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Ruthenium-catalyzed reduction of *N*-alkoxy- and *N*-hydroxyamides

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ABSTRACT

A ruthenium-catalyzed reduction of *N*-alkoxy- and *N*-hydroxyamides was found to afford corresponding amides in good to high yields. A simple $RuCl_3$/Zn–Cu/alcohol system, without the addition of any other ligands, exhibited a high catalytic activity, and therefore the present reaction does not require a stoichiometric amount of metals or metal complexes as reductants. When β-substituted-α,β-unsaturated *N*-methoxyamides were employed as substrates, concurrent hydrogenation of the olefin moiety proceeded slowly with deprotection of the methoxy group. In the reduction of *N*-hydroxyamides, the alcoholic solvent was found to function as a hydrogen donor.

1. Introduction

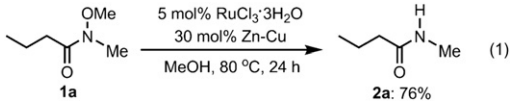
N-Alkoxy- and *N*-hydroxyamides (hydroxamic acids and their derivatives) have been widely used as biologically active compounds [1–3] as well as versatile synthetic intermediates [4]. In the synthesis of β-lactams [5] and compounds derived from *O*-alkyl oximes [6], the alkoxy groups of the alkoxyamide moieties are utilized as protecting groups, and Li [5a,7], Cp_2TiCl_2/Zn (or Mn) [5d], H_2–Pd/C and $TiCl_3$ [5b,c], $TiCl_3$ only [8] and SmI_2 [6] have been employed as reductants in conventional methods for deprotection. *N*-Hydroxyamides can be reduced by titanium complexes as well [5b–d]. As non-metal reductants, *tert*-butyldimethylsilyl triflate/triethylamine [9] and an organic neutral super-electron donor [10] have also been reported. These reactions occur via single-electron transfer and require a stoichiometric amount of metals, metal complexes or organic reductants.

During the course of our investigation on the reactions of Weinreb amides in the presence of ruthenium complexes, we found that the N–O bond cleavage occurred efficiently to afford the corresponding deprotected amides. We report here a novel catalytic reduction of *N*-alkoxyamides using a simple $RuCl_3$/Zn–Cu/alcohol system, which was also found to be effective for the reduction of *N*-hydroxyamides.

2. Results and discussion

2.1. Optimization of reaction conditions

Initially, *N*-methyl-*N*-methoxybutyramide (**1a**), which is known as a Weinreb amide [4a], was treated with 5 mol% of $RuCl_3 \cdot 3H_2O$ and 30 mol% of Zn–Cu couple in MeOH at 80 °C under an argon atmosphere. The reduction proceeded to give the deprotected product, *N*-methylbutyramide (**2a**), in 76% NMR yield after 24 h (Eq. (1)).



(1)

The catalytic activity of other ruthenium complexes such as $[RuCl_2(CO)_3]_2$, $RuCl_2(PPh_3)_3$, $[RuCl_2(1,5\text{-cyclooctadiene})]_n$, $[RuCl_2(2,5\text{-norbornadiene})]_n$, $[Cp^*RuCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl), $RuCl_4$(2,2′-bipyridine), $[RuCl_2(C_6H_6)]_2$, and $[RuCl_2(p\text{-cymene})]_2$ was examined in the presence of Zn–Cu in MeOH. In most cases, the yields were less than 30% and none were comparable to $RuCl_3$. In the absence of Zn–Cu, $Ru(C_6H_6)$(methyl acrylate)$_2$ [11], a zerovalent complex, was employed for the reaction in toluene at 130 °C for 24 h. However, this resulted in a low yield (21%). We also attempted the reactions with additives such as monodentate/bidentate nitrogen or phosphorous ligands (5–10 mol%) under the same reaction conditions as in Eq. (1); however, lower yields of the product (12–46%) were obtained in all cases.

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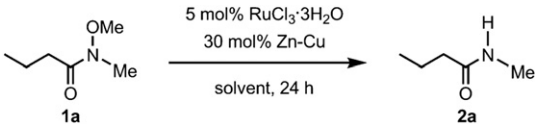
Table 1
Effects of various solvents and reaction temperatures.[a]



Entry	Solvent	Temp. (°C)[b]	Conversion of **1a** (%)[c]	Yield of **2a** (%)[c]
1	MeOH	80	76	76
2	EtOH	80	83	83
3	EtOH	100	97	97
4	2-PrOH	100	90	90
5	2-BuOH	110	78	73
6	EtOH/H_2O = 10:1	100	50	43

[a] Reaction conditions: amide **1a** (0.50 mmol), $RuCl_3 \cdot 3H_2O$ (0.025 mmol), Zn–Cu (0.15 mmol), and solvent (1.0 mL) for 24 h.
[b] Bath temperature.
[c] Determined by ^1H NMR. Dibenzyl ether was used as an internal standard.

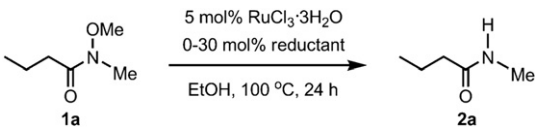
Next we examined the effects of various solvents and reaction temperatures (Table 1). The use of EtOH instead of MeOH gave a slightly higher yield of **2a** (entry 2) and raising the bath temperature to 100 °C gave the best result of 97% (entry 3). Secondary alcohols such as 2-PrOH and 2-BuOH were also effective; however, these lowered the yield as compared to that of EtOH (entries 4 and 5). The presence of a certain amount of water (EtOH/H_2O = 10:1) considerably inhibited the reduction (entry 6).

