ORGANIC LETTERS

2009
Vol. 11, No. 3
625−627

Rhodium-Catalyzed Methylthio Transfer Reaction between Ketone α-Positions: Reversible Single-Bond Metathesis of C−S and C−H Bonds

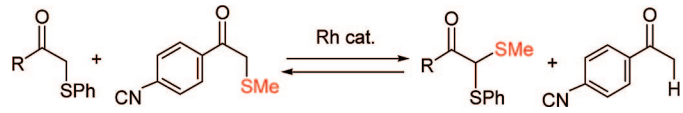
Mieko Arisawa, Katsunori Suwa, and Masahiko Yamaguchi*,†

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan

yama@mail.pharm.tohoku.ac.jp

Received November 19, 2008

ABSTRACT



In the presence of a catalytic amount of $RhH(PPh_3)_4$ and 1,2-bis(diphenylposphino)ethane (dppe), α-phenylthio ketones were methylthiolated with *p*-cyano-α-methylthioacetophenone giving α-phenylthio-α-methylthio ketones. The methylthio transfer reaction between the ketone α-positions was reversible and at equilibrium, and the methylthio group was transferred in preference to the phenylthio group. The reaction of tertiary alkyl methylthiomethyl ketones proceeded in high yields; the reaction of diastereomeric 4-(*tert*-butyl)-2-phenylthiocyclohexanones gave an axial 2-methylthiolated product.

Transition-metal-catalyzed reversible cleavage (or formation) of the C−S bond is a novel reaction that can be used for the synthesis of organosulfur compounds. The organometallic intermediates possessing the C−M and/or M−S structure formed by this process exhibit various reactivities, transferring either carbon or sulfur groups to other organic molecules, and the overall processes result in the formation of new C−S bonds as well as C−C, S−S, or C−H bonds.[1] The reversibility of the reaction broadens the scope of the synthesis if the equilibrium can be shifted to a desired product.

In addition, such reactions allow the organosulfur synthesis to be carried out under mild conditions and in an energy saving manner, when compared with the conventional synthesis employing stoichiometric amounts of bases and highly reactive sulfur reagents.To develop such a novel and efficient method, understanding and control of the reactivity of the C−M and/or M−S intermediates is critical. During our investigations on the development of rhodium-catalyzed transformations of organosulfur compounds,[2a] we reported rhodium-catalyzed alkylthio exchange reactions of 1-(alkylthio)alkynes[2b] and thioesters.[2c] The reactions, a single-bond metathesis of C−S and S−S bonds, contained reversible C−S bond cleavage and formation and reached equilibrium rapidly. The C−C bond formation reaction by the single-bond metathesis of C−S and C−S bonds has also been developed.[2d] In this paper, we describe a novel rhodium-catalyzed reaction containing reversible C−S bond cleavage and C−H activation: the intermolecular transfer of a methylthio group between the ketone α-positions

† WPI Research Center, Advanced Institute for Materials Research, Tohoku University, Sendai 980-8577, Japan.

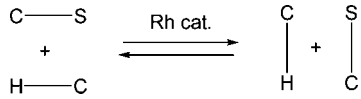
(1) Examples of metal-catalyzed reactions with C−S bond cleavage. Dehydrosulfurization reaction. Review: (a) Sánchez-Delgado, R. A. Hydrodesulfurization and Hydrodenitrogeneation. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M., Eds.; Elsevier: Amsterdam, 2007; Vol. 1, p 759. Organometallic substitution reaction. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637. (c) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 43. (d) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449. (e) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (f) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (g) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803.

(2) (a) Arisawa, M.; Yamaguchi, M. *Pure Appl. Chem.* **2008**, *80*, 993. (b) Arisawa, M.; Fujimoto, K.; Morinaka, S.; Yamaguchi, M. *J. Am. Chem. Soc.* **2005**, *127*, 12226. (c) Arisawa, M.; Kubota, T.; Yamaguchi, M. *Tetrahedron Lett.* **2008**, *49*, 1975. (d) Arisawa, M.; Tagami, Y.; Yamaguchi, M. *Tetrahedron Lett.* **2008**, *49*, 1593.

