Organic LETTERS

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Direct Production of Enaminones from Terminal Alkynes via Rhodium-Catalyzed Reaction of Formamides with *N*-Sulfonyl-1,2,3-triazoles

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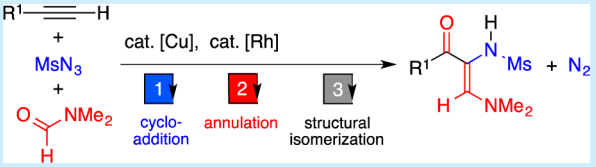
Supporting Information

ABSTRACT: A rhodium-catalyzed reaction of formamides with *N*-sulfonyl-1,2,3-triazoles is developed to formulate a new one-pot procedure for the direct synthesis of α-amino enaminones from terminal alkynes.



Enaminones serve as versatile intermediates for the synthesis of a wide variety of heterocycles contained in biologically active compounds,[1] and their synthesis from readily available starting materials has been an area of active research.[2−4] Now, we report a simple method for the synthesis of enaminones from terminal alkynes, *N*-sulfonyl azides, and formamides. Of note is that three different bonds, *i.e.*, a C−N single bond, a C═O double bond, and a C═C double bond are installed regioselectively across the C≡C triple bond in one pot (Figure 1).

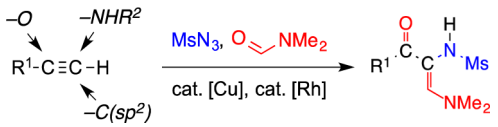
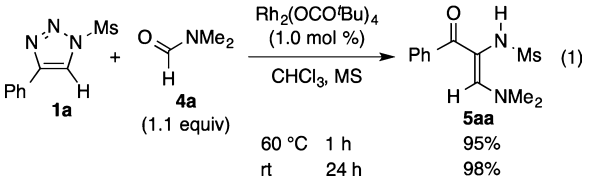


Figure 1. Construction of enaminones from terminal alkynes by introducing three different bonds.

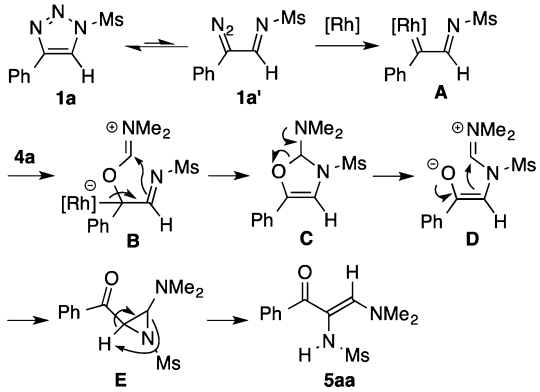
N-Sulfonyl-1,2,3-triazoles react with transition metal complexes to generate α-imino metal carbene complexes,[5] which react with various compounds of nucleophilic character.[6] Even formyl groups are nucleophilic enough to add to the carbenoid carbon. For example, a reaction with simple aldehydes produces 4-oxazolines.[7] On the other hand, α,β-unsaturated aldehydes give rise to 2,3-dihydropyrroles.[8] Fokin et al. recently reported that ketones were formed with the use of relatively stereodemanding secondary amides.[9] These studies led us to examine the use of tertiary formamides as the nucleophilic partner[10] with the expectation of the production of the corresponding 2-amino-4-oxazolines. Thus, 1-mesyl-4-phenyl-1,2,3-triazole (**1a**) was prepared from phenylethyne (**2a**) and mesyl azide (**3a**) according to the authentic procedure using copper(I) thiophene-2-carboxylate (CuTC).[11] Then, the triazole **1a** (0.20 mmol) was mixed with *N*,*N*-dimethylformamide (DMF; **4a**, 1.1 equiv), a rhodium pivalate dimer (1.0 mol %), and 4 Å molecular sieves (MS) in chloroform (2 mL), and the mixture was heated at 60 °C for 1 h (eq 1). Much to our surprise, not



the expected 2-amino-4-oxazoline but α-amino-substituted enaminone **5aa** was formed exclusively and isolated in 95% yield after chromatographic purification.[12] The reaction proceeded even at room temperature. The formal metathesis of a C≡C triple bond and a C═O double bond occurs with the simultaneous incorporation of an amino substituent.

