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Direct Synthesis of Isothiocyanates from Isonitriles by Molybdenum-Catalyzed Sulfur Transfer with Elemental Sulfur†

Waldemar Adam,‡ Rainer M. Bargon,*,‡ Sara G. Bosio,‡ Wolfdieter A. Schenk,§ and Dietmar Stalke§

Institut für Organische Chemie and Institut für Anorganische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany,

adam@chemie.uni-wuerzburg.de

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The direct molybdenum-catalyzed sulfuration of a variety of isonitriles with elemental sulfur or propene sulfide as sulfur donors affords the corresponding isothiocyanates in good yields and under mild reaction conditions. A catalytic cycle is suggested, in which the molybdenum oxo disulfur complex operates as the active sulfur-transferring species. A novel adduct between the isonitrile and the molybdenum complex has been characterized by X-ray analysis and its association constant determined by UV−vis spectroscopy, but this adduct appears not to be involved in the sulfur-transfer process.

Introduction

In striking contrast to the variety of effective metal catalysts that are known for oxygen transfer reactions,[1] analogous sulfur-transfer processes are to date still rather scarce. So far, only three cases for the metal-catalyzed episulfidation of alkenes have been reported, namely the ruthenium-catalyzed episulfidation of cyclohexene,[2a] the rhodium-catalyzed episulfidation of norbornene and norbornadiene,[2b] and the molybdenum-catalyzed episulfidation of strained cyclic alkenes.[2c] Recently, Chandrasekaran and co-workers used a molybdenum complex to transform alkyl halides to disulfides, with latter added in situ to Michael acceptors such as α,β-unsaturated enones.[3] An attempted preparation of isothiocyanates by sulfur transfer to isonitriles with a stoichiometric amount of a molybdenum−disulfido complex was also reported, but instead of isothiocyanates, the corresponding thioureas were obtained.[4]

Our encouraging results in the metal-catalyzed episulfidation[2c] of cyclic olefins motivated us to assess whether isonitriles may be catalytically sulfurated by elemental sulfur with molybdenum−oxo complex **2** as catalyst; presumably a molybdenum disulfur complex[5] would operate as the sulfur-transfer agent. Such a direct synthesis of isothiocyanates has been documented in the sulfuration of isonitriles by an as yet unidentified sulfur-containing metalloenzyme[6b] and would correspond to a biomimetic methodology.[6]

The synthesis of isothiocyanates,[7] which exist in nature as marine sesquiterpenes,[8] has been extensively studied over the past decades, since they play an important role as anti-proliferatives[9] and in the therapy of blood cancer,[10] as enzyme inhibitors for the HIV virus,[11] and as herbicides.[12] They may be prepared from amines,[13] organic halides,[14] alkenes,[15] aldehydes,[16] and isonitriles.[17] These methods require stoichiometric amounts of reagents and often the hazardous thiophosgene or its derivatives need to be utilized.[13] In regard to the direct

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‡ Institut für Organische Chemie.

§ Institut für Anorganische Chemie.

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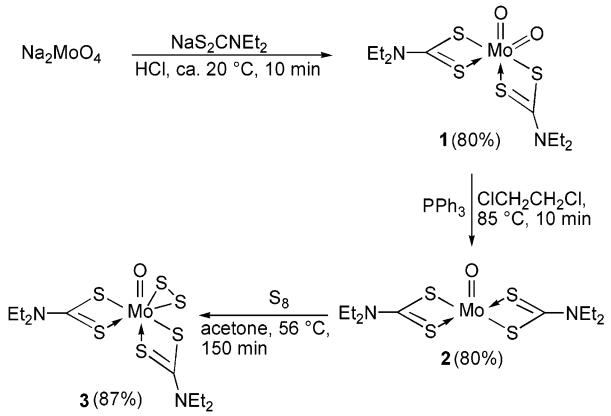
SCHEME 1. Preparation of the Molybdenum Complexes 2 and 3



method with elemental sulfur, only the selenium- and tellurium-catalyzed sulfurations of isonitriles have been reported,[17] but the toxicity of these chalcogens limits their use. These drawbacks we have now circumvented by developing the first direct molybdenum-catalyzed sulfuration of isonitriles with elemental sulfur, to afford a variety of isothiocyanates in good yields. Herein we report the results of this novel sulfuration and offer a mechanism for the catalytic sulfur-transfer process.

