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Rhenium-Catalyzed Regio- and Stereoselective Synthesis of γ-Thio-α,β-unsaturated Ketones via Insertion of Terminal Alkynes into the C–S Bond

Mitsumi Nishi, Yoichiro Kuninobu,*,† and Kazuhiko Takai*

Division of Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

kuninobu@mol.f.u-tokyo.ac.jp; ktakai@cc.okayama-u.ac.jp

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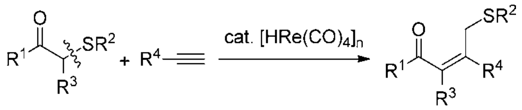
ABSTRACT



regio- and stereoselectively

The reaction of α-thioketones and alkynes in the presence of a rhenium catalyst, $[HRe(CO)_4]_n$, gave γ-thio-α,β-unsaturated ketones in excellent yields. The alkynes were inserted into the carbon–sulfur bond of the α-thioketones, and isomerization of a double bond provided the products with high regio- and stereoselectivities. This reaction also proceeded in an intramolecular fashion.

Regio- and stereoselective insertion of alkynes into the single bond of organic substrates is a useful and important strategy for synthesizing multisubstituted alkenes. Utilization of transition metal catalysts for such transformations is a promising method for practical uses; however, problems of regio- and stereoselectivities should first be solved. Recently, several transformations with high regio- and stereoselectivities have been reported[1] including ours.[2]

Many natural products, drugs, and organic functional materials contain sulfur atoms and are used as reagents, oxidants, and leaving groups in synthetic organic chemistry. When organosulfur compounds are synthesized by the above-mentioned insertion method, several difficulties arise. For example, the formation of radical species by homolytic cleavage of the carbon–sulfur bond which can sometimes react to produce regio- and stereoisomers, and the organosulfur compounds can cause poisonining of the transition metal catalysts. To overcome these difficulties, rhodium, palladium, platinum, and gold salts (or complexes) are usually employed as catalysts for insertion of a molecule into a C–S bond (carbothiolation),[3] such as

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[†] Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

(1) For recent examples, see: (a) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771. (b) Huffman, M. A.; Liebeskind, L. S.; Pennington, W. T. *Organometallics* **1992**, *11*, 255. (c) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629. (d) Kondo, T.; Nakamura, A.; Okada, T.; Suzuki, N.; Wada, K.; Mitsudo, T.-a. *J. Am. Chem. Soc.* **2000**, *122*, 6319. (e) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T.-a. *Angew. Chem., Int. Ed.* **2004**, *43*, 5369. (f) Murakami, M.; Itahasi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976. (g) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (h) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423. (i) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639. (j) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932. (k) Murakami, M.; Ashida, S. *Chem. Commun.* **2006**, 4599. (l) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (m) Shibata, T.; Nishikawa, G.; Endo, K. *Synlett* **2008**, 765. (n) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594. (o) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (p) Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412. (q) Chen, X.; Chen, D.; Lu, Z.; Kong, L.; Zhu, G. *J. Org. Chem.* **2011**, *76*, 6338.

(2) (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368. (b) Kuninobu, Y.; Takata, H.; Kawata, A.; Takai, K. *Org. Lett.* **2008**, *10*, 3133. (c) Kuninobu, Y.; Kawata, A.; Nishi, M.; Takata, H.; Takai, K. *Chem. Commun.* **2008**, 6360. (d) Kuninobu, Y.; Kawata, A.; Nishi, M.; Yudha, S. S.; Chen, J.; Takai, K. *Chem.—Asian J.* **2009**, *4*, 1424. (e) Kuninobu, Y.; Matsuzaki, H.; Nishi, M.; Takai, K. *Org. Lett.* **2011**, *13*, 2959.

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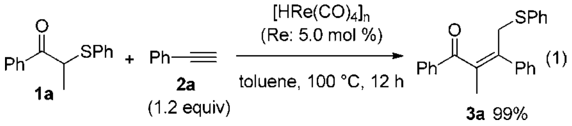
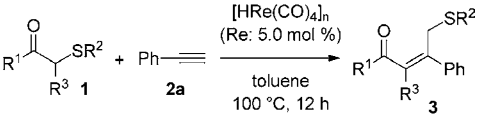
alkynylthiolation,[4] arylthiolation,[5] alkenylthiolation,[6] allylthiolation,[7] acylthiolation,[8] iminothiolation,[9] alkylthiolation,[10] intramolecular carbothiolation,[11] and so on.[12,13] We report herein the first example of insertion of alkynes into the C−S bond of α-thioketones, followed by isomerization of the olefin moiety to give γ-thio-α,β-unsaturated ketones with high regio- and stereoselectivity using a rhenium catalyst.

