Synthetic Methods

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A Reaction of Triazoles with Thioesters to Produce β-Sulfanyl Enamides by Insertion of an Enamine Moiety into the Sulfur–Carbonyl Bond**

Tomoya Miura, Yoshikazu Fujimoto, Yuuta Funakoshi, and Masahiro Murakami**

Abstract: *N-Sulfonyl-1,2,3-triazoles react with thioesters in the presence of a rhodium(II) catalyst to produce β-sulfanyl enamides in a stereoselective manner. The reaction proceeds through generation of an α-imino rhodium carbene complex, nucleophilic addition of the sulfur atom of a thioester onto the carbenoid carbon atom, and subsequent intramolecular migration of the acyl group from the sulfur atom to the imino nitrogen atom. The method is successfully applied to a ring-expansion reaction of thiolactones, thus leading to the formation of sulfur-containing lactams.*

N-Sulfonyl-1,2,3-triazoles are readily prepared by a copper(I)-catalyzed cycloaddition reaction of terminal alkynes with sulfonyl azides.[1] Their ring–chain tautomerization generates α-imino diazo compounds, although the equilibrium lies far towards the triazole form, in general.[2] Transition-metal catalysts, especially rhodium(II) carboxylate dimers, can efficiently trap the transient α-imino diazo compounds in the form of an α-imino carbene complex, which exhibits a variety of unique reactivities depending on the substrates.[3] In the reactions with unsaturated compounds such as alkynes,[4] allenes,[5] nitriles,[3a] aldehydes and imines,[6] isocyanates and isothiocyanates,[7] and indoles,[8] they serve as the 1,3-dipoles to afford the corresponding [3+2] cycloadducts. When reacted with alcohols[9] and amides,[10] they offer an enamine moiety which inserts into the O–H and N–H bonds, respectively. As a continuation of our studies on the application of *N*-sulfonyl-1,2,3-triazoles as carbene precursors, we became interested in the reactions with organosulfur compounds[11] because of the importance of sulfur-containing compounds in the field of pharmaceuticals (Figure 1).[12]

We have recently shown that the reaction with thionoesters [RC(S)OR′] leads to the formation of 4-thiazolines, which are further converted into 2,5-disubstituted thiazoles by deprotective aromatization.[13] In contrast, there is no report which describes the reaction of thioesters [RC(O)SR′] with rhodium(II)-stabilized carbene complexes, including α-imino carbene complexes.[14] We now report that, when thioesters are subjected to the rhodium(II)-catalyzed reaction with *N*-sulfonyl-1,2,3-triazoles, the sulfur–carbonyl bond is cleaved[15] and an enamine moiety is inserted to give β-sulfanyl enamides with a *Z* configuration.[16,17]

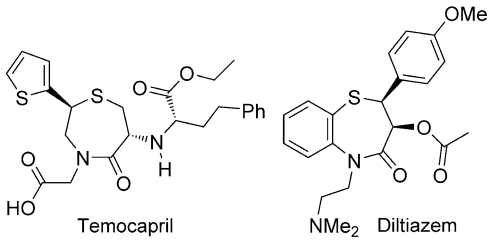
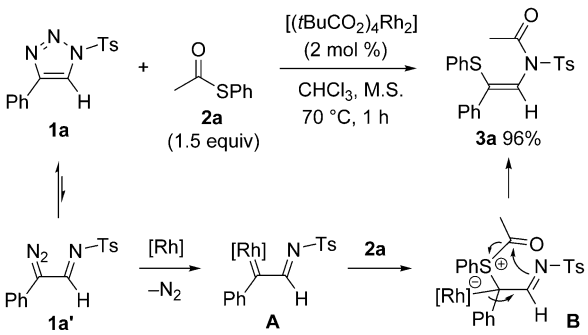


Figure 1. Commercially available drugs with a sulfur-containing medium-ring lactam.

