Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7701-7704, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10029-6

Rhenium Catalyzed Sulfurization of Phosphorus(III) Compounds with Thiiranes: New Reagents for Phosphorothioate Ester Synthesis

Jeffrey B. Arterburn*, and Marc C. Perry

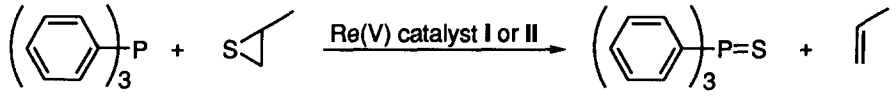
Department of Chemistry & Biochemistry, New Mexico State University
Box 30001 / 3C, Las Cruces, NM 88003, USA

Abstract: A new method for the mild sulfurization of phosphorus(III) compounds with thiiranes catalyzed by $ReOCl_3(PPh_3)_2$ (**I**) or $ReOCl_3(SMe_2)OPPh_3$ (**II**) is reported. The novel catalytic sulfur transfer reactions are rapid and occur efficiently under ambient conditions in organic solvents. This methodology enabled propylene sulfide to be used as a sulfurizing agent for the synthesis of a protected nucleotide phosphorothioate ester. © 1997 Elsevier Science Ltd.

Catalytic oxygen atom transfer reactions have proven to be extremely useful for oxidations in organic syntheses, and these successes serve as a stimulus for the development of other catalytic processes for heteroatom transfer. There has been a great deal of interest in sulfurization reagents that are soluble in organic solvents, particularly for the solid phase synthesis of oligonucleotide phosphorothioates. Some of the reagents that have been used for the sulfurization of phosphite triesters include: tetraethylthiuram disulfide,[1] benzoyl disulfide, phenylacetyl disulfide,[2] 3*H*-1,2-benzodithiole-3-one 1,1-dioxide,[3] 3-ethoxy-1,2,4-dithiazoline-5-one,[4] 1,2,4-dithiazolidine-3,5-dione,[5] dibenzoyl tetrasulfide and bis(*O*,*O*-diisopropoxyphosphinothioyl) disulfide.[6] Some of the problems with available reagents include slow reaction times, incomplete sulfurization, side reactions, expense, and the need to synthesize unavailable compounds. Thiiranes are known to undergo desulfurization reactions with phosphorus(III) compounds at high temperatures, producing the phosphine sulfide and alkene with retention of stereochemistry.[7] The high concentrations and temperatures that are typically required for this reaction are unsuitable for oligonucleotide phosphorothioate syntheses, and thiiranes have not been used in this context to the best of our knowledge. Thiiranes such as propylene sulfide are commercially available (1997 Aldrich price = \$0.13 $mmol^{-1}$.), and could be used for sulfurization reactions if competing oligomerization,[8] and decomposition to S_8 were avoided.[9] Transition metal atoms,[10] complexes,[11] and surfaces[12] promote the stoichiometric desulfurization of thiiranes. The rhodium(I) catalyzed reaction of thiiranes with carbon monoxide was the first homogenous catalytic desulfurization reported,[13] but attempts to effectively catalyze sulfur transfer from thiiranes to phosphines with transition metal complexes have been unsuccessful.[14] Our interest in rhenium-catalyzed oxygen atom transfer reactions[15] led us to investigate the

possibility of developing related catalytic sulfur-transfer reactions from thiiranes using available rhenium(V) complexes as catalyst precursors.[16]

In an NMR-scale experiment $ReOCl_3(PPh_3)_2$ (I) (6 mg, 7.2 x 10^{-3} mmol, 5 mol %) was added to propylene sulfide (10 μL, 0.14 mmol) in $CDCl_3$, immediately producing a green solution containing corresponding amounts of propene and triphenylphosphine sulfide $SPPh_3$ derived from the PPh_3 ligands in (I). The addition of one equivalent of triphenyl phosphine PPh_3 (37 mg, 0.14 mmol) resulted in a brown solution, and complete catalytic sulfur transfer from propylene sulfide to PPh_3 was evident by NMR spectroscopy within 5 minutes at ambient temperature (eq. 1). This rapid and efficient sulfur transfer reaction was also catalyzed by the complex $ReOCl_3(SMe_2)(OPPh_3)$ (II).[16] The effectiveness of the Re-catalyzed reactions was evident by comparison with a control experiment, using identical concentrations of thiirane and PPh_3 in the absence of rhenium oxo catalysts I or II, which resulted in only 7% conversion to $SPPh_3$ after 24 hrs.

eq. 1 

A series of preparative scale sulfurization reactions were conducted by adding the catalyst (II) to reaction solutions containing the thiirane and phosphorous(III) compounds shown in Table 1. Complete conversion was evident in all cases from analysis of the crude reaction mixtures by NMR, and the isolated yields of the sulfurized products after chromatography (silica gel, CH_2Cl_2/CH_3OH eluent) ranged from very good to excellent (85-100%). The product yields and conversion times for the sulfurization of PPh_3 were very similar for reactions carried out using either dichloromethane or acetonitrile as solvents. The Re-catalyzed reaction of PPh_3 with cyclohexene sulfide also occurred rapidly. The sulfurization reactions of phosphites and hexamethylphosphorous triamide were somewhat slower, paralleling the general trends in reactivity found for the uncatalyzed reactions, however all of these Re-catalyzed reactions were complete within 30 minutes at room temperature.