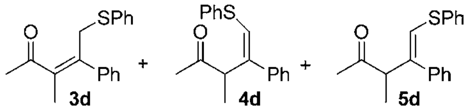
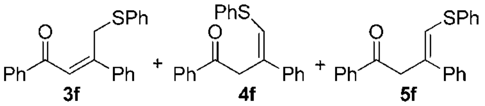
Treatment of α-thioketone **1a** with 1.2 equiv of alkyne **2a** in the presence of a catalytic amount of the rhenium catalyst, $[\mathrm{HRe(CO)_4}]_n$, in toluene at 100 °C for 12 h gave γ-thio-α,β-unsaturated ketone **3a** in 99% yield (eq 1).[14−16] The single product **3a** was obtained in excellent yield among the possible regio- and stereoisomers.



First, we investigated the scope of α-thioketones (Table 1). α-Thioketones with an electron-donating or -withdrawing group on the aromatic ring at the R^1 position gave γ-thio-α,β-unsaturated ketones **3b** and **3c** in 97% and 90% yields, respectively (entries 1 and 2). The desired reaction proceeded well without loss of the bromine atom (entry 2). When α-thioketone **1d** having a methyl group at the R^1 position was employed, the conversion was quantitative; however, a mixture of three regio- and stereoisomers **3d**, **4d**, and **5d** was formed (entry 3). The corresponding γ-thio-α,β-unsaturated ketone **3e** was obtained in 74% yield using α-thioketone **1e** bearing an aliphatic substituent at the R^2 position (entry 4). In the case of using an α-thioketone without a substituent at the α-position, **1f**, a mixture of three regio- and stereoisomers **3f**, **4f**, and **5f** was generated (entry 5). The desired reaction did not occur when 2-methyl-1-phenyl-2-(phenylthio)-1-propanone and ethyl 2-(methylthio)acetate were used. The insertion reaction did not proceed when using 2-phenoxypropiophenone and 2-phenoxyacetophenone (β-keto ethers) instead of α-thioketones **1a** and **1f**.

Table 1. Reactions between Several α-Thioketones **1** and Phenylacetylene (**2a**)[a]



entry	R^1	R^2	R^3		product	% yield
1	4-MeOC_6H_4	Ph	Me	**1b**	**3b**	97
2	4-BrC_6H_4	Ph	Me	**1c**	**3c**	90
3	Me	Ph	Me	**1d**	 **3d** **4d** **5d** **3d** + **4d** + **5d**	99 [9:48:43][b]
4[c]	Ph	$^{n}C_{12}H_{25}$	Me	**1e**	**3e**	74
5[d]	Ph	Ph	H	**1f**	 **3f** **4f** **5f** **3f** + **4f** + **5f**	58 [8:75:17][e]

[a] **2a** (1.2 equiv). [b] The ratio of **3d**, **4d**, and **5d** is given in square brackets. [c] 135 °C. [d] **2a** (2.0 equiv), 135 °C. [e] The ratio of **3f**, **4f**, and **5f** is given in square brackets.

Next, the scope of alkynes was investigated (Table 2). The corresponding γ-thio-α,β-unsaturated ketones **3g** and **3h** were provided in excellent yields when aryl alkynes with an electron-donating or -withdrawing group at the *para*-position, **2b** and **2c**, respectively, were used (entries 1 and 2). Aryl acetylene bearing a bromine atom, **2d**, afforded γ-thio-α,β-unsaturated ketone **3i** in 99% yield without loss of the bromine atom (entry 3). The corresponding γ-thio-α,β-unsaturated ketones **3j** and **3k** were produced when aryl acetylenes having a methoxy group at the *meta*- or

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(3) For a review, see: (a) Kuniyasu, H.; Kurosawa, H. *Chem.—Eur. J.* **2002**, *8*, 2660. (b) Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2006**, *35*, 1320. (c) Kuniyasu, H.; Kambe, N. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 701.