Initially, 4-phenyl-1-tosyl-1,2,3-triazole (**1a**) was prepared from phenylacetylene and tosyl azide according to the procedure using copper(I) thiophene-2-carboxylate (CuTC).[1c] The triazole **1a** (0.20 mmol) was mixed with *S*-phenyl thioacetate (**2a**, 0.30 mmol), [(*t*BuCO$_2$)$_4$Rh$_2$] (2.0 mol %), and 4 Å molecular sieves (M.S.) in chloroform (2 mL), and the mixture was heated at 70 °C for 1 hour (Scheme 1). After chromatographic isolation from silica gel, *N*-(2-phenyl-2-(phenylthio)vinyl)-*N*-tosylacetamide (**3a**) was obtained in 96% yield as a single stereoisomer within the detection limits of ^{1}H NMR spectroscopy.[18] The configuration of the double bond of **3a** was confirmed as *Z* by NOE studies. In a formal sense, an enamine moiety was stereoselectively inserted into the sulfur–carbonyl bond of **2a**. We assume that the reaction is initiated by a ring–chain tautomerization of **1a** to generate the α-diazo imine **1a′**, which reacts with a rhodium(II) catalyst to afford the α-imino carbene



Scheme 1. Rhodium(II)-catalyzed reaction of the triazole **1a** with the thioester **2a**. Ts = 4-toluenesulfonyl.

[*] Dr. T. Miura, Y. Fujimoto, Y. Funakoshi, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University
Katsura, Kyoto 615-8510 (Japan)
E-mail: tmiura@sbchem.kyoto-u.ac.jp
murakami@sbchem.kyoto-u.ac.jp

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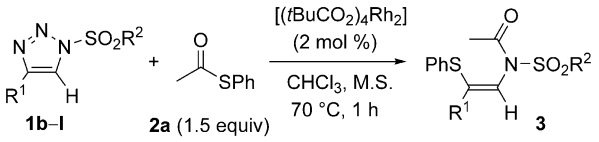
complex **A**. The sulfur atom of **2a** is more nucleophilic than the carbonyl oxygen atom for nucleophilic addition to the electrophilic carbene center of **A**, thus forming the zwitterionic intermediate **B**. The anionic rhodium of **B** releases an electron pair, which induces intramolecular acyl migration from the sulfur atom to the imino nitrogen atom to give the *Z* isomer of **3a** stereoselectively.[19]

The triazoles **1**, having a variety of substituents at the C4-position were subjected to the sequential sulfenylation/acyl migration reaction with *S*-phenyl thioacetate (**2a**; Table 1).

Table 1: Rhodium(II)-catalyzed reaction of various triazoles (**1**) with *S*-phenyl thioacetate (**2a**).[a]



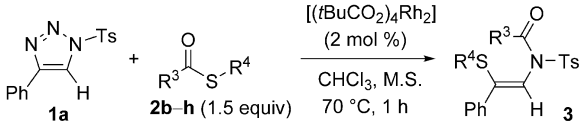
Entry	**1**	R^1	R^2	**3**	Yield [%][b]
1	**1b**	*p*-Tol	*p*-Tol	**3b**	95
2	**1c**	*p*-$MeOC_6H_4$	*p*-Tol	**3c**	88
3	**1d**	*p*-$CF_3C_6H_4$	*p*-Tol	**3d**	86
4	**1e**	3-thienyl	*p*-Tol	**3e**	82
5	**1f**	1-cyclohexenyl	*p*-Tol	**3f**	89[c]
6	**1g**	*n*Pr	*p*-Tol	**3g**	30[c]
7	**1h**	Ph	*p*-$MeOC_6H_4$	**3h**	88
8	**1i**	Ph	*p*-Br-C_6H_4	**3i**	92
9	**1j**	Ph	*o*-Tol	**3j**	80
10	**1k**	Ph	Me	**3k**	80
11	**1l**	Ph	*n*Bu	**3l**	78

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), and M.S. (40 mg) in $CHCl_3$ (2 mL) were heated at 70 °C for 1 h in the presence of $[(tBuCO_2)_4Rh_2]$ (4.0 μmol). [b] Yield of isolated product (average of two runs). [c] **2a** (2.0 mmol) in $CHCl_3$ (0.5 mL) in the presence of $[(tBuCO_2)_4Rh_2]$ (10 μmol).

Triazoles (**1b–e**) possessing aryl and heteroaryl groups reacted well to afford the corresponding products **3b–e** in yields ranging from 82 to 95% (entries 1–4). Notably, the *Z* isomers were exclusively obtained. The 1-cyclohexenyl-substituted triazole **1f** successfully participated in the reaction (entry 5). However, the *n*-propyl-substituted triazole **1g** gave the product **3g** in 30% yield as a result of an intramolecular 1,2-hydride shift occurring with the rhodium carbene complex[20] (entry 6). Not only aryl sulfonyl groups but also alkyl sulfonyl groups were compatible and afforded the products **3h–l** in good yields (entries 7–11).