The time required for complete sulfurization of triethyl phosphite was reduced to less than 5 minutes by pre-forming the active catalyst from precursor (I) using a 3-fold excess of propylene sulfide, followed by addition of the phosphite to the reaction mixture. Using this procedure, the dimethoxytrityl protected 2-deoxythymidine dimethyl phosphite ester was quantitatively sulfurized to the corresponding phosphorothioate derivative at room temperature (eq. 2), the purity was indicated by a single ^{31}P-NMR ($CDCl_3$) signal at δ 71.4.

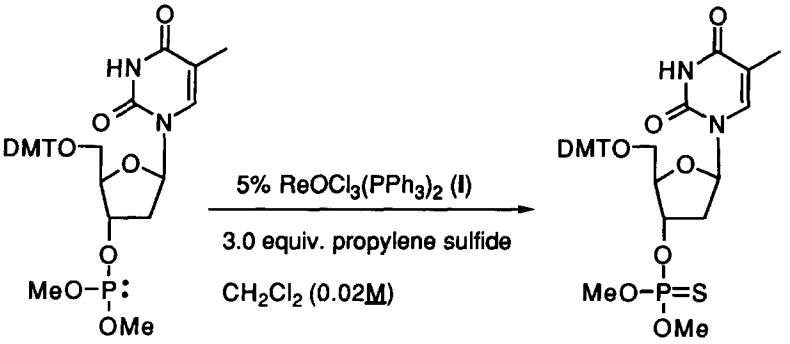
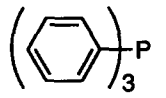
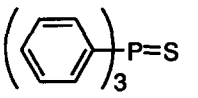
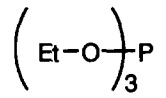
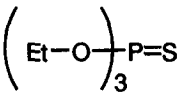
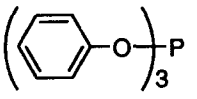
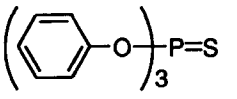
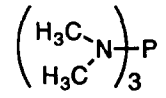
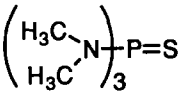
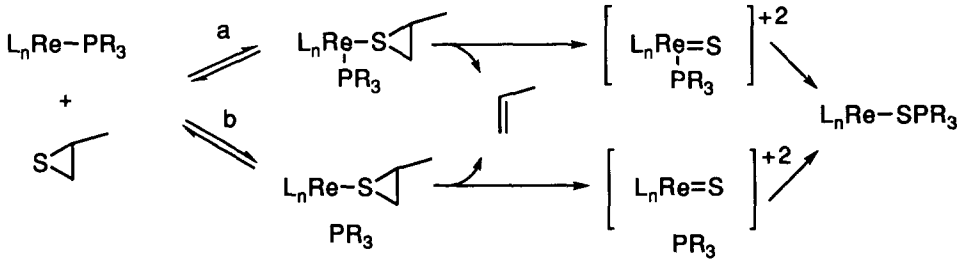
eq. 2 

Table 1 Re-Catalyzed Sulfurization of P(III) Compounds with Thiiranes

entry	substrate	conditions[a]	time (min)[b]	product	yield (%)
1		A	5		95
2	" "	B	5	" "	95
3	" "	C	5	" "	95
4		A	20		85
5		A	30		93
6		A	20		100

[a]Reaction conditions: thiirane / R_3P / $ReOCl_3(SMe_2)(OPPh_3)$ (II) / solvent (0.13M)
Method A: propylene sulfide (1.1) / 1.0 / 0.05 / CH_2Cl_2
Method B: propylene sulfide (1.1) / 1.0 / 0.05 / CH_3CN
Method C: cyclohexene sulfide (1.1) / 1.0 / 0.05 / CH_2Cl_2
[b]Determined by monitoring reaction via ^1H NMR spectroscopy.

The reactions between thiiranes and trivalent phosphorus compounds are generally believed to take place via a concerted process. Possible mechanisms for the Re-catalyzed reaction are outlined in Scheme 1. Two classes of thiirane complexes are possible intermediates along paths (a) and (b), which differ by the presence or absence of a coordinated PR_3 ligand. The sulfur transfer step could conceivably occur inter or intramolecularly via direct nucleophilic attack of phosphorus on the coordinated thiirane sulfur atom, or subsequent to an additional oxidative step generating a more electrophilic intermediate sulfido complex.