The effects of reductants were also examined (Table 2). Even in the absence of a reductant, the reaction proceeded to give 13% of **2a** (entry 1). Although 5 mol% of Zn–Cu did not operate well (entry 2), both conversion and yield were critically improved by using more than 15 mol% (entries 3 and 4). Either Zn or Mg did not compare with Zn–Cu (entries 5 and 6).

2.2. Scope of substrates

The optimized reaction conditions found above were applied to several *N*-alkoxyamides (Table 3). Decreasing the precatalyst loading to 2 mol% slightly lowered the yield (entry 2), whereas decreasing to 1 mol% resulted in substantially low conversion (54%) and yield (34%) (entry 3). Relatively bulky *N*-methyl-*N*-methoxypivalamide (**1b**) was converted to *N*-methylpivalamide (**2b**) in 24 h (entry 4). *N*-Methyl-*N*-methoxybenzamide (**1c**) afforded *N*-methylbenzamide (**2c**) in high yield (entry 5). In addition, the reaction of *N*-methoxybutyramide (**1d**) having an amide proton proceeded smoothly to give butyramide (**2d**) (entry 6). A benzyloxy protected amide, *N*-methyl-*N*-benzyloxybutyramide (**1e**), also afforded **2a** (entry 7) with the formation of benzyl alcohol (65%) and benzaldehyde (21%), whereas the reaction of *N*-methyl-*N*-isopropoxybutyramide (**1f**) was sluggish, probably because of steric hindrance (entry 8). The reduction was also found to be applicable to *N*-hydroxyamides **1g**–**i**, resulting in **2a**, *N*-phenylbutyramide (**2e**), and **2d**, respectively (entries 9–11). Although all the substrates converted in these cases, the yields varied from moderate to high depending on the substituents on the nitrogen atoms.

Table 2
Effects of reductants.[a]



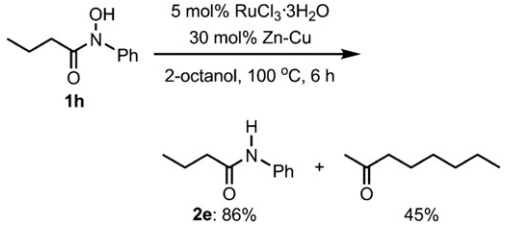
Entry	Reductant	Amount (mol%)	Conversion of **1a** (%)[b]	Yield of **2a** (%)[b]
1	None		16	13
2	Zn–Cu	5	33	13
3	Zn–Cu	15	91	91
4	Zn–Cu	30	97	97
5	Zn	30	100	86
6	Mg	30	50	34

[a] Reaction conditions: amide **1a** (0.50 mmol), $RuCl_3 \cdot 3H_2O$ (0.025 mmol), reductant (0–0.15 mmol), and EtOH (1.0 mL) at 100 °C for 24 h.
[b] Determined by ^1H NMR. Dibenzyl ether was used as an internal standard.

The present method was applied to β-substituted-α,β-unsaturated *N*-methoxyamides (Table 4) [12]. The deprotection proceeded as well, but hydrogenation of the olefin moiety occurred simultaneously. When *N*-methyl-*N*-methoxycrotonamide (**3a**) was employed, there was a low yield of *N*-methylcrotonamide (**4a**), whereas in the case of *N*-methyl-*N*-methoxycinnamamide (**3b**), the yield of deprotected product **4b** was up to 93% after 6 h and that of deprotected/hydrogenated product **2f** was 6% (entry 2) [13]. In the both cases, the formation ratios of **4**/**2** were high at the early stage (3 h), and the highest yields of **4** were observed after 6 h. The yields of **4** decreased after 24 h along with the further formation of **2**. Whereas the conversions of the substrate **3b** and the total yields of the products **4b** and **2f** are well balanced (entry 2), the conversions of **3a** are approximately 15–30% higher than the total yields of **4a** and **2a** (entry 1). The imbalance may be attributable to the strong coordination of π-acidic α,β-unsaturated amides **3a** and/or **4a** to ruthenium, by which they cannot be detected as free amides. The aforementioned changes in the yields of the products **4** and **2** with time, and the fact that hydrogenated products of **3** without deprotection were not formed during the course of the reactions, indicate that the deprotection rather than the hydrogenation from **3** proceeds preferentially to afford **4**, and then the hydrogenation of **4** would follow.

2.3. Possible reaction mechanisms

To elucidate the role of the solvent molecule in the catalytic cycle, the reduction of **1h** was performed in 2-octanol at 100 °C for 6 h (Eq. (2)). As a result, 2-octanone was formed in 45% NMR yield along with the formation of deprotected amide **2e** in 86% NMR yield. Although a small amount of 2-octanone (9%) was detected even in the absence of **1h** under the same reaction conditions as in Eq. (2), these results imply the participation of the solvent as a hydrogen donor in the catalytic cycle of the reduction.



Taking these observations into consideration, three possible reaction mechanisms are proposed as shown in Scheme 1. In each mechanism, either a zerovalent ruthenium complex or a divalent ruthenium hydride complex is supposed to be involved as a catalytically active species. Zerovalent ruthenium complexes such as Ru(1,5-cyclooctadiene)(1,3,5-cyclooctatriene), Ru(benzene)(1,3-cyclohexadiene) [14] and Ru{$P(OMe)_3$}(dimethyl muconate)$_2$ [15] are known to be formed from $RuCl_3 \cdot 3H_2O$ in the presence of Zn and appropriate ligands in an alcoholic solvent, and divalent ruthenium hydride species can be generated under the similar reaction conditions as well [15]. In Path A, *N*-alkoxy- or *N*-hydroxyamide **1** coordinates to zerovalent ruthenium species **5** to