Oxone-mediated Methoxy Thiocyanation of 1,1-Disubstituted Olefins in Methanol

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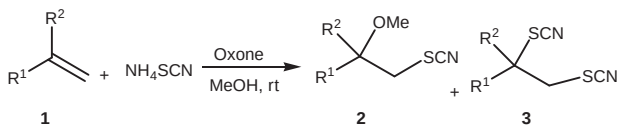
Reactions of 1,1-disubstituted olefins with oxone and ammonium thiocyanate in methanol gave the corresponding 1-methoxy-2-thiocyano adducts in various yields.

As part of continuing efforts to explore a wider application range of oxone in oxidative addition of thiocyanate to other kinds of C=C double bond,[1] further study was carried out to extend the substrate scope for terminal alkenes, particularly for 1,1-disubstituted olefins.

Several methods for the oxidative thiocyanation of alkenes have been developed[2] upon using an oxidant such as iodosobenzene diacetate (IBDA),[2a,2b,2c] I_2/ICl,[2d] ceric ammonium nitrate (CAN)[2e,2f] and $(SCN)_2$,[2g] in which 1,2-dithiocyanates were mainly yielded in most cases. It is noticed that the product structures and distributions are strongly oxidant- and solvent-dependent, additional to the substrate structures and reaction conditions. In general, the yields of thiocyanates were low and monothiocyanates hardly obtained as major outcomes.[2a,2b] Hence, to learn the oxidative reactivity of oxone in the addition of thiocyanate to alkenes, to obtain a clear insight into the affects of oxidant on the thiocyanation of alkenes, and to develop alternative approaches accessible to the thiocyanation of alkenes are of considerable academic interest. Otherwise, an oxidative vicinal addition of alkoxy and nucleophile to the C=C double bond of olefins was found to occur in alcoholic solvents.[3]

In the present work, we will disclose our results on the formally simultaneous addition of methoxy and thiocyanate to the terminal C=C double bond of 1,1-disubstituted olefins in their reactions with oxone, as an oxidant, and ammonium thiocyanate, as a thiocyanating reagent, in methanol (Scheme 1).[1] New findings from the experiment have led us to a good understanding of the oxidant- and solvent-dependent addition of thiocyanate to olefins.

In a typical experiment, a solution of 118 mg of 1a (1.0 mmol) and 167 mg of ammonium thiocyanate (2.2 mmol) in 10 mL of anhydrous methanol was treated with 924 mg of oxone (1.5 mmol), allowed to stir at room temperature and monitored by TLC. After completion of the reaction, the mixture was filtered and dried under vacuum. The products were purified by column chromatography on aluminum oxide neutral-gel (200–300 mesh, ethyl acetate/hexane) and provided as colorless liquid. They were characterized by ^{1}H and ^{13}C NMR, IR, FAB-MS or EIMS, and HR-ESI-MS. The reaction led to the corresponding 1-methoxy-2-thiocyano added olefins **2** as major products and 1,2-dithiocyanated olefins **3** as minor outcomes (Table 1).



1 2 3

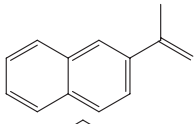
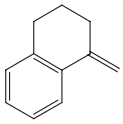
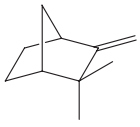
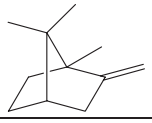
Scheme 1.

The results in Table 1 indicate that the thiocyanation preferred to occur regioselectively at the terminal carbon atom of C=C double bond. Otherwise, the methoxy substituent in **2** shows that methanol molecule participated the addition to olefins as a nucleophile, leading to methoxylated products.[3]

The reaction time in Table 1 clearly shows the substrates displaying various reactivities toward the methoxy thiocyanation. The speed of reactions appears to be influenced mainly by electronic effects arising from substituents. An electron-donating group linked at the para-position on the ring (**1b** and **1c**) facilitated the reaction, whereas an electron-withdrawing group slowed the reaction of **1f** and **1g**. It was so slow for **1g** as to have no thiocyanated product obtained. Another phenyl group at the α-C (**1e**) led to highly slow the formation of end product.

Since solvent highly affected the addition of thiocyanate to a C=C double bond, the effects of solvent on reaction proceeding

Table 1. Methoxy thiocyanation of 1,1-disubstituted olefins in methanol

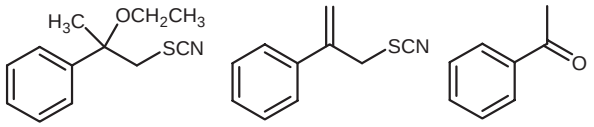
Entry	R^1	R^2	t^a/h	Product yield/%[b]	
				2	**3**
1a	Ph	CH_3	0.33	77	8.1
1b	4(CH_3)Ph	CH_3	0.25	71	5.4
1c	4(OCH_3)Ph	CH_3	0.30	72	6.1
1d	Ph	CH_3CH_2	0.56	70	6.3[c]
1e	Ph	Ph	20	69	10
1f	4(Br)Ph	CH_3	24	75	9.4
1g	4(NO_2)Ph	CH_3	36	—	—
1h			0.67	73	15
1i			0.25	81	3.0
1j			2	41	—
1k			1	35	—
1m			1.5	71	—

[a]The reaction time. [b]Isolated yields of the products after column chromatography. [c]The dithiocyanated product was unstable.