We propose the following mechanism for the unexpected formation of the enaminone **5aa** from triazole **1a** and DMF (**4a**) (Scheme 1). Initially, reversible ring−chain tautomerization of the triazole **1a** generates α-diazo imine **1a′**, which reacts with rhodium(II) to afford α-imino rhodium carbene complex

Scheme 1. Proposed Mechanism for the Formation of Enaminones 5aa

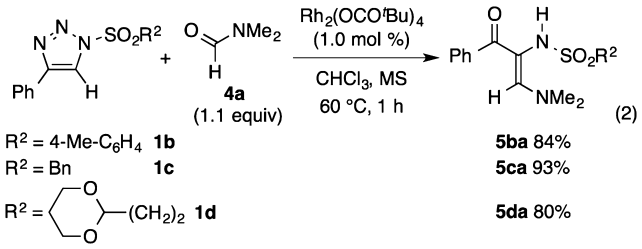


Received: April 14, 2014
Published: April 28, 2014

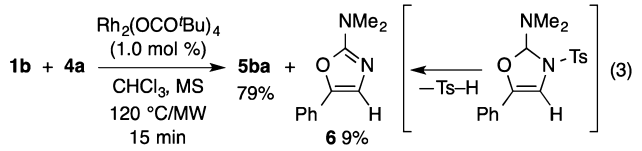
dx.doi.org/10.1021/ol5010774 | *Org. Lett.* 2014, 16, 2760−2763

A with extrusion of molecular nitrogen. Nucleophilic addition of the formyl group of **4a** to the electrophilic carbene center gives zwitterionic intermediate **B**. The anionic rhodium releases an electron pair, which induces the imino nitrogen to attack the carbon of the iminium ion, producing 4-oxazoline intermediate **C**.[7] The C−O bond of the *N*,*O*-hemiaminal moiety is cleaved, and the resulting zwitterionic species **D** recyclizes to aziridine intermediate **E**. Finally, the aziridine ring is opened to rearrange into the enaminone **5aa**.[13]

With respect to the substituent on the sulfonyl group, *p*-tolyl, benzyl, and 2-(1,3-dioxan-2-yl)ethyl[14] groups are all suitable (eq 2). The product **5ba** was a crystalline compound, and its structure was confirmed by a single-crystal X-ray analysis.

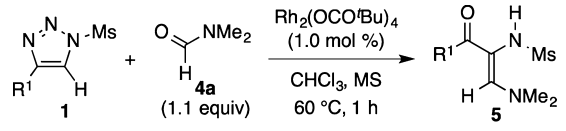


When the reaction of **1b** was carried out at 120 °C under microwave irradiation, 2-amino-oxazole **6** was isolated in 9% yield in addition to the enaminone **5ba** (eq 3). The formation of **6** is consistent with elimination of *p*-toluenesulfinic acid from the 4-oxazoline intermediate corresponding to **C**, which supports the mechanism shown in Scheme 1.



Various triazoles **1** were subjected to the reaction with DMF at 60 °C (Table 1). Triazoles **1e−i** possessing an aryl group at the 4-position all reacted well to afford the corresponding products **5ea−ia** in high yields ranging from 92% to 97% (entries 1−5). Of note was that even alkyl-substituted triazoles **1j−l** gave the products **5ja−la** in high yields, despite the possibility of a 1,2-hydride shift occurring with the rhodium carbene complex (entries 6−8).[15]

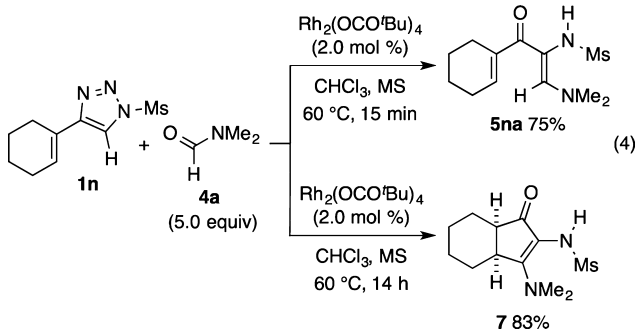
Table 1. Rh(II)-Catalyzed Reaction of Various Triazoles 1e−m with DMF (4a)[a]



