence on yield or reaction time. We therefore excluded these additives in subsequent reactions. Running the reactions open to the air had no influence for benzylic aldehydes, but

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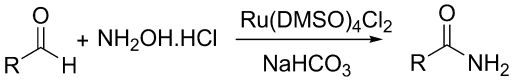
Table 1
Results for the conversion of aldoximes to amides.

Entry	Aldoxime R=	Time (h)	Solvent	Conversion (%)	Yield[a] (%)
1	(E)-C_6H_5	8	toluene	>99	>99
2	(Z)-C_6H_5	8	toluene	>99	>99
3	(E)-C_6H_5[b]	8	toluene	>99	nd
4	(E)-C_6H_5[c]	8	toluene	>99	>99
5	(4-NO_2)C_6H_4	6	toluene	>99	48
6	$C_6H_5CH{=}CH$	6	toluene	71	71
7	2-furyl	6	toluene	>99	>99
8	C_3H_7	6	toluene	>99	49
9	(4-NO_2)C_6H_4	6	acetonitrile	31	31
10	2-furyl	6	acetonitrile	48	38

Reaction conditions: 0.164 mmol oxime, 5 mol% $Ru(DMSO)_4Cl_2$, and 1 mL of solvent at refluxed (110 °C, Toluene; 82 °C MeCN) under N_2 atmosphere.
[a] Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.
[b] 1 equiv. *p*-toluenesulfonic acid added.
[c] 1 equiv. potassium tert-butoxide added.

gave decreased yields and unknown product mixtures were found for substrates with easily oxidizable C–H bonds, such as for cinnemaldehyde oxime. Aldoximes with electron withdrawing groups such as 4-nitrobenzaldehydeoxime (Table 1, Entry 5) reacted completely, but gave slightly lower yields. Consistent with other Ru catalysts [9,10], ketoximes were inert under our conditions.



(3)

Having established the conversion of aldoximes to amides, we investigated the more useful conversion of aldehydes to amides (Eq. (3) and Table 2). We were initially discouraged to find poor conversions and yields under the same conditions, even after 48 h (Table 2, Entries 1–4). In most of these cases, large amounts of aldehyde starting material and traces of the oxime intermediate remained at the end of the reaction. Therefore the formation of the oxime was the problem, not the later oxime to aldehyde conversion. Switching to a more polar solvent, MeCN, we found better conversion and yield at shorter times and lower temperatures (Table 2, Entries 5–10). For example, with cinnemaldehyde as substrate after 6 and 48 h in refluxing toluene, we saw 74% of the cinnemaldehyde remained, and only 9% of the corresponding amide was found (Entry 4). However, in MeCN 80% of the product was now formed after only 6 h: only cinnemaldehyde oxime, and no aldehyde remained, supporting our hypothesis that the reaction between the hydroxylamine hydrochloride, base, and the aldehyde limited the reaction in toluene. This prompted us to reevaluate the reactions in Table 1 with MeCN as solvent. Interestingly, yields were lower after 6 h indicating that the solvent effects are not straightforward. This is consistent with the presence of traces of oxime found in the MeCN reactions in Table 2, suggesting that MeCN enables good conversion to the oxime, but slower conversion to the amide; toluene is good for the amide conversion, but not great for the oxime formation.

Table 2
Results for the conversion of aldehydes to amides.

Entry	Aldehyde R=	Time (h)	Solvent	Conversion (%)	Yield[a] (%)
1	Ph	6	toluene	>99	24
2	(4-NO_2)C_6H_4	48	toluene	17	17
3	(4-Me)C_6H_4	48	toluene	nd	nd
4	$C_6H_5CH{=}CH$	48	toluene	9	9
5	Ph	6	acetonitrile	78	30
6	(4-NO_2)C_6H_4	6	acetonitrile	79	79
7	(4-CF_3O)C_6H_4	6	acetonitrile	75	68
8	(4-Me)C_6H_4	6	acetonitrile	35	35
9	$C_6H_5CH{=}CH$	6	acetonitrile	83	80
10	2-furyl	6	acetonitrile	60	60

Reaction conditions: 0.164 mmol oxime, 0.164 mmol sodium bicarbonate, 0.164 mmol hydroxylamine hydrochloride, 5 mol% $Ru(DMSO)_4Cl_2$, and 1 mL of solvent were refluxed (110 °C, toluene; 78 °C MeCN).
[a] Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

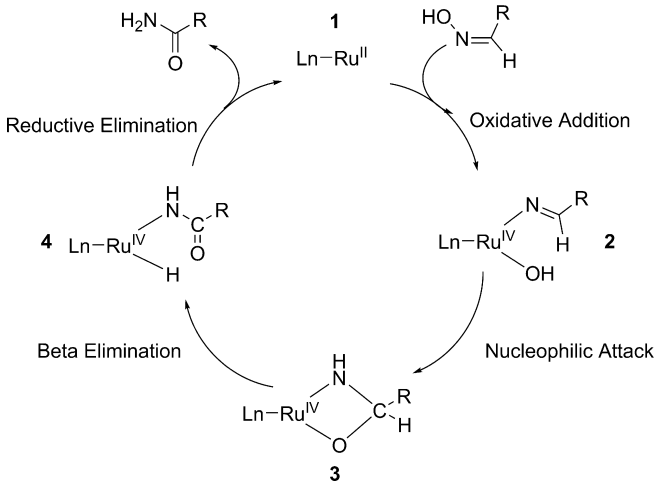
The mechanism is still under investigation, however several points are clear. If Ru(II) acted merely as Lewis acid we would expect to see product from the classical Beckmann rearrangement, such as secondary amides from ketoximes. If Ru(II)/(IV) conversion is possible in this system, an alternative mechanism (Scheme 1) can be proposed: oxidative addition of the aldoxime N–OH bond to Ru(II), followed by nucleophilic attack on the co-ordinated imine in **2**, then β-elimination of cyclometallated **3**, and finally reductive elimination to give the amide. Notably, water cannot eliminate from **2**, and no nitrile is observed. This explains the absence of nitrile products in this system.