10.1021/ol802619e CCC: $40.75
Published on Web 01/13/2009

and a single bond metathesis of C−S and C−H bonds to form C−H and C−S bonds (Scheme 1). α-Phenylthio

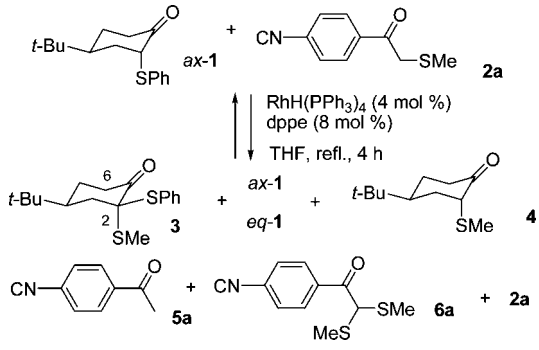
Scheme 1



ketones underwent methylthiolation reaction at the α-position giving α-phenylthio-α-methylthio ketones, and α-methylthio-*p*-cyanoacetophenone was found to be an efficient methylthio transfer reagent for this reaction. This study revealed a novel reactivity of the C−Rh and/or Rh−S intermediates formed by reversible C−S bond cleavage.

When (2*R**,4*S**)-4-(*tert*-butyl)-2-thiophenylcyclohexanone *ax*-**1** (5 equiv) and α-methylthio-*p*-cyanoacetophenone **2a** were reacted in the presence of $RhH(PPh_3)_4$ (4 mol %) and dppe (8 mol %) in refluxing THF for 4 h, (2*R**,4*S**)-4-(*tert*-butyl)-2-methythio-2-phenylthiocyclohexanone **3** was obtained in 45% yield based on **2a** and *p*-cyanoacetophenone **5a** in 84% yield (Table 1, entry 5). A 3:2 mixture of *ax*-**1**

Table 1. α-Methylthio Transfer Reaction of *ax*-**1** and **2a**



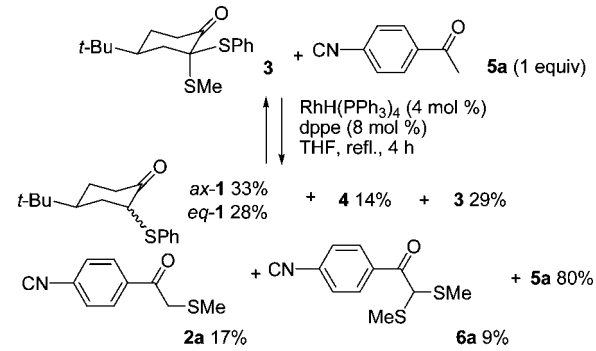
		yield[a] (%)					
entry	**1** (equiv)	**3**	**5a**	**1**[b]	**4**	**2a**	**6a**
1	0.33	12[c]	30[c]	79	7	48	19
2	1	21	58	85	1	35	10
3	3	37	70	87	2	40	6
4[d]		30	55	94	5	43	7
5	5	45	84	92	1	11	4

[a] Yield based on **2a**. [b] Yield of 3:2 mixtures of *ax*-**1** and *eq*-**1** based on **1**. [c] Yield based on **1**. [d] The isomer *eq*-**1** was used.

and *eq*-**1** was recovered quantitatively, which was accompanied by a very small amount of α-methylthiolated cyclohexanone **4** (1%), a methylthio exchanged product of *ax*-**1**. Other products isolated include α,α-dimethylthioacetophenone **6a** (4%) and the recovery of **2a** (11%). The phenylthio C−S bond of *ax*-**1** was not affected, and only the methylthio C−S bond reacted. The product **3** was obtained as a single isomer, and its stereochemistry was determined by the presence of NOE between the 2-methylthio protons and the *axial*-6-proton. When the molar ratio *ax*-**1/2** was changed from 5 to 1, the yields of **3** and **5a** decreased (entries 2 and 3). The use of 3 equiv of **2a** decreased the yield of **3** and increased the yield of **6a**, the methylthio transfer product from **2a** to another **2a** (entry 1). Two methylthio transfer processes, the transformation of *ax*-**1** to **3** and **2a** to **6a**, appear to compete. These results indicate the formation of a C−Rh species at the α-position of **1**, which underwent methylthiolation with **2a** liberating **5a**. The formation of **5a** in larger amounts compared with **3** may be partly due to reduction by the phosphine.[3]