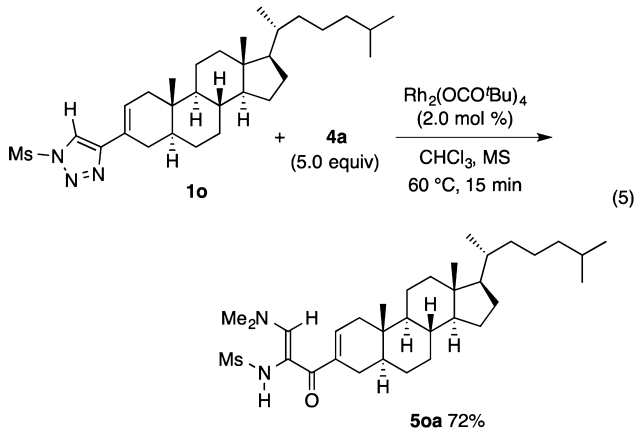
entry	triazole **1** R[1]		product **5**	yield (%)
1	4-Me-C_6H_4	**1e**	**5ea**	97
2	4-MeO-C_6H_4	**1f**	**5fa**	93
3	4-MeO_2C-C_6H_4	**1g**	**5ga**	94[b]
4	4-CF_3-C_6H_4	**1h**	**5ha**	92
5	3-thienyl	**1i**	**5ia**	93
6	^{n}Hex	**1j**	**5ja**	91[c]
7	$BzO(CH_2)_4$	**1k**	**5ka**	91[c]
8	$(phth)N(CH_2)_4$	**1l**	**5la**	92[c]
9	EtO	**1m**	**5ma**	56[c]

[a] **1** (0.20 mmol), **4a** (0.22 mmol), $Rh_2(OCO^tBu)_4$ (2.0 μmol), and MS (40 mg) in $CHCl_3$ (2 mL). [b] 3 h. [c] **4a** (1.0 mmol) in $CHCl_3$ (0.5 mL).

Whereas it has been reported that 1-cyclohexenyl-substituted triazole **1n**[16] undergoes an intramolecular cyclization to give 2,3-fused pyrrole in the absence of DMF,[17] it underwent the intermolecular reaction with DMF selectively to give divinyl ketone **5na**, which is suggestive of the relatively strong nucleophilicity of DMF.[18] Interestingly, a prolonged reaction time caused the ensuing Nazarov cyclization to afford 2-cyclopentenone **7**.



The synthetic applicability of the present reaction was demonstrated by the reaction using the substrate **1o** derived from 5α-cholestan-3-one (eq 5).

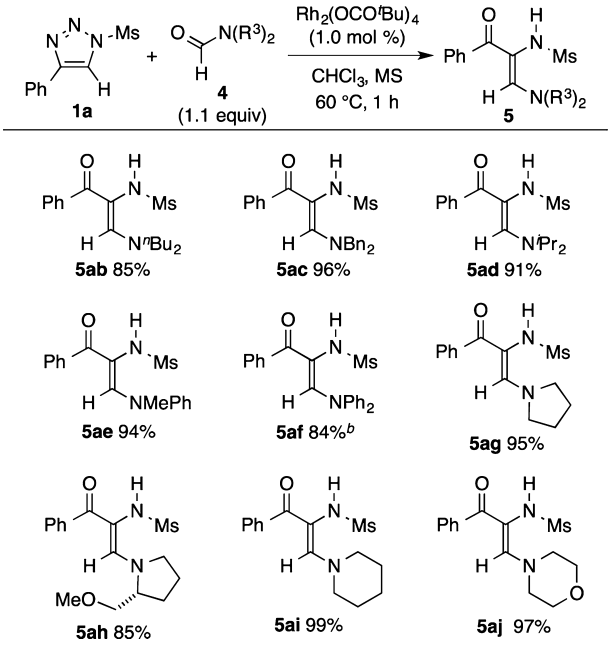


Various tertiary formamides prepared from acyclic and cyclic secondary amines successfully participated in the reaction with the 1-mesyltriazole **1a**, and the corresponding products were obtained in good to high yields (Scheme 2). However, secondary formamides derived from primary amines such as *N*-methylformamide failed to participate in the reaction. This is probably because the −NH group either directly adds to the rhodium carbene complex **A** or provides the imino nitrogen of intermediate **B** with a proton.[9]

With the reaction of formamides with triazoles in hand, we next developed an all-in-one-pot synthesis of enaminones starting from terminal alkynes (Table 2). Substrates **2a**, **3a**, and **4a**, copper(I) and rhodium(II) catalysts, and chloroform were put in a reaction vessel, and the mixture was stirred at room temperature. After 6 h, **2a** and **3a** were both consumed to generate triazole **1a**. Then, the reaction mixture was stirred at 60 °C for 1 h, and the following chromatographic purification afforded the enaminone **5aa** in 83% isolated yield based on the

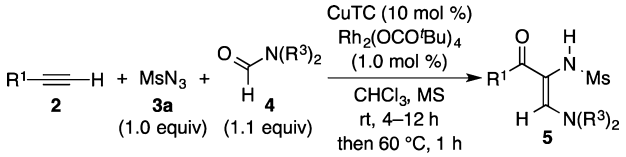
dx.doi.org/10.1021/ol5010774 | Org. Lett. 2014, 16, 2760−2763

Scheme 2. Rh(II)-Catalyzed Reaction of Triazoles 1a with Various Formamides 4b–j[a]



[a]The same reaction conditions with those in Table 1. [b] Toluene (2 mL) at 100 °C.