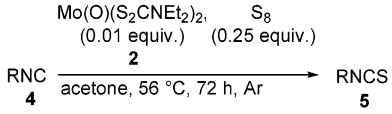
Results

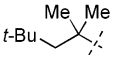
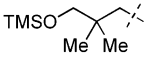
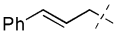
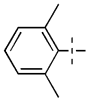
Molybdenum disulfur complex **3** was prepared according to the literature procedure in three steps from sodium molybdate (Scheme 1).[5,18,19] Ligation of diethyl dithiocarbamate with molybdate yielded dioxo complex **1** in 80% yield,[18] which was readily reduced by triphenylphosphine to air-sensitive oxo complex **2** in 80% yield.[19] The latter was heated in refluxing acetone with a stoichiometric amount of elemental sulfur to afford disulfur complex **3**, which acts as the active sulfur-transferring agent.[5]

Treatment of isonitriles **4** with an excess of elemental sulfur and a catalytic amount (0.01 equiv) of molybdenum−oxo complex **2** in refluxing acetone under an inert atmosphere of argon gas resulted in isothiocyanates **5** in up to 93% yield (Table 1). The consumption of isonitriles **4** was complete within 72 h, as monitored by TLC and ^{13}C NMR spectroscopy. This long reaction time could be reduced to 23 h for isonitrile **4b** (compare entries 2 and 3), with only a small decrease in the yield when 0.05 equiv of catalyst **2** was used.

Isothiocyanates **5** were purified by Kugelrohr distillation and the heat-sensitive derivatives by silica gel chromatography. When in a control experiment molybdenum catalyst **2** was omitted, the direct reaction of isonitrile **4b** with elemental sulfur in refluxing acetone gave only traces (<5%) of isothiocyanate **5b** even after 69 h, as detected by ^{13}C NMR spectroscopy. Thus, for the first time a variety of aliphatic and aromatic isonitriles

TABLE 1. Catalytic Sulfuration of Isonitriles 4 with Elemental Sulfur (S_8) as Sulfur Donor



Entry	R	RNC	yield [%][a] RNCS (**5**)
1	$CH_3(CH_2)_7$-	**4a**	93
2		**4b**	92
3		**4b**	80[b]
4		**4c**	88
5	*t*-Bu-	**4d**	80
6		**4e**	78
7	Bn-	**4f**	61
8		**4g**	68
9		**4h**	91
10	1-Naph-	**4i**	68

[a] Yield of pure isolated isothiocyanate after distillation, except **5d**, which was isolated by silica gel chromatography. [b] 0.05 equiv of catalyst **2** were used; 100% consumption of the isonitrile **4** after 23 h.

4 have been catalytically sulfurated with elemental sulfur. This catalytic sulfur-transfer process tolerates functionalities such as the trimethylsiloxy group in isonitrile **4e** (entry 6) and the carbon−carbon double bond in isonitrile **4g** (entry 8). The yields of the isolated products are generally good to excellent (Table 1).

Alkenyl isonitrile **4j** and isonitrile **4k** with an electron-withdrawing substituent could not be transformed to their isothiocyanates **5** with elemental sulfur under the conditions given in Table 1. The failure of this sulfur-transfer method with elemental sulfur is due to the fact that isonitrile **4j** and isothiocyanate **5k** do not persist in boiling acetone in the presence of Lewis acid.[20] However, when propene episulfide was used as the sulfur donor, the catalytic sulfuration was achieved in very good yield already at 20−25 °C in methylene chloride (Table 2).

As in the case of **4g**, the carbon−carbon double bond of isonitrile **4j** is not attacked under these sulfur-transfer conditions. Even base- or acid-sensitive functional groups as the hydroxy group in isonitrile **4l** and the acetal functionality in **4m** are easily transformed in good yields to their isothiocyanates **5**.

To assess whether in this unprecedented catalytic sulfuration process the molybdenum disulfur complex **3** operates as a sulfur-transferring species, complex **3** was independently synthesized (Scheme 1) and allowed to react with isonitrile **4b**. As anticipated, the authentic molybdenum disulfur complex **3** effects the sulfuration of isonitrile **4b** (Scheme 2). When stoichiometric amounts of complex **3** and isonitrile **4b** were employed, TLC

(17) (a) Fujiwara, S.; Shin-Ike, T.; Okada, K.; Aoki, M.; Sonoda, N. *Tetrahedron Lett.* **1992**, *33*, 7021−7024. (b) Fujiwara, S.; Shin-Ike, T.; Okada, K.; Aoki, M.; Sonoda, N. *Tetrahedron Lett.* **1991**, *32*, 3503−3506. (c) Tanaka, S.; Uemura, S.; Okano, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2785−2788.

