Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 1727–1729
Tetrahedron Letters

Rhodium-catalyzed synthesis of isothiocyanate from isonitrile and sulfur

Mieko Arisawa, Masanori Ashikawa, Atsushi Suwa and Masahiko Yamaguchi*

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

Received 22 December 2004; revised 7 January 2005; accepted 7 January 2005
Available online 29 January 2005

Abstract—Rhodium complexes $RhH(PPh_3)_4$ and $Rh(acac)(CH_2{=}CH_2)_2$ catalyze sulfuration of isonitrile with sulfur giving isothiocyanates in high yields. The metal-catalyzed reaction is rapid in refluxing acetone, and completes within 3 h in most cases. The reaction exhibits induction period, which disappeared by preheating sulfur in refluxing acetone for 1.5 h. Use of several organic polysulfides in this transformation was examined in order to compare the reactivity.

Utilization of sulfur is a challenging synthetic methodology for the preparation of organosulfur compounds. Conventional methods, however, in general required harsh conditions. It was considered that transition metal catalyzed activation of elemental sulfur could be an interesting approach to control such sulfuration reaction. We investigated catalytic cleavage of organic disulfides with transition metal catalysts, which was utilized in the transformations such as disulfide exchange[1] or addition to unsaturated compounds.[2] As for the activation of elemental sulfur, we recently reported the catalytic exchange reaction of sulfur atom between organic polysulfides and elemental sulfur.[3] As an extension of the sulfur activation methodology, we describe here rhodium-catalyzed sulfuration reaction of isonitriles giving isothiocyanates.

Isothiocyanates are a group of compounds possessing biological activities, and a variety of methods were developed for their synthesis.[4] Reaction of isonitrile and a sulfur reagent is a convenient method, if sulfur could be used in the presence of an appropriate catalyst. Such transformation was reported by Sonoda employing selenium or tellurium catalysts.[5] As for the transition metal method, molybdenum catalyst was examined by Bargon and co-workers.[6] The reaction, however, was sluggish, and required 72 h in refluxing acetone for completion in the presence of 1 mol % complex. Described in the present study is a rhodium-catalyzed reaction of isonitrile and sulfur giving isothiocyanate. The reaction is much faster than the molybdenum method, and completes in most cases within 3 h at acetone reflux employing the same catalyst loading.

To a mixture of $RhH(PPh_3)_4$ (1 mol %) in acetone was added cyclohexyl isonitrile **1**, and the solution was stirred for 5 min at room temperature. Then, sulfur (1.2 atom equivalents) was added, and the mixture was heated at reflux for 2 h giving cyclohexyl isothiocyanate **2** in 91% yield (Table 1).[7] The rhodium complex is critical for the reaction, and **2** was not detected in its absence after 2 days at 50 °C in a sealed NMR tube. Triphenylphosphine sulfide was formed in 80% yield during the sulfuration, and the phosphine ligand appears not to be essential for the reaction. In accordance, screening of the metal complexes[8] revealed that a non-phosphine complex $Rh(acac)(CH_2{=}CH_2)_2$ was also effective, and gave the product in 88% yield under the same reaction conditions. In this case, the amount of sulfur could be reduced to 1.1 atom equivalents, since it was not consumed by phosphine. Several aliphatic and aromatic isonitriles were reacted with sulfur in the presence of $RhH(PPh_3)_4$ or $Rh(acac)(CH_2{=}CH_2)_2$, which gave similar results. It may reasonably be assumed that both reactions proceeded via the same active rhodium species lacking the phosphine ligand.

The reactions of $RhH(PPh_3)_4$ and $Rh(acac)$-$(CH_2{=}CH_2)_2$ catalysts exhibited induction periods. For example, the reaction of **1** and sulfur in the presence

---

Keywords: Rhodium complex; Sulfur; Isothiocyanate; Isonitrile; Induction period.

* Corresponding author. Tel.: +81 22 217 6812; fax: +81 22 217 6811; e-mail: yama@mail.pharm.tohoku.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.069

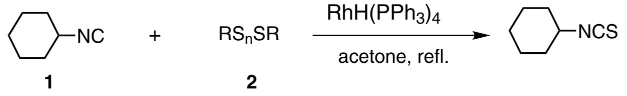
Table 1. Rh-catalyzed synthesis of isothiocyanate

$$\mathrm{RNC} + \mathrm{S_8} \xrightarrow[\text{acetone, refl.}]{\mathrm{RhH(PPh_3)_4}\text{ or }\mathrm{Rh(acac)(CH_2{=}CH_2)_2}} \mathrm{RNCS}$$

R	Time/h	Yield/%	
		Cat A[a]	Cat B[a]
cyclo-C_6H_{11}–	2	91	88
n-C_8H_{17}–	2	94	94
t-$BuCH_2CMe_2$–	1.5	90	87
$PhCH_2$–	2.5	95	91
$HOCH_2CMe_2CH_2$–	3	83	90
$Me_3SiOCH_2CMe_2CH_2$–	1.5	96	92
2,6-$Me_2C_6H_3$–	2.5	96	91
p-ClC_6H_4–	8	87	87
p-MeC_6H_4–	3	92	90
p-$MeOC_6H_4$	6	93	88

[a] Cat A: $RhH(PPh_3)_4$. Cat B: $Rh(acac)(CH_2{=}CH_2)_2$.