Table 2. All-in-One-Pot Synthesis of 5 Starting from Terminal Alkynes 2[a]



entry	1-alkynes 2		formamides 4		product 5	yield (%)
	R^1		$N(R^3)_2$			
1	Ph	**2a**	$N(Me)_2$	**4a**	**5aa**	83
2	4-MeO-C_6H_4	**2b**	$N(Me)_2$	**4a**	**5fa**	61[b]
3	4-CF_3-C_6H_4	**2c**	$N(Me)_2$	**4a**	**5ha**	56
4	^{n}Hex	**2d**	$N(Me)_2$	**4a**	**5ja**	59[c]
5	Ph	**2a**	$N(Bn)_2$	**4c**	**5ac**	74
6	Ph	**2a**	$N(^i Pr)_2$	**4d**	**5ad**	75
7	Ph	**2a**		**4g**	**5ag**	74
8	Ph	**2a**		**4i**	**5ai**	78
9	Ph	**2a**		**4j**	**5aj**	77

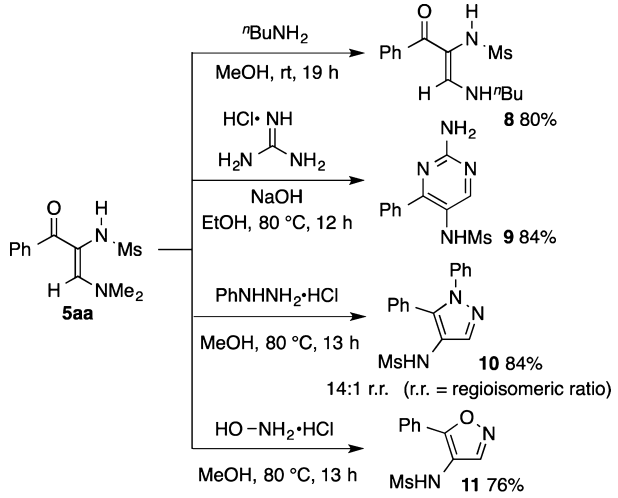
[a]On a 0.20 mmol scale. [b]CH_2ClCH_2Cl (2 mL). [c]**4a** (0.60 mmol) in $CHCl_3$ (1 mL).

alkyne **2a** (entry 1). Similar results were obtained when the reaction of **2a** was carried out on a 10 mmol scale or even at room temperature.[19] This one-pot procedure minimizes generation of waste solvents.

Various enaminones **5** were synthesized from other combinations of terminal alkynes **2** and formamides **4** and isolated in moderate to good yields through a single workup/purification procedure (entries 2–9).

Synthetic utilities unique to the enaminone **5aa** were exemplified by further derivatizations shown in Scheme 3. A

Scheme 3. Synthetic Derivatizations of Enaminone 5aa



reaction with butylamine caused replacement of the dimethylamino group at the β-position to furnish secondary amine **8**, which was difficult to prepare by using *N*-butylformamide in the present reaction. Various heterocycles such as pyrimidine **9**, pyrazole **10**, and isoxazole **11** were readily synthesized by treatment with guanidine, phenylhydrazine, and hydroxylamine, respectively.

In summary, we have developed a new method for the synthesis of α-amino enaminones, which serve as useful building blocks for the construction of various nitrogen-containing frameworks. Terminal alkynes can be used as starting materials, and multiple functionalities are regioselectively installed across the C≡C triple bonds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for the new compounds, details of the X-ray analysis, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. Biing-Jiun Uang (National Tsing Hua University) in celebration of his 60th birthday. We thank Dr. Y. Nagata (Kyoto University) for his kind help in the X-ray analysis. This work was supported by MEXT (Grant-in-Aid for Scientific Research on Innovative Areas Nos. 22105005 and 24106718, Young Scientists (A) No. 23685019, Scientific Research (B) No. 23350041) and JST (ACT-C).

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(18) The enaminone **5na** was obtained in 47% yield together with recovered **1n** (31%) when 1.1 equiv of **4a** was used.

(19) See the Supporting Information for details.

dx.doi.org/10.1021/ol5010774 | *Org. Lett.* 2014, 16, 2760−2763