(4) (a) Arisawa, M.; Igarashi, Y.; Tagami, Y.; Yamaguchi, M.; Kabuto, C. *Tetrahedron Lett.* **2011**, *52*, 920. (b) Iwasaki, M.; Fujino, D.; Wada, T.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Chem.—Asian J.* **2011**, *6*, 3190.

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(7) Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *Org. Lett.* **2007**, *9*, 263.

(8) (a) Minami, Y.; Kuniyasu, H.; Kambe, N. *Org. Lett.* **2008**, *10*, 2469. (b) Minami, Y.; Kuniyasu, H.; Miyafuji, K.; Kambe, N. *Chem. Commun.* **2009**, 3080.

(9) Minami, Y.; Kuniyasu, H.; Sanagawa, A.; Kambe, N. *Org. Lett.* **2010**, *12*, 3744.

(10) (a) Choi, N.; Kabe, Y.; Ando, W. *Tetrahedron Lett.* **1991**, *32*, 4573. (b) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649.

(11) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. See also, refs 1h and 10b.

(12) (a) Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* **2001**, *123*, 2899. (b) Kamiya, I.; Kawakami, J.-i.; Yano, S.; Nomoto, A.; Ogawa, A. *Organometallics* **2006**, *25*, 3562. (c) Ozaki, T.; Nomoto, A.; Kamiya, I.; Kawakami, J.-i.; Ogawa, A. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 155.

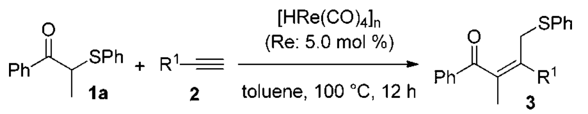
(13) Another method to synthesize organosulfur compounds is insertion of carbon monoxide or isocyanides into the C−S bond; see: (a) Khumtaveeporn, K.; Alper, H. *J. Org. Chem.* **1994**, *59*, 1414. (b) Tobisu, M.; Ito, S.; Kitajima, A.; Chatani, N. *Org. Lett.* **2008**, *10*, 5223.

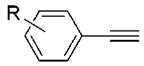
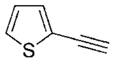
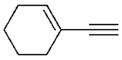
(14) Investigation of several catalysts (alkyne (2.4 equiv), 135 °C): $\mathrm{Re_2(CO)_{10}}$, >99%; $\mathrm{ReBr(CO)_5}$, 10%; $\mathrm{[ReBr(CO)_3(thf)]_2}$, 28%; $\mathrm{Mn_2(CO)_{10}}$, 11%; $\mathrm{MnBr(CO)_5}$, trace; and $\mathrm{Pd(OAc)_2}$, $\mathrm{PtCl_2}$, $\mathrm{PtCl_4}$; no reaction.

(15) This reaction did not proceed under UV irradiation or in the presence of azobisisobutyronitrile (AIBN, radical initiator) instead of the rhenium catalyst. These results indicate that this reaction does not proceed via a radical mechanism.

(16) In this reaction, the carbonyl group of α-thioketone **1a** is necessary to promote the reaction. In fact, insertion of alkyne **2a** into the C−S bond of phenethyl phenyl sulfide did not proceed.

Table 2. Reactions between α-Thioketone **1a** and Several Alkynes **2**[a]



entry	alkyne		product	% yield
				
1	R = 4-MeO	**2b**	**3g**	95
2[b]	4-CF_3	**2c**	**3h**	90
3	4-Br	**2d**	**3i**	99
4	3-MeO	**2e**	**3j**	98
5	2-MeO	**2f**	**3k**	91
6[c]		**2g**	**3l**	80
7		**2h**	**3m**	92
8	$^{n}C_{10}H_{21}$—≡	**2i**	**3n**	78[d]