Table 2. Rh-catalyzed sulfuration of **1** with organic polysulfide



Entry	RS$_n$R	Time/h	Yield/%[a]
1	(n-Bu)$_2$S$_3$	1.5	7
2	(p-tol)$_2$S$_3$	1.5	1
3		5	82
4	Et$_2$S$_4$	1.5	68[a]
5	(p-tol)$_2$S$_4$	1.5	11[b]
6		5	94
7	(p-ClC$_6$H$_4$)$_2$S$_4$	1.5	10

[a] Recovered polysulfides: disulfide (12%), trisulfide (53%), tetrasulfide (20%), pentasulfide (5%), and hexasulfide (1%).

[b] Recovered polysulfides: disulfide (32%), trisulfide (30%), tetrasulfide (19%), and pentasulfide (19%).

of $RhH(PPh_3)_4$ started after ca. 40 min, and completed after 80 min (Fig. 1). It was ascribed to the slow formation of the true active species. Notably, the treatment of sulfur in refluxing acetone for 1.5 h prior to the reaction resulted in the disappearance of the induction period, which suggested the formation of an active 'sulfur' species.

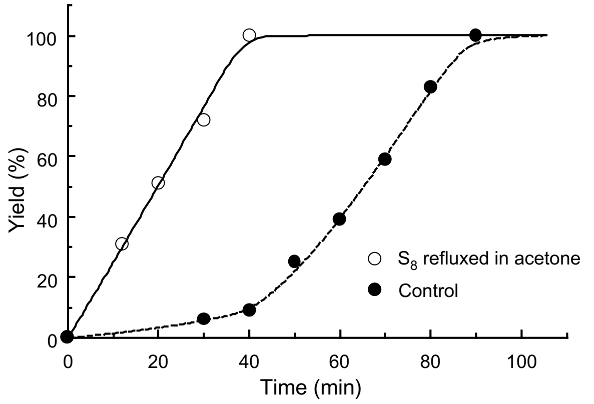
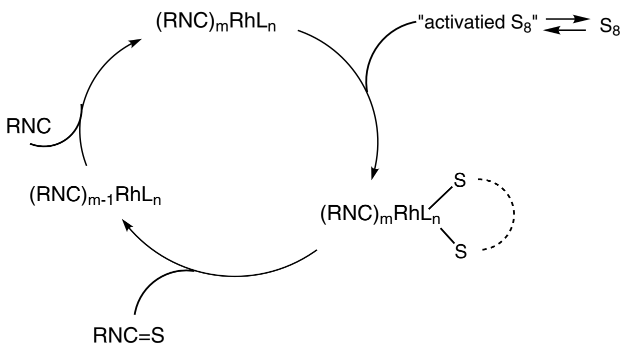


Figure 1. Time course of $RhH(PPh_3)_4$ catalyzed conversion of **1 to 2.**

In order to compare the reactivity of the sulfur reagents, equimolar amounts of organic polysulfides were reacted with **1** in refluxing acetone for 1.5 h in the presence of $RhH(PPh_3)_4$ (1 mol %) (Table 2). Diphenyl disulfide did not react with **1** under the conditions. The reactions of several trisulfides and tetrasulfides gave **2**, although less efficient than elemental sulfur. Dibutyl trisulfide[9] and di(*p*-tolyl) trisulfide[10] gave **2** in less than 20% yield after 1.5 h (entries 1 and 2). Diethyl tetrasulfide[11] turned out to be more reactive, and **2** was obtained in 68% yield (entry 4). The recovered diethyl polysulfides in this reaction contained mostly trisulfide (53%) with smaller amounts of disulfide (12%), tetrasulfide (20%), and the higher homologs. The sulfur transfer proceeded fairly cleanly from the tetrasulfide to **1** with the formation of trisulfide, and disproportionation of the polysulfides is not significant. Higher reactivity of the alkyl tetrasulfide compared to the alkyl trisulfide can be ascribed to the S–S bond dissociation energy, which was reported to be the following order: RSS–SSR < RSS–SR.[12] Di(*p*-tolyl) and di(*p*-chlorophenyl) tetrasulfides,[10] however, were less effective compared to diethyl tetrasulfide (entries 5 and 7). The recovered di(*p*-tolyl) polysulfides were a mixture of comparable amounts of disulfide (32%), trisulfide (30%), tetrasulfide (29%), and pentasulfide (19%). The sulfur exchange reaction rapidly took place in these aromatic cases, and the sulfuration of **1** was slower. It is noticed that the polysulfide sulfuration also exhibits induction period as indicated by the reactions of aromatic trisulfide and tetrasulfide (entries 3 and 6). The results again suggested the formation of reactive polysulfide species during the sulfur exchange reaction.[13]

