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Synthesis of α-Amino Ketones from Terminal Alkynes via Rhodium-Catalyzed Denitrogenative Hydration of *N*-Sulfonyl-1,2,3-triazoles

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Supporting Information

ABSTRACT: *N*-Sulfonyl-1,2,3-triazoles react with water in the presence of a rhodium catalyst to produce α-amino ketones in high yield. An intermediary α-imino rhodium(II) carbenoid undergoes insertion into the O−H bond of water. This transformation formally achieves 1,2-aminohydroxylation of terminal alkynes in a regioselective fashion when combined with the copper(I)-catalyzed 1,3-dipolar cycloaddition with *N*-sulfonyl azides.

α-Amino ketones constitute an important class of biologically active compounds. For example, they are key substructures of bupropion[1] and brephedrone,[2] which are used in the clinical treatment of psychological disorders. α-Amino ketones also serve as valuable intermediates for the synthesis of 2-amino alcohols[3] and various nitrogen-containing heterocycles.[4] Therefore, the development of new methods for synthesizing α-amino ketones from readily available materials is highly desired.[5−9] We report herein a rhodium(II)-catalyzed denitrogenative hydration reaction of *N*-sulfonyl-1,2,3-triazoles that opens a new synthetic route leading to α-amino ketones from terminal alkynes. Formally, this transformation achieves regioselective 1,2-aminohydroxylation of terminal alkynes, providing a complement to the one reported by Chang[10] and Fokin[11] using a copper(I) catalyst in terms of regioselectivity (Figure 1).

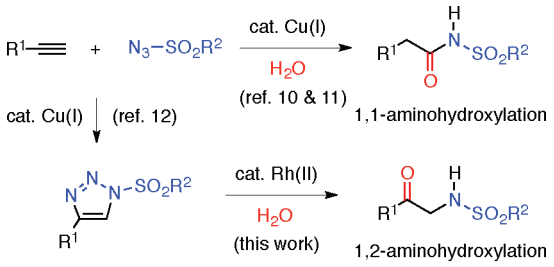

Figure 1. Two pathways for the formal aminohydroxylation of terminal alkynes.

N-Sulfonyl-1,2,3-triazoles have become readily accessible materials since the copper-catalyzed 1,3-dipolar cycloaddition reaction of *N*-sulfonyl azides with terminal alkynes was reported in 2007.[12] Subsequently, a few groups developed their transformations in which the diazo group was replaced by organic molecules such as nitriles, alkynes, alkenes, and alkanes.[13−15] Rhodium(II) and nickel(0) catalysts generate highly reactive α-imino metal carbenoids through denitrogenation of α-diazo imines, which are formed by ring−chain tautomerization. We envisaged that the insertion of α-imino metal carbenoids into the O−H bond of water[16] would result in the formation of α-imino alcohols (tautomers of α-amino ketones), constituting a denitrogenative hydration reaction of *N*-sulfonyl-1,2,3-triazoles. Thus, various transition-metal catalysts were examined in the reaction of 4-phenyl-1-(*N*-tosyl)-1,2,3-triazole (**1a**) with water. Whereas the use of nickel(0) and copper(II) complexes led to the formation of complex mixtures, the desired reaction proceeded under reaction conditions using rhodium(II) complexes that were originally reported for the nitrile insertion;[13a] when a chloroform solution of **1a** and water (10 equiv) in the presence of $Rh_2(Oct)_4$ (0.5 mol %, Oct = octanoate) was heated at 140 °C for 15 min under microwave irradiation (MW),[17] 2-tosylamino-1-phenylethanone (**2a**) was produced in 91% isolated yield (Table 1, entry 1). Substrates **1b−g** possessing a variety of aryl groups, also prepared from the corresponding terminal alkynes by the 1,3-dipolar cycloaddition reaction, all reacted facilely with water to afford the corresponding products **2b−g** in yields of 89−94% (entries 2−7). Whereas 1-cyclohexenyl-substituted substrate **1h** successfully participated in the hydration reaction to give the product **2h** in 92% yield (entry 8), cyclohexyl-substituted substrate **1i** afforded the product **2i** in only 26% yield (entry 9). This was because β-hydride migration preferentially occurred with the rhodium carbenoid intermediate to give α,β-unsaturated *N*-tosyl imine **3i** (62%).[13a,c,18] However, we found that when $Rh_2(t\text{-}BuCO_2)_4$ (0.5 mol %) was used under basic aqueous conditions [KOH (1.0 equiv) and water (50 equiv) in chloroform (0.05 M)], the formation of **3i** decreased considerably and the yield of **2i** increased to 78% (entry 10). Remarkably, this modified system was also effective for primary-alkyl-substituted substrates **1j−m**, affording the products **2j−m** in high yield (entries 11−14). The reaction of unsubstituted substrate **1n** afforded α-amino aldehyde **2n**, albeit in low yield; **2n** was unstable toward silica gel and therefore was converted to the corresponding 2-amino alcohol **4n** for isolation by treatment with $NaBH_4$ in wet ethanol (entry 15).