Various thioesters (**2**) were subjected to the sequential reaction with **1a** (Table 2).[21] The *S*-aryl and *S*-alkyl thioesters **2b–f** afforded the corresponding products **3m–q** in yields ranging from 65 to 91% (entries 1–5). The *O*-(*tert*-butyl) *S*-phenyl thiocarbonate **2g** was also converted into the *N*-Boc-substituted product **3r** (entry 6). Although it has been reported that the reaction with allyl phenyl sulfide causes [2,3]-sigmatropic rearrangement to give α-allyl-α-phenylsulfanyl imines,[11a,b] *S*-allyl thioacetate (**2h**) resulted in the selective formation of the β-phenylsulfanyl enamide **3s** through an acyl migration process (entry 7).

Table 2: Rhodium(II)-catalyzed reaction of 4-phenyl-1-tosyl-1,2,3-triazole (**1a**) with various thioesters (**2**).[a]



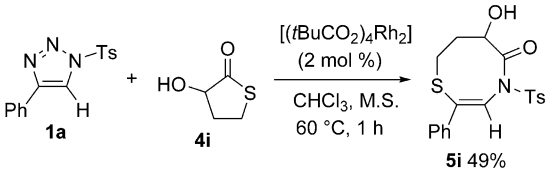
Entry	**2**	R^3	R^4	**3**	Yield [%][b]
1	**2b**	Me	*p*-$MeOC_6H_4$	**3m**	91
2	**2c**	Me	*p*-NCC_6H_4	**3n**	65
3	**2d**	Me	Et	**3o**	86[c]
4	**2e**	Ph	Ph	**3p**	67
5	**2f**	Ph	*n*Bu	**3q**	78
6	**2g**	*t*BuO	Ph	**3r**	54
7	**2h**	Me	Allyl	**3s**	94[d]

[a] The reaction conditions were the same as those in Table 1. [b] Yield of isolated product (average of two runs). [c] 90 °C. [d] 3 h.

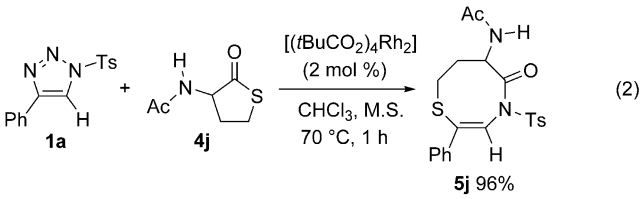
We next envisaged that, if cyclic thioesters (thiolactones) were used as the substrate, an analogous acyl migration process would expand the ring size by three atoms,[22] thus forming medium-sized lactams containing a vinyl sulfanyl moiety. Thus, the five-membered thiolactone **4a** was reacted with **1a** under the standard reaction conditions (Table 3, entry 1). The eight-membered lactam **5a** was produced in 83% yield through a sequential sulfenylation/acyl migration process, as we expected. The ring-expansion reaction worked well with the substituted γ-thiolactones **4b–e** to give the corresponding eight-membered lactams **5b–e** in yields ranging from 77 to 98% (entries 2–5). The unsaturated γ-thiolactone **4f** afforded the product **5f** in 79% yield (entry 6). Four- and six-membered thiolactones, **4g** and **4h**, respectively, were converted into the corresponding seven- (**5g**) and nine-membered lactams (**5h**; entries 7 and 8).

The chemoselectivity of the present ring-expansion reaction was investigated by employing thiolactones possessing hydroxy and amide groups, which are prone to other reactions such as O–H and N–H insertion reactions.[9,10] The reaction of **1a** with the hydroxy-substituted thiolactone **4i** afforded the ring-expanded product **5i** as the major product (49% yield) [Eq. (1)]. The amide-substituted thiolactones **4j** and **4k** also gave rise to the ring-expanded products **5j** and **5k**, respectively, in high yields [Eqs (2) and (3); Boc = *tert*-butoxycarbonyl]. These results indicate that the sulfenylation reaction occurred preferentially over the O–H and N–H insertion reactions.