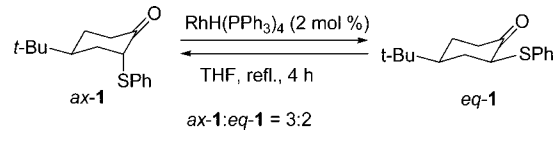
The reversibility of the methylthio transfer reaction was then examined. When equimolar amounts of **3** and **5a** were treated with rhodium catalyst in refluxing THF for 4 h, **1** was obtained in 61% yield as a mixture of *ax*-**1** and *eq*-**1** (Scheme 2). Regarding the acetophenone derivative, **2a**

Scheme 2



(17%) and **6a** (9%) were obtained. Thus, the methylthio transfer reaction between the ketone α-positions was concluded to be an equilibrium. That **2a** was formed from **5a** indicates the methylthio transfer reaction is not restricted to the α-phenylthio ketones, and various carbonyl compounds can be α-methylthiolated using appropriate combinations of substrates and catalyst. The reaction of the equatorial isomer *eq*-**1** gave **3** in 30% yield along with **5a** in 55% yield (Table 1, entry 4). That the same configuration of **3** was obtained both from *ax*-**1** and *eq*-**1** indicated the involvement of the same C−Rh intermediate. In addition, the methylthiolation of the intermediate was shown to occur at the *axial* site. The C−H activation and isomerization of **1** were confirmed to be catalyzed by the rhodium complex. When *ax*-**1** was treated with $RhH(PPh_3)_4$ (2 mol %) in refluxing THF for 4 h, a 3:2 mixture of *ax*-**1** and *eq*-**1** was obtained (Scheme 3).[4] No

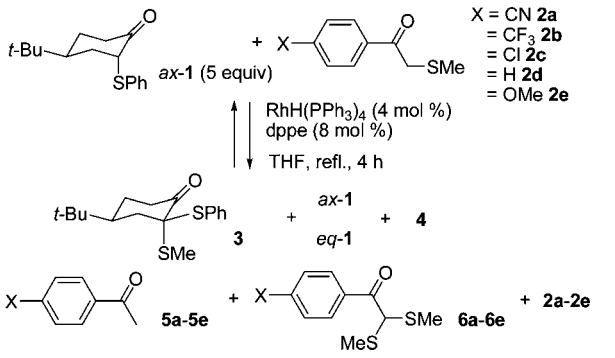
Scheme 3



reaction occurred in the absence of the complex, and dppe was not required for this reaction.

To compare the methylthio transfer ability of other ketones, several α-methylthioacetophenones with different *para* substituents were reacted with *ax*-**1** (5 equiv). When α-methylthiolated acetophenenone **2d** or *p*-methoxyacetophenone **2e** was used, **3** was obtained in low yields (Table 2, entries 4 and 5). In the case of **2e**, a substantial alkylthio

Table 2. Effect of the MethylthioTransfer Reagent



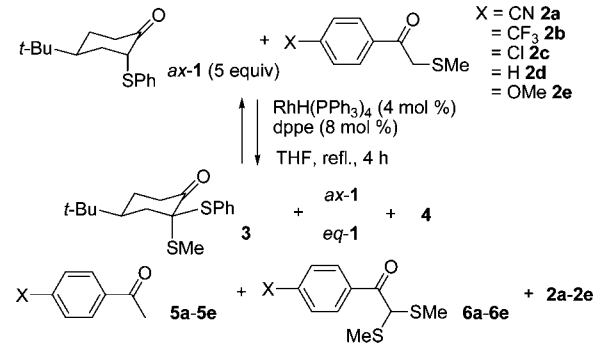
			yield[a] (%)					
entry	X		**3**	**5**	**1**[b]	**4**	**2**	**6**
1	CN	**a**	45	84	55	1	11	4
2	CF_3	**b**	38	74	85	6	17	trace
3	Cl	**c**	17	30	89	12	65	2
4	H	**d**	6	67	82	8	7(65)[c]	ND[d]
5	MeO	**e**	2	29	88	43[e]	26(44)[c]	ND[d]

[a] Yield based on **2**. [b] Yield of 3:2 mixtures of *ax*-**1** and *eq*-**1** based on **1**. [c] Yield of α-phenylthiolated acetophenone $ArCOCH_2SPh$. [d] Not detected. [e] A 6:1 mixture of **4** and its equatorial isomer.