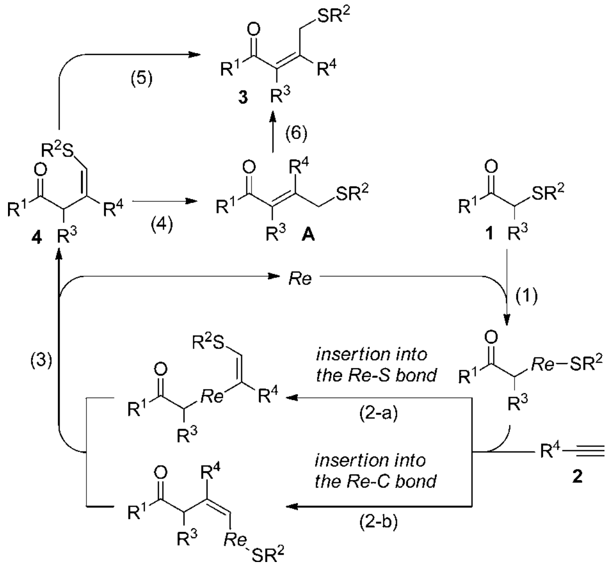
[a] **2** (1.2 equiv). [b] 24 h. [c] **2g** (2.0 equiv). [d] Single product was obtained. However, the stereochemistry of **3n** was not determined.

ortho-position, **2e** and **2f**, respectively, were used (entries 4 and 5). The insertion reaction also proceeded when a terminal alkyne with a heteroaromatic ring, **2g**, was employed as the substrate (entry 6). Enyne **2h** and aliphatic acetylene **2i** also gave the corresponding γ-thio-α,β-unsaturated ketones **3m** and **3n** in 92% and 78% yields, respectively (entries 7 and 8). However, the desired reaction did not proceed with the internal alkynes of diphenylacetylene, 1-phenyl-1-propyne, and 6-dodecyne, and (triisopropylsilyl)acetylene even at a higher temperature.

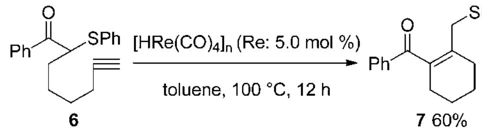
Although insertion of unsaturated bonds into a C–C bond of β-keto sulfones was observed in previous work,[17] the insertion occurred at the C–S single bond based on the structure of product **3a** in eq 1.

The proposed mechanism for the formation of unsaturated ketones **3** and **4** is as follows (Scheme 1): (1) oxidative addition of α-thioketone **1** to the rhenium center (C–S bond activation);[18] (2-a) insertion of alkyne **2** to the formed Re–S bond or (2-b) insertion of alkyne **2** to the formed Re–C bond; (3) reductive elimination to give γ-thio-α,β-unsaturated ketone **4**; (4) isomerization of the olefin moiety of **4** to provide **3** and/or **A**; and (5) isomerization of **A** to **3** due to thermodynamic stability.

Scheme 1. Proposed Mechanism for the Formation of γ-Thio-α,β-unsaturated Ketones **3** and **4**



The insertion reaction also proceeded in an intramolecular fashion (eq 2). By treating the α-thioketones having a 5-hexynyl chain at the α-position, **6**, with a catalytic amount of the rhenium catalyst, intramolecular insertion occurred and the corresponding cyclohexene derivative **7** was afforded in 60% yield.



(2)

In summary, we have succeeded in the rhenium-catalyzed regio- and stereoselective synthesis of γ-thio-α,β-unsaturated ketones from α-thioketones and alkynes by insertion of alkynes into the C–S bond of α-thioketones. This is the first example of carbothiolation of an alkyne by an α-thioketone and subsequent isomerization. In addition, cyclic γ-thio-α,β-unsaturated ketones could be synthesized by the intramolecular reaction. We hope that this reaction will become a useful method to synthesize organosulfur compounds.

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Supporting Information Available. General experimental procedure and characterization data for γ-thio-α,β-unsaturated ketones. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

[17] In the case of β-keto sulfones instead of α-thioketones, alkynes insert into a C–C single bond of β-keto sulfones. See: ref 2e.

[18] For recent examples of transformations via oxidative addition to a C–S bond, see: (a) Arisawa, M.; Toriyama, F.; Yamaguchi, M. *Chem. Pharm. Bull.* **2010**, *58*, 1349. (b) Arisawa, M.; Toriyama, F.; Yamaguchi, M. *Tetrahedron Lett.* **2011**, *52*, 2344.