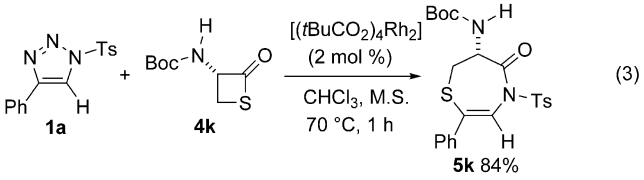
The one-pot synthesis of β-sulfanyl enamides starting from terminal alkynes was carried out to demonstrate the practical convenience of the present method [Eqs (4) and (5)]. Initially, a solution of phenylacetylene (**6**; 1.0 equiv), tosyl azide (1.0 equiv), and CuTC (5.0 mol%) in chloroform



(1)



(2)



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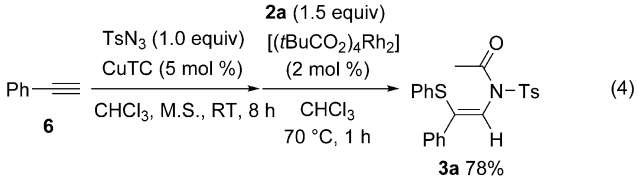
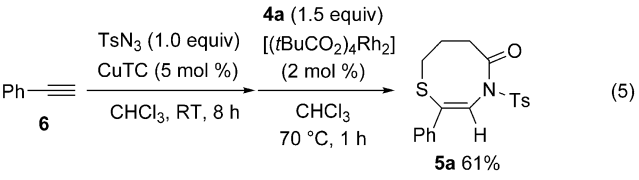


(4)

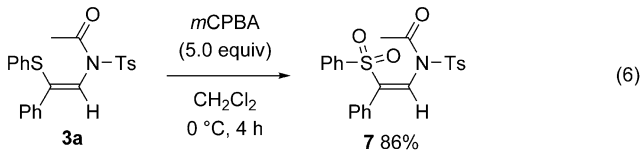


(5)

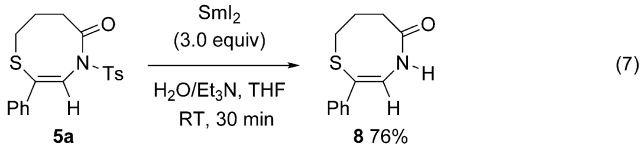
was stirred at room temperature for 8 hours, thus generating **1a** in situ. Then, the thioesters (1.5 equiv) and [(*t*Bu-CO_2)$_4$$Rh_2$] (2.0 mol%) were added to the same reaction vessel, which was heated at 70°C for 1 hour. The products **3a** and **5a** were obtained in good yields. Thus, the crude reaction mixture, including the copper catalyst, could be directly subjected to the rhodium-catalyzed reaction in the second step, thus saving a significant amount of time and solvent required for a workup/purification procedure after the first 1,3-dipolar cycloaddition.[23]

The sulfanyl moiety of **3a** was oxidized upon treatment with *m*-chloroperbenzoic acid (*m*CPBA) to give the β-sulfonyl enamide **7** with retention of the geometry [Eq. (6)].

The secondary amide **8** was obtained when **5a** was detosylated using samarium(II) iodide in the presence of water and triethylamine [Eq. (7); THF = tetrahydrofuran].[24]

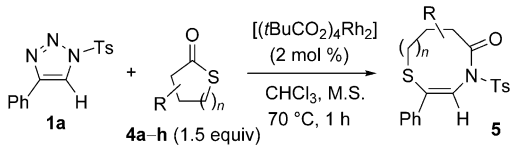


(6)



(7)

Table 3: Rhodium(II)-catalyzed ring expansion of thiolactones (**4**) with **1a**.[a]



Entry	4	5	Yield [%][b]
1	**4a**	**5a**	83 (81)[c]
2	**4b**	**5b**	92
3	**4c**	**5c**	77
4	**4d**	**5d**	89
5	**4e**	**5e**	98
6	**4f**	**5f**	79
7	**4g**	**5g**	87
8	**4h**	**5h**	75

[a] The reaction conditions were the same as those in Table 1. [b] Yield of the isolated product (average of two runs). [c] Yield obtained on a 4.0 mmol scale using 1.2 g of **1a**.

In summary, we have disclosed the unique reactivity of thioesters toward α-imino rhodium complexes, and developed a new method for the regio- and stereoselective synthesis of β-sulfanyl enamides starting from terminal alkynes. The procedure was successfully applied to the ring-expansion reaction of thiolactones, thus leading to the formation of medium-membered lactams containing a vinyl sulfanyl moiety.

Keywords: carbenoids · copper · heterocycles · rhodium · sulfur

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