Table 2. Solvent effects on the methoxy thiocyanation of **1a**

Solvent	T/h[a]	Conv /%[b]	Product yield/%[c]				
			2a	**3a**	**4a**	**5a**	**6a**
Methanol	24	99.0	89.4	9.6	—	—	—
Ethanol	24	97.4	—	7.3	82.8	7.2	—
CH_2Cl_2	24	56.8	—	26.3	—	28.9	—
CH_3CN	24	56.6	—	19.9		17.0	19.6
CCl_4	24	18.3	—	7.1	—	11.1	—
THF[d]	36	0	—	—	—	—	—

[a]The reaction time. [b]% Conversion = (moles of reaction substrate/moles of limiting reactant)* 100%. [c]Isolated yields of the products by GC-MS; %Yield = (moles of product/moles of limiting reactant not recovered)* 100%. [d]Tetrahydrofuran.



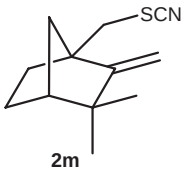
4a **5a** **6a**

Scheme 2.

and product yield were carefully investigated using **1a** as a substrate. The results are gathered in Table 2. It is very clear that the product distributions and yields are highly solvent-dependent. Ethanol provided an ethoxy group to **4a** (Scheme 2) in a similar fashion to methanol.[3] The conversions and product yields were quite similar in both methanol and ethanol. Thus, Table 2 suggests that protic solvents such as methanol and ethanol are favorable for thiocyanations. In contrast to those, aprotic solvents led to a sharp decrease in conversions, even no reaction occurred in tetrahydrofuran (THF). Moreover, in non-alcoholic solvents the yields of **3** went up, but not exclusively,[2f] and **5a** was yielded instead of **2** (Scheme 2). This is rationalized in terms of the lack of alkoxy group sources from alcoholic solvents. In some cases the oxidized product such as **6a** (Scheme 2) was obtained. Facts which support the above understanding are: (a) Dithiocyanated products were minor outcomes in protic solvents, whereas they became major products instead of methoxylated products in aprotic solvents; and (b) **5a** became a major outcome in aprotic solvents.

In this work, the substrates were extended to **1j**, **1k**, and **1m** (Table 1). The products derived from **1j** and **1k** were still the corresponding 1-methoxy-2-thiocyanates. Nevertheless, the yields dropped off. The reason may be due to less stable reaction intermediates. **1m** was an exception. Its ultimate product **2m**[4] was assigned to that as containing a C=C double bond and losing a methyl group, as drawn in Scheme 3.

In conclusion, several new issues on this methoxy thiocyanation have been approached: (a) Oxone is a potential oxidant in the thiocyanation of alkenes. The product structures and distributions for oxone-mediated additions were quite different from other oxidative thiocyanations of alkenes;[2] (b) Substituents at the terminal C=C double bonds highly affect the regioselectivity of thiocyanation occurring at the terminal carbon atom of C=C double bond; and (c) The product structures and distributions are strongly solvent-dependent. Protic solvents such as methanol and ethanol are much favorable for this reaction. In particular, the alcoholic molecule participates in this reaction as a nucleophile, leading to alkoxylated products.



2m

Scheme 3.

The products so formed possess good fungicidal activity and are available for further chemical manipulations, transforming to various sulfur functional groups and sulfur-containing heterocycles.[5,6] Otherwise, the existence of thiocyanato group in several biologically active natural products is of significance.[7,8]

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References and Notes

1 G. L. Wu, Q. Liu, Y. L. Shen, W. T. Wu, L. M. Wu, *Tetrahedron Lett.* **2005**, *46*, 5831.
2 a) A. De Mico, R. Margarita, A. Mariani, G. Piancatelli, *Tetrahedron Lett.* **1996**, *37*, 1889. b) M. Bruno, R. Margarita, L. Parlanti, G. Piancatelli, M. Trifoni, *Tetrahedron Lett.* **1998**, *39*, 3847. c) A. D. Mico, R. Margarita, A. Mariani, G. Piancatelli, *Chem. Commun.* **1997**, 1237. d) P. D. Woodgata, H. H. Lee, P. S. Rutledge, *Tetrahedron Lett.* **1976**, *18*, 1531. e) V. Nair, L. G. Nair, T. G. George, A. Augustine, *Tetrahedron* **2000**, *56*, 7607. f) V. Nair, L. G. Nair, *Tetrahedron Lett.* **1998**, *39*, 4585. g) R. J. Maxwell, L. S. Gilbert, *J. Org. Chem.* **1977**, *42*, 1515.
3 A. Onoe, S. Uemura, M. Okano, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2818.
4 Supporting information available: spectroscopic data for **2m** and possible reaction mechanism for the formation of **2m** shown in Scheme S1 (PDF). This material is available free of charge via the Internet at http://www.csj.jp/journals/chem-lett/index.html.
5 See reviews: a) J. L. Wood, in *Organic Reactions*, ed. by R. Adams, John Wiley & Sons, New York, **1946**, Vol. 3, Chap. 6, p. 240. b) S. Harusawa, T. Shioiri, *J. Synth. Org. Chem. Jpn.* **1981**, *39*, 741.
6 F. D. Toste, F. LaRonde, I. W. J. Still, *Tetrahedron Lett.* **1995**, *36*, 2949.
7 F. Shahidi, in *Sulfur Compounds in Foods*, ed. by C. J. Massinan, M. E. Keelan, American Chemical Society, Washington, DC, **1994**, Vol. 9, p. 106.
8 R. G. Mehta, J. Liu, A. Constantinou, C. F. Tomas, M. Hawthorne, M. You, C. Gerhaccuser, J. M. Pezzuto, R. C. Moon, R. M. Moriarty, *Carcinogenesis* **1995**, *16*, 399.

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