exchange reaction took place, as indicated by the formation of **4** (43%) and α-phenylthioacetophenone (44%). *p*-Trifluoromethylacetophenone **2b** gave **3** in 38% yield (entry 2). The results indicated a higher methylthio transfer ability of the acetophenone derivatives with electron-withdrawing *para* groups. The reaction of dimethyl disulfide (1 equiv) and *ax*-**1** gave **3** only in 2% yield with the recovery of **1** in 79% as a 3:2 mixture of diastereomers, which was accompanied by a 5:2 mixture of **4** and its isomer (14%).

The reaction of adamantyl phenylthiomethyl ketone, *tert*-butyl phenylthiomethyl ketone, and 1-methylcyclohexyl phenylthiomethyl ketone with **2a** gave the methylthiolated products in 87%, 78%, and 84% yields, respectively (Scheme 4). Although the yields in this methylthiolation reaction were under thermodynamic control, these products were obtained in high yields. The reaction of **2a** and *p*-methoxy-α-phenylthioacetophenone **7** is an interesting example of the selective methylthio transfer giving *p*-methoxy-α-methylthio-

Scheme 4



α-phenylthioacetophenone **8** (45%) and **5a** (78%). Dithioacetals derived from **2a** and *p*-methoxyacetophenone **5e** were not formed.

α,α-Dialkylthio ketones have been used as intermediates in organic synthesis, and the conventional synthesis from ketones and α-alkylthio ketones employed stoichiometric amounts of bases to generate enolates or highly reactive sulfenylating reagents such as sulfenyl sulfones.[5] The synthesis described herein has the advantage of not using such high energy reagents, which irreversibly produce waste byproducts. It should also be noted that unsymmetrical thioacetals were obtained by this method.

A rhodium catalyst brings a single-bond metathesis reaction of C−H and C−S bonds to equilibrium. Similar to proton transfer at the ketone α-position via enol/enolates under acidic/basic conditions, the methylthio group can be transferred in an intramolecular fashion via rhodium intermediates possessing C−Rh and/or Rh−S structures. We have also shown that the methylthio group can be introduced to and removed from organic molecules under equilibrium, and studies to explore efficient methylthio transfer reagents, catalysts, and systems to shift equilibrium are now underway.

Acknowledgment. This work was supported by JSPS (Nos. 16109001 and 17689001), and WPI Initiative, MEXT, Japan. M.A. expresses her thanks for the Grant-in-Aid for Scientific Research on Priority Areas, "Advanced Molecular Transformation of Carbon Resources", from MEXT (Nos. 18037005 and 19020008).

Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802619E

(3) When **2a** was reacted with $RhH(PPh_3)_4$ (4 mol %) and dppe (8 mol %) in refluxing THF for 4 h, **5a** was obtained in 9% yield. No reaction took place when Rh complex or phosphine was not added.

(4) Related observation with 2-phenylthiocyclohexanone. (a) Özbal, H.; Zajac, W. W., Jr. *Tetrahedron Lett.* **1979**, *20*, 4821. Also see: (b) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(5) For examples: $O_2NC_6H_4SSMe$. (a) Grossert, J. S.; Dubey, P. K. *Chem. Commun.* **1982**, 1183. (b) Tsunetsugu, J.; Ikeda, T.; Suzuki, N.; Yaguchi, M.; Sato, M.; Ebine, S.; Morinaga, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 785. (c) Trost, B. M.; Mao, M. K.-T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965. (d) Sugihara, Y.; Wakabayashi, S.; Saito, N.; Murata, I. *J. Am. Chem. Soc.* **1986**, *108*, 2773. RSTs. (e) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *J. Org. Chem.* **1971**, *36*, 1137. (f) Trost, B. M.; Hiroi, K.; Jungheim, L. N. *J. Org. Chem.* **1980**, *45*, 1839. (g) Tosaka, A.; Ito, S.; Miyazawa, N.; Shibuya, M.; Ogasawara, K.; Iwabuchi, Y. *Heterocycles* **2006**, *70*, 153. Na_2Te/disulfide. (i) Padmanabhan, S.; Ogawa, T.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1358.