Next, the variation of the sulfonyl group of **1** was examined in the reaction with water using $Rh_2(Oct)_4$ as the catalyst (Table 2). 4-Methoxybenzenesulfonyl, 4-bromobenzenesulfonyl, and 2-naphthalenesulfonyl triazoles **1o−q** were similarly reactive, furnishing α-amino ketones **2o−q** in high yield (entries 1−3). Not only arylsulfonyl groups but also

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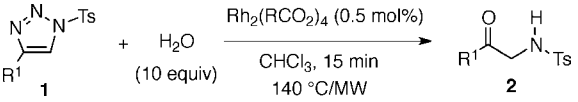
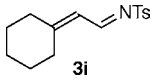
Table 1. Rh(II)-Catalyzed Denitrogenative Hydration Reaction of 4-Substituted 1-(*N*-Tosyl)-1,2,3-triazoles 1a−m[a]



entry	1	R^1	2	yield (%)[b]
1	**1a**	Ph	**2a**	91
2	**1b**	4-MeC_6H_4	**2b**	89
3	**1c**	4-PhC_6H_4	**2c**	94
4	**1d**	4-$MeOC_6H_4$	**2d**	92
5	**1e**	4-$CF_3C_6H_4$	**2e**	90
6	**1f**	4-$EtO_2CC_6H_4$	**2f**	90
7	**1g**	3-thienyl	**2g**	91
8	**1h**	1-cyclohexenyl	**2h**	92
9	**1i**	Cy	**2i**	26[c]
10	**1i**	Cy	**2i**	78[d]
11	**1j**	n-Hex	**2j**	88[d]
12	**1k**	$(CH_2)_4OBz$	**2k**	93[d]
13	**1l**	$(CH_2)_4OTBS$	**2l**	94[d]
14	**1m**	$(CH_2)_4N(phth)$	**2m**	89[d]
15	**1n**	H	**4n**	38[e]

[a]Conditions: **1** (0.20 mmol) and H_2O (2.0 mmol, 10 equiv) in $CHCl_3$ (4 mL) were heated at 140 °C for 15 min in the presence of $Rh_2(Oct)_4$ (1.0 μmol) under microwave irradiation, unless otherwise noted. [b]Isolated yields (averages of 2 runs). [c]**3i** was formed in 62% yield.

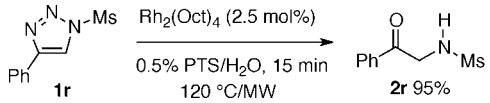


3i

[d]Using $Rh_2(t\text{-}BuCO_2)_4$ (1.0 μmol) under basic aqueous conditions [KOH (0.2 mmol) and H_2O (10 mmol, 50 equiv) in $CHCl_3$ (4 mL)]. [e]The reaction was worked up with $NaBH_4$ (0.20 mmol) in 3:2 EtOH/H_2O (4.5 mL).

alkylsulfonyl groups were suitable; methyl, *n*-butyl, benzyl, and 2-(trimethylsilyl)ethylsulfonyl triazoles **1r−u** were all competent substrates (entries 4−7). Thus, the reaction was highly general with respect to the R^2 substituent on the sulfonyl group.

This denitrogenative hydration reaction operated without any problem when only water was used as the solvent in the presence of the nonionic amphiphile PTS[19] (eq 1).



(1)

A plausible mechanism for the production of **2** from **1** and water is depicted in Scheme 1. Initially, a ring−chain tautomerization of *N*-sulfonyl-1,2,3-triazole **1** generates α-diazo imine **1′**,[20] although the equilibrium lies far to the left. Diazo tautomer **1′** reacts with rhodium(II) with release of molecular dinitrogen to give α-imino rhodium carbenoid **A**.

Scheme 1. Plausible Mechanism for the Formation of 2 from 1 and Water

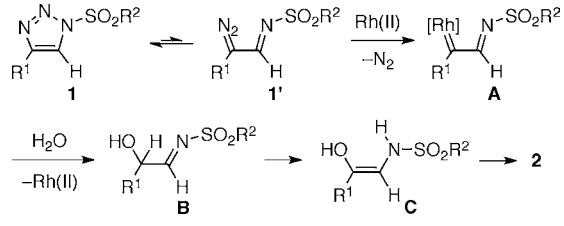
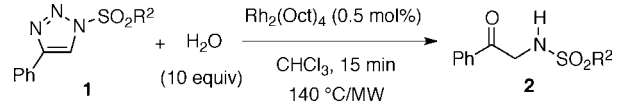


Table 2. Rh(II)-Catalyzed Denitrogenative Hydration Reaction of 4-Phenyl 1-(*N*-Sulfonyl)-1,2,3-triazoles 1o−u[a]