3. Experimental

Except where noted, all the reactions were conducted using standard Schlenk techniques under nitrogen, using dry glassware and solvents. Toluene and acetonitrile were passed through an activated alumina column before use. NMR spectra were recorded at room temperature using $CDCl_3$ and DMSO-d_6 on 400 and 500 MHz Bruker spectrometers and referenced to the internal standard peak (δ in ppm and J in Hz). All organic reagents were purchased from Sigma Aldrich and Alfa Aesar, and ruthenium trichloride from Pressure Chemicals Company. $Ru(DMSO)_4Cl_2$ was synthesized according to literature methods [14].

3.1. Representative procedure for the rearrangement of aldoximes to amides

To a flame-dried Schlenk tube equipped with a magnetic stirbar were added oxime (0.164 mmol) and catalyst (4 mg, 1.64 μmol). After filling the tube with N_2 using three vacuum-N_2 cycles, dry and degassed toluene (1 mL) was added with a syringe, and the mixture was refluxed for the time indicated in the tables. After cooling, 1,3,5-trimethoxybenzene (9 mg, 55 μmol) and 1 mL methanol were added to the mixture. The contents were transferred to a round bottom flask, and all solvent was removed under reduced pressure. The resulting solid was dissolved in DMSO-d_6, and filtered through Celite into an NMR tube for analysis. NMR data were found to be identical to literature values, and are reported below.



Scheme 1. Proposed mechanism for the Ru(II) catalyzed rearrangement of aldoximes.

3.2. Representative procedure for the conversion of aldehydes to amides

To a flame-dried Schlenk tube equipped with a magnetic stirbar were added oxime (0.164 mmol), hydroxylamine hydrochloride (0.164 mmol, 11.3 mg), $NaHCO_3$ (0.164 mmol, 13.6 mg) and catalyst (4 mg, 1.64 μmol). After filling the tube with N_2 using three vacuum-N_2 cycles, dry and degassed toluene or acetonitrile (1 mL) was added with a syringe, and the mixture was refluxed for the time indicated in the tables. After cooling, 1,3,5-trimethoxybenzene (9 mg, 55 μmol) and 1 mL methanol were added to the mixture. The contents were transferred to a round bottom flask, and all solvent was removed under reduced pressure. The resulting solid was dissolved in DMSO-d_6, and filtered through Celite into an NMR tube for analysis.

3.3. Benzamide (Table 1, Entries 1–4)

(>99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (2H, m), 7.52 (1H, t, *J*, 7.4 Hz), 7.44 (2H, t, *J*, 7.6 Hz), 5.85 (2H, br s, NH_2). ^{13}C NMR (100 MHz, CDCl3): δ 169.8, 133.5, 132.21, 128.8, 121.53.

3.4. 4-Nitrobenzamide (Table 1, Entry 5)

(>99%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.29 (3H, m), 8.09 (2H, d, *J*, 8.8 Hz), 7.72 (1H, NH). ^{13}CNMR (100 MHz, DMSO-d_6): δ 166.2, 149.1, 139.9, 128.9, 123.4.

3.5. Cinnamide (Table 1, Entry 6)

(71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (1H, d, *J*, 15.7 Hz), 7.49 (2H, m), 7.36 (3H, m), 6.44 (1H, d, *J*, 15.7 Hz), 5.69 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 142.8, 134.7, 130.2, 129.1, 128.2, 119.7.

3.6. 2-Furamide (Table 1, Entry 7)

(>99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (1H, m), 7.15 (1H, d, *J*, 3.50 Hz), 6.50 (1H, dd, *J*, 3.46 Hz, 1.73 Hz), 5.89 (2H, br s). 13CNMR (100 MHz, CDCl3): δ 160.2, 147.6, 144.6, 115.4, 112.5.

3.7. Butyramide (Table 1, Entry 8)

(49%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (2H, s), 2.18 (2H, t, *J*, 7.46 Hz), 1.64 (2H, m), 0.95 (3H, t, *J*, 7.37 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 38.0, 19.1, 13.9.

3.8. 4-(Trifluoromethoxy)benzamide (Table 2, Entry 7)

(68% from the aldehyde). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (1H, s), 7.99 (2H, m), 7.51 (1H, s), 7.45 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 150.3, 133.4, 129.8, 121.7, 120.6.

3.9. Toluamide (Table 2, Entry 8)

(35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (2H, d, *J*, 8.20 Hz), 7.23 (2H, m), 6.04 (2H, br s), 2.38 (3H, s). 13C NMR (400 MHz, $CDCl_3$): δ 169.5, 142.8, 130.7, 129.5, 127.6, 21.7.

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