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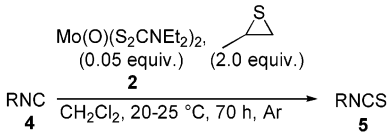
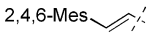
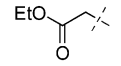
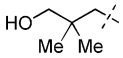
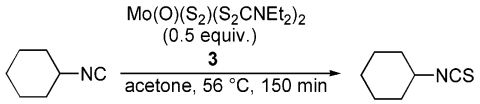
TABLE 2. Catalytic Sulfuration of the Functionalized Isonitriles 4 with 2-Methylthiirane as Sulfur Donor



Entry	R	RNC	yield [%] RNCS (**5**)
1		**4j**	81[a]
2		**4k**	87[b]
3		**4l**	81[b]
4		**4m**	89[a]

[a] Yield of pure isolated isothiocyanate after silica gel chromatography. [b] Yield of pure isolated isothiocyanate after distillation.

SCHEME 2. Stoichiometric Sulfuration of the Isonitrile 4b with the Preformed Disulfur Complex 3



monitoring revealed that 0.5 equiv of disulfur complex **3** was consumed and isonitrile **4b** was completely converted to isothiocyanate **5b**; the latter was isolated in 70% yield. Evidently, both sulfur atoms of the disulfur ring in the molybdenum complex are active for sulfur transfer. Thus, we propose that elemental sulfur and propene sulfide transform in situ molybdenum complex **2** to the active sulfur-transferring species **3**, which reacts in a 1:2 stoichiometry with isonitrile **4** to afford isothiocyanate **5**.

The possibility of ligation of isonitrile substrate **4** with the molybdenum−oxo catalyst **2** to generate the **2**/**4** adduct was probed spectroscopically. When the two were mixed in dry dichloromethane, a sudden color change from red to dark green was observed; the UV−vis absorption spectrum (see Figure S1, Supporting Information) exhibits two absorption bands at 362 and 504 nm. On gradual addition of isonitrile **4h** to a 10^{-4} M solution of complex **2** in dichloromethane, the absorption band at 504 nm decreased proportionally in intensity; but even on addition of 100 equiv of isonitrile, the absorption band of free complex **2** at 384 nm still persisted. Evidently, isonitrile and the oxo complex are in equilibrium with their adduct **2**/**4h**. Indeed, at a significantly higher concentration (0.38 M) of complex **2**, only 3 equiv of isonitrile **4h** was sufficient to convert complex **2** nearly completely to its isonitrile adduct **2**/**4h**, since no absorption of free complex **2** was observed in the FTIR spectrum (Figure S2, Supporting Information). Free isonitrile **4h** possesses a characteristic sharp vibration at 2122 cm^{-1}, the free molybdenum−oxo complex **2** at 1520 and 967 cm^{-1}; the latter are assigned[21] to the two degenerate CN and the oxo vibrations. Adduct **2**/**4** between isonitrile **4h** and oxo complex **2** displays four new sharp bands at 2118, 1511, 1490, and 936 cm^{-1}, of which the first one is assigned to the bound isonitrile and the other three to the symmetrical and unsymmetrical CN and molybdenum oxo vibrations of the **2**/**4h** adduct; the characteristic band at 967 cm^{-1} of free oxo complex **2** was absent.

The association constant (K_c) of adduct **2**/**4h** was determined photometrically (see Supporting Information): $K_c = 140 \pm 10\ M^{-1}$. Similarly, with isonitrile **4d**, $K_c = 18.4 \pm 6.8\ M^{-1}$ was obtained for adduct **2**/**4d**. These results indicate that in concentrated solutions of isonitrile **4** in the presence of a catalytic amount of complex **2**, the essentially exclusive species is isonitrile adduct **2**/**4**. Under these favorable conditions, it was anticipated that a crystalline adduct could be obtained for X-ray structural analysis. Indeed, when a hot, saturated solution of oxo complex **2** in neat isonitrile **4d** was allowed to cool to room temperature under the rigorous exclusion of air, after several days of standing, adduct **2**/**4d** between isonitrile **4d** and oxo complex **2** crystallized out, whose X-ray structure is shown in Figure S6 (Supporting Information). The isonitrile ligand occupies an equatorial position of the distorted octahedron with a Mo−C bond of 2.12 Å, which is typical for similar molybdenum(IV)−oxo/isonitrile complexes.[22] One of the dithiocarbamates exhibits different Mo−S bond lengths of 2.52 and 2.71 Å to the molybdenum center and coordinates as a $Et_2NC(=S)S^-$ ligand. This fact rationalizes the two CN vibrations in the IR spectrum. The equatorial dithiocarbamate ligand shows two equivalently bonded sulfur atoms with nearly identical Mo−S bond lengths of 2.42 and 2.46 Å; it acts as a $Et_2NC(S)_2^-$ ligand.