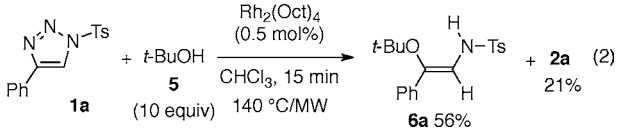


entry	1	R^2	2	yield (%)[b]
1	**1o**	4-$MeOC_6H_4$	**2o**	98
2	**1p**	4-BrC_6H_4	**2p**	86
3	**1q**	2-naphthyl	**2q**	90
4	**1r**	Me	**2r**	95
5	**1s**	n-Bu	**2s**	93
6	**1t**	Bn	**2t**	93
7	**1u**	$Me_3Si(CH_2)_2$	**2u**	99

[a]Conditions: **1** (0.20 mmol) and H_2O (2.0 mmol, 10 equiv) in $CHCl_3$ (4 mL) were heated at 140 °C for 15 min in the presence of $Rh_2(Oct)_4$ (1.0 μmol) under microwave irradiation. [b]Isolated yields (averages of 2 runs).

Subsequent insertion of **A** into the O−H bond of water leads to the formation of α-imino alcohol **B**,[16] regenerating the rhodium(II) catalyst. Finally, imine−enamine tautomerization furnishes α-amino enol **C**, and keto−enol tautomerization follows to give α-amino ketone **2**.

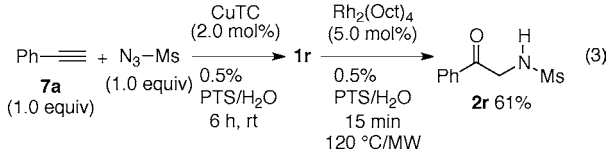
To obtain mechanistic insights, an analogous reaction was carried out using *tert*-butyl alcohol (**5**) instead of water (eq 2).



(2)

α-Amino enol ether **6a** was isolated in 56% yield along with α-amino ketone **2a** (21%). The formation of **6a** can also be explained by assuming that the carbenoid insertion into the O−H bond of **5** is followed by imine−enamine tautomerization.

A one-pot synthesis of α-amino ketones *starting from terminal alkynes* was carried out to demonstrate the practical convenience of the present method (Table 3). Treatment of terminal alkynes (**7**, 1.0 equiv) with tosyl azide (1.0 equiv) in the presence of CuTC (10 mol %, TC = thiophene-2-carboxylate) generated *N*-sulfonyl-1,2,3-triazoles **1**.[12b] Next, water (10 equiv), $Rh_2(Oct)_4$ (0.5 mol %), and chloroform were added to the reaction mixture, which was further stirred at 140 °C for 15 min under microwave irradiation. The corresponding α-amino ketones **2** were isolated in overall yields of 52−79%. In addition, the one-pot reaction was successfully executed using only water as the solvent, although a higher loading of the rhodium(II) catalyst was required (eq 3). It is



(3)

noteworthy that molecular dinitrogen is the only waste product in this sequential transformation.

In conclusion, the present method, when combined with the copper(I)-catalyzed 1,3-dipolar cycloaddition of *N*-sulfonyl azides with terminal alkynes, formally achieves 1,2-amino-hydroxylation of terminal alkynes in a regioselective fashion, which is difficult to execute with hitherto known methods.

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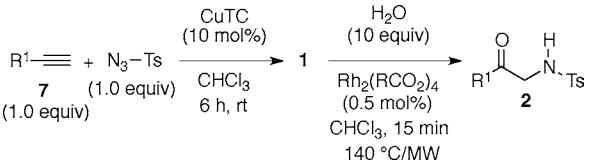
Table 3. Synthesis of α-Amino Ketones from Terminal Alkynes 7 in One Pot[a]



entry	7	R^1	2	yield (%)[b]
1	**7a**	Ph	**2a**	79
2	**7g**	3-thienyl	**2g**	63
3	**7h**	1-cyclohexenyl	**2h**	52
4	**7i**	Cy	**2i**	65[c]
5	**7j**	n-Hex	**2j**	79[c]

[a]Conditions: A solution containing **7** (0.20 mmol), tosyl azide (0.20 mmol), and CuTC (20 μmol) in $CHCl_3$ (1 mL) was stirred at rt for 6 h, and then H_2O (2.0 mmol, 10 equiv) and $Rh_2(Oct)_4$ (1.0 μmol) in $CHCl_3$ (3 mL) were added. The resulting mixture was heated at 140 °C for 15 min under microwave irradiation. [b]Isolated yields (averages of 2 runs). [c]Using $Rh_2(t\text{-}BuCO_2)_4$ (1.0 μmol) under basic aqueous conditions [KOH (0.20 mmol) and H_2O (10 mmol, 50 equiv) in $CHCl_3$ (3 mL)].

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Microwave irradiation was essential to gain a reasonable rate of the hydration reaction. When a chlorobenzene solution of **1a** and water (10 equiv) in the presence of $Rh_2(Oct)_4$ (0.5 mol %) was simply heated at 140 °C for 15 min without microwave irradiation, **2a** was formed in 32% yield along with other unidentified compounds.

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