Scheme 1. Possible Mechanism for Re-Catalyzed Sulfurization

The kinetic parameters and mechanistic details of these reactions, efforts to isolate catalytically relevant rhenium complexes, and further application of this methodology in synthesis are currently being investigated.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, for support of this research.

REFERENCES AND NOTES

1. Vu, H.; Hirschbein, B. L. *Tetrahedron Lett.* **1991**, *32*, 3005-3008.
2. a) Kamer, P. C. J.; Roelen, H. C. P. F.; van den Elst, H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1989**, *30*, 6757-6760. b) Roelen, H. C. P. F.; Kamer, P. C. J.; van den Elst, H.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 325-331.
3. a) Iyer, R. P.; Egan, W.; Regan, J.; Beaucage, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 1253-1254. b) Iyer, R. P.; Phillips, L. R.; Egan, W.; Regan, J. B.; Beaucage, S. L. *J. Org. Chem.* **1990**, *55*, 4693-4699.
4. Chen, L.; Thompson, T. R.; Hammer, R. P.; Barany, G. *J. Org. Chem.* **1996**, *61*, 6639-6645.
5. a) Xu, Q.; Musier-Forsyth, K.; Hammer, R. P.; Barany, G. *Nucleic Acids Res.* **1996**, *24*, 1602-1607. b) Xu, Q.; Barany, G.; Hammer, R. P.; Musier-Forsyth, K. *Nucleic Acids Res.* **1996**, *24*, 3643-3644.
6. Wyrzykiewicz, T. K.; Ravikumar, V. T. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1519-1522.
7. a) Neureiter, N. P.; Bordwell, F. G. **1959**, *81*, 578-580. b) Denney, D. B.; Boskin, M. J. **1960**, *82*, 4736-4738. c) Sidky, M. M.; Mahran, M. R.; Boulos, L. S. *J. für Prakt. Chemie* **1970**, *312*, 51-54. d) Kobayashi, Y.; Ando, A.; Kawada, K.; Kumadaki, I. *J. Org. Chem.* **1980**, *45*, 2966-2968. e) Collazo, L. R.; Guziec, F. S. J. *J. Org. Chem.* **1993**, *58*, 43-46.
8. a) Adams, R. D.; Queisser, J. A.; Yamamoto, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 10674-10675. b) Adams, R. D.; Yamamoto, J. H.; Holmes, A.; Baker, B. J. *Organometallics* **1997**, *16*, 1430-1439.
9. a) Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* **1988**, *29*, 4177-80. b) Kamata, M.; Murayama, K.; Miyashi, T. *Tetrahedron Lett.* **1989**, *30*, 4129-4132.
10. Reid, A. H.; Shevlin, P. B.; Webb, T. R.; Yun, S. S. *J. Org. Chem.* **1984**, *49*, 4728-4730.
11. a) King, R. B. *Inorg. Chem.* **1963**, *2*, 326-327. b) Hall, K. A.; Critchlow, S. C.; Mayer, J. M. *Inorg.Chem.* **1991**, *30*, 3593-3594. c) Adams, R. D.; Babin, J. E.; Mathur, P.; Natarajan, K.; Wang, J. G. *Inorg. Chem.* **1989**, *28*, 1440-5.
12. a) Roberts, J. T.; Friend, C. M. *J. Am. Chem. Soc.* **1987**, *109*, 7899-7900. b) Calhorda, M. J.; Hoffman, R.; Friend, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 50-61.
13. Calet, S.; Alper, H. *Tetrahedron Lett.* **1986**, *27*, 3573-3576.
14. Proulx, G.; Bergman, R. G. *Organometallics* **1996**, *15*, 133-141.
15. a) Arterburn, J. B.; Nelson, S. L. *J. Org. Chem.*, **1996**, *61*, 2260-2261. b) Arterburn, J. B.; Perry, M. C. *Tetrahedron Lett.* **1996**, *37*, 7941-7944.
16. Trichlorooxobis(triphenylphosphine)rhenium, $ReOCl_3(PPh_3)_2$, (I) is commercially available from the Aldrich Chemical Co., or can be easily prepared using the procedure of Johnson, N. P.; Lock, C. J. L.; Wilkinson, G. *Inorg. Synth.* **1967**, *9*, 145-148. The complex $ReOCl_3(SMe_2)(OPPh_3)$ (II) was prepared as described by Bryan, J. C.; Stenkamp, R. E.; Tulip, T. H.; Mayer, J. M. *Inorg. Chem.* **1987**, *26*, 2283-2288.
17. 5'-Dimethoxytrityl-2'-deoxyThymidine,3'-[(O-methyl)-(N,N-diisopropyl)]-phosphonamidite was purchased from Glen Research, and was converted to the dimethylphosphite ester by the standard method in the presence of 1*H*-tetrazole.

(*Received in USA* 30 *July* 1997; *revised* 27 *August* 1997; *accepted* 28 *August* 1997)