Discussion

The above experimental data for the molybdenum-mediated sulfuration of isonitriles by elemental sulfur is mechanistically rationalized in terms of the catalytic cycle proposed in Scheme 3. First, molybdenum complex **2** reacts with elemental sulfur to generate disulfur complex **3**, the active sulfur-transferring species in the catalytic sulfuration of isonitriles **4**. Complex **3** is then desulfurized successively by two isonitrile molecules back to complex **2** through intermediate **A**, as previously suggested for complex **3** in its reaction with triphenylphosphine.[23] Furthermore, similar molybdenum oxo−sulfido complexes have been isolated with sterically demanding ligands.[24]

The mechanistic details for the sulfur transfer in the catalytic cycle are offered in Scheme 4, in which only the sulfur transfer by the disulfur functionality is being considered.

The mechanistically simpler option (path a) involves direct intermolecular attack of the nucleophilic isocyanide[25] on the disulfur ring of complex **3** (generated from **2** by sulfuration) and subsequent sulfur transfer to

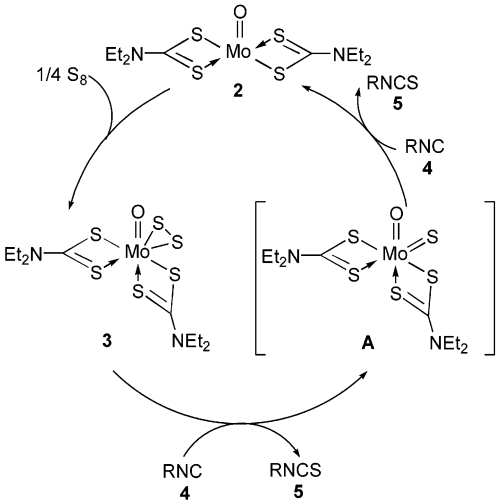
(21) Jowitt, R. N.; Mitchell, P. C. H. *J. Chem. Soc. A* **1969**, 2632−2636.

(22) (a) Lippard, S. J. *Prog. Inorg. Chem.* **1976**, *21*, 91−103. (b) Lam, C. T.; Lewis, D. L.; Lippard, S. J. *Inorg. Chem.* **1976**, *15*, 989−991. (c) Carmona, E.; Galindo, A.; Guille-Photin, C.; Sanchez, L. *Polyhedron* **1988**, *7*, 1767−1771. (d) Arzoumanian, H.; Corao, C.; Krentzien, H.; Lopez, R.; Teruel, H. *J. Chem. Soc., Chem. Commun.* **1992**, 856−858.

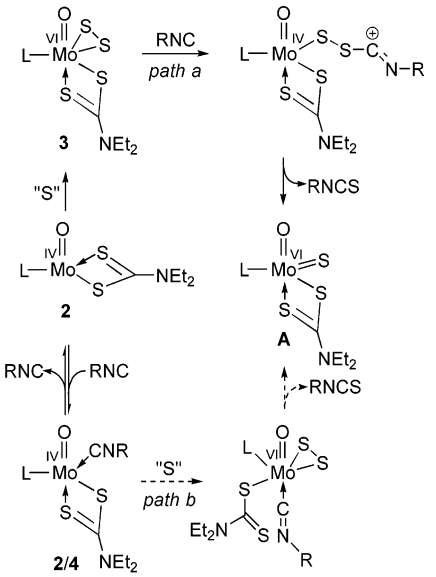
(23) Xiaoquing, S.; Huixing, Y.; Degang, H. *Int. J. Chem. Kinet.* **1989**, *21*, 749−755.

(24) Young, C. G.; Laughlin, L. J.; Colmanet, S.; Scrofani, S. D. B. *Inorg. Chem.* **1996**, *35*, 5368−5377.