The mechanism likely involves the initial formation of a low valent rhodium complex $(RNC)_mRhL_n$ from isonitrile and a rhodium species (Scheme 1). An activated sulfur species generated from elemental sulfur undergoes oxidative addition to the complex, and transfer of sulfur atom to isonitrile takes place giving isothiocyanate.[14,15] The mechanism is consistent with the observation that it is essential to add isonitrile to the rhodium complex prior to the addition of sulfur. Otherwise, no reaction took place.



Scheme 1.

Acknowledgements

This work was supported by grants from the Japan Society of Promotion of Science (Nos. 14207094 and 16109001). M.A. thanks support from NEDO of Japan (No. 02A44003d).

References and notes

1. Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2003**, *125*, 6624.
2. Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 763; Arisawa, M.; Suwa, A.; Fujimoto, K.; Yamaguchi, M. *Adv. Synth. Catal.* **2003**, *345*, 560; Arisawa, M.; Kozuki, Y.; Yamaguchi, M. *J. Org. Chem.* **2003**, *68*, 8964.
3. Arisawa, M.; Tanaka, K.; Yamaguchi, M., submitted for publication.
4. For examples, see: Moore, M. L.; Crossely, F. S. *Org. Synth.* **1955**, *3*, 599; Dyer, E.; Johnson, J. B. *J. Am. Chem. Soc.* **1932**, *54*, 781; Baxter, J. N.; Cymerman-Craig, J.; Moyle, M.; White, R. A. *J. Chem. Soc.* **1956**, 659; Bruson, H. R.; Eastes, J. W. *J. Am. Chem. Soc.* **1937**, *59*, 2012.
5. Fujiwara, S.; Shin-Ike, T.; Sonoda, N.; Aoki, M.; Okada, K.; Miyoshi, N.; Kambe, N. *Tetrahedron Lett.* **1991**, *32*, 3503; Fujiwara, S.; Shin-Ike, T.; Okada, N.; Aoki, M.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1992**, *33*, 7021.
6. Adam, W.; Bargon, R. M.; Bosio, S. G.; Schenk, W. A.; Stalke, D. *J. Org. Chem.* **2002**, *67*, 7037.
7. In a two-necked flask equipped with a reflux condenser were placed tetrakis(triphenylphosphine)hydriderhodium (1 mol %, 5.8 mg), cyclohexyl isonitrile **1** (0.5 mmol, 54.6 mg), and elemental sulfur (1.0 mmol atom, 32 mg) in acetone (1 mL) under an argon atmosphere. The mixture was stirred and heated in oil bath at reflux for 1.5 h. Then, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel giving cyclohexyl isothiocyanate **2** (62 mg, 89%). Purification of isonitrile by repeated recrystallization or distillation is very important for the high yield sulfuration, which may be due to the catalyst deactivation by small amounts of impurity.
8. Metal complexes examined were as follows, all of which exhibited modest activities: $Pd(OAc)_2$, $RhCl(PPh_3)_3$, $[RhCl(cod)]_2$, $Rh(cod)BF_4$, $Rh(acac)(CO)_2$.
9. Banerji, A.; Kalena, G. P. *Tetrahedron Lett.* **1980**, *21*, 3003.
10. Zysman-Colman, E.; Harpp, D. N. *J. Org. Chem.* **2003**, *68*, 2487.
11. Andrzej, Z. R.; Harpp, D. N. *Tetrahedron Lett.* **2000**, *41*, 7169.
12. Allen, T. L. *J. Chem. Phys.* **1959**, *31*, 1039; Kende, I.; Pickering, T. L.; Tobolsky, A. V. *J. Am. Chem. Soc.* **1965**, *87*, 5582.
13. For examples: Tebbe, F. N.; Wasserman, E.; Peet, W. G.; Vatvars, A.; Hayman, A. C. *J. Am. Chem. Soc.* **1982**, *104*, 4971; Bosser, G.; Anouti, M.; Paris, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1993.
14. Insertion of isonitrile into Pd–S bond: Kuniyasu, H.; Sugoh, K.; Su, M. S.; Kurosawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4669.
15. Pd-catalyzed reaction of disulfide and isonitrile: Kuniyasu, H.; Maruyama, A.; Kurosawa, H. *Organometallics* **1998**, *17*, 908.