SCHEME 3. Catalytic Cycle for the Molybdenum-Mediated Sulfuration of Isonitriles 4 with Elemental Sulfur as Donor



SCHEME 4. Mechanistic Options for the Sulfur Transfer[a]



[a] Path a involves the direct nucleophilic attack on the molybdenum complex **3** (L = −S−C(=S)−NEt_2) by the isonitrile **4** and Path b is for the isonitrile adduct **2/4**.

release isothiocyanate **5** and complex **A**. In the more involved option, the sequence of the mechanistic events is reversed: Isonitrile **4** first ligates to the molybdenum atom of complex **2** to form the observed **2**/**4** adduct (Fig. S6) and subsequently, after sulfuration, the intramolecular sulfur transfer takes place (path b). The latter process implies a template effect,[26] since both the sulfur acceptor (the isocyanide) and the activated sulfur donor (disulfur ring) are bound to a common molybdenum metal center. Of these two mechanistic options, the direct sulfur transfer (path a) is favored electronically for the following

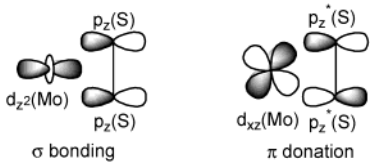


FIGURE 1. σ bonding and π donation by the disulfur functionality.

reasons: Although our spectral studies have demonstrated the coordination of isocyanide **4** to the electron-deficient molybdenum center of oxo complex **2** to afford adduct **2**/**4** (Figure S6), such ligation is expected to diminish the nucleophilic character of the isocyanide, which expectedly reduces its reactivity toward acceptance of the sulfur atom from the disulfur ring. To suppose that the electronic roles of the reacting partners are reversed, that is, the sulfur atom of the disulfur ring acts as nucleophile and the sulfur atom is transferred nucleophilically to the electrophilically activated isonitrile ligated at the molybdenum metal center, is in conflict with the electronic nature of the disulfur functionality: In disulfur complex **3**, the molybdenum is in its +VI oxidation state such that the electron-deficient d^0 metal center accepts an electron pair from the disulfur unit by σ bonding as well as by π donation (Figure 1). The latter reduces the π^*-antibonding character of the disulfur ligand and activates electrophilically this functionality in the disulfur molybdenum oxo disulfur complex **3** toward nucleophilic attack, in the present case by the isonitrile nucleophile.[27] The reduced bond length (2.01 Å[28]) and, consequently, increased π bond order (0.43[29]) for the sulfur−sulfur bond in the disulfur ring, as well as the lower negative charge at the sulfur atoms,[27] substantiate the electrophilic nature of the disulfur functionality in molybdenum oxo complex **3**. It is, therefore, quite unlikely that sulfur transfer takes place when the isonitrile is ligated to complex **3** (path b) and presumably the direct nucleophilic attack (path a) operates preferably. Consequently, analogous to triphenylphosphine and other inorganic nucleophiles,[23,30] we propose that direct nucleophilic attack of the isonitrile on the electrophilic disulfur functionality (path a in Scheme 4) affords the isothiocyanate **5** product.

Conclusion

We have demonstrated that the molybdenum-catalyzed sulfur-atom transfer to isonitriles proceeds under mild reaction conditions to afford a variety of isothiocyanates in good yields without the need of base. This unprecedented catalytic method provides a promising economical access to isothiocyanates from readily available isonitriles and elemental sulfur; the latter is the most abundant and cheapest sulfur source. In the catalytic cycle, a molybdenum oxo disulfur complex operates as the active sulfur-transferring species and the sulfur atom

(25) (a) Halleux, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 752. (b) Avetisyan, E. A.; Gambaryan, N. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, *11*, 2559−2562.

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(27) Müller, A.; Jaegermann, W.; Enemark, J. H. *Coord. Chem. Rev.* **1982**, *46*, 245−280.

(28) Dirand, J.; Ricard, L.; Weiss, R. *Inorg. Nucl. Chem. Lett.* **1975**, *11*, 661−664.

(29) Nordvik, A. *Acta Chem. Scand.* **1966**, *20*, 1885−1891.

(30) Leonard, K.; Plute, K.; Haltiwanger, R. C.; Rakowski Dubois, M. *Inorg. Chem.* **1979**, *18*, 3246−3251.

is transposed during the direct nucleophilic attack of the isonitrile on the electrophilically activated disulfur functionality.

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Supporting Information Available: Full reaction procedures, spectroscopic and elemental analytical data on isolated compounds, and details of the X-ray structure determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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