Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Desulfurization of aromatic polysulfides with triphenylphosphine

Eli Zysman-colman[a]; Patrick G. Farrell[a]; David N. Harpp[a]
[a] Department of Chemistry, McGill University, Montreal, Quebec, Canada

To cite this Article Zysman-colman, Eli , Farrell, Patrick G. and Harpp, David N.(2004) 'Desulfurization of aromatic polysulfides with triphenylphosphine', Journal of Sulfur Chemistry, 25: 2, 101 — 109
To link to this Article: DOI: 10.1080/1741599042000203364
URL: http://dx.doi.org/10.1080/1741599042000203364

J. Sulfur Chemistry
Vol. 25, Nos. 2–3, April–June 2004, 101–109

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Desulfurization of aromatic polysulfides with triphenylphosphine

ELI ZYSMAN-COLMAN, PATRICK G. FARRELL
and DAVID N. HARPP*

Department of Chemistry, McGill University, Montreal, Quebec,
Canada H3A 2K6

(*Received 17 November 2003; in final form 21 January 2004*)

The room temperature reaction of bis(4-methylbenzene) di- (**3**), tri- (**4**) and tetrasulfide (**5**) with triphenylphosphine has been followed by ^{1}H NMR. Mechanistic aspects of the cleavage of **3** and the desulfurization of **4** and **5**, with concomitant formation of triphenylphosphine sulfide, are discussed. While tetrasulfide **5** is desulfurized over 10× faster than trisulfide **4**, preliminary experiments indicate that **5** is not sufficiently reactive to efficiently transfer a sulfur atom to oligodeoxyribonucleotides.

Keywords: Disulfides; Trisulfides; Tetrasulfides; Desulfurization; Triphenylphosphine

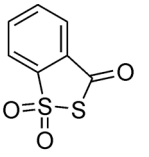
1. Introduction

The phosphorothioate class of oligodeoxyribonucleotides is one of the most heavily investigated and promising new modulators of gene expression [1–4]. Such antisense drugs have already been approved, as in formivirsen [5] (Vitravene), or are in clinical trials in both Europe and the United States for the treatment of CMV retinitis in AIDS patients [6]. In the development of these compounds, it is crucial that the sulfurization step be highly efficient for maximum nuclease-resistance.

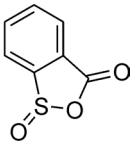
During the past few years, various sulfurizing molecules have been investigated [7–22]. Of these, the Beaucage reagent (**1**) has been used extensively for the synthesis of phosphorothioate drugs due to its rapid transfer of sulfur. However, its non-optimal solubility properties sometimes cause this reagent to have inconsistent sulfurization efficiency, in part due to the formation of a cyclic by-product **2** which acts as an oxidizing reagent [10, 23, 24]. Due to its significant cost it is not amenable for large-scale use.

* Corresponding author. E-mail: david.harpp@mcgill.ca

J. Sulfur Chemistry
ISSN 1741-5993 print; ISSN 1741-6000 online
http://www.tandf.co.uk/journals
DOI: 10.1080/1741599042000203364



1



2

There is a need for an inexpensive and efficient sulfurizing reagent that is easy and economical to prepare. We recently reported a series of inexpensive polysulfides containing labile sulfur atoms [25] that might serve as potent sulfur-transfer reagents in the formation of phosphorothioates. We have therefore investigated the room temperature reactions of these polysulfides with a model phosphine to demonstrate their efficacy prior to attempted use on oligonucleotides.

We chose triphenylphosphine (Ph_3P) as our model phosphine ligand; although phosphites are sulfurated in the synthesis of the nucleotides of interest, Arbuzov rearrangement would complicate the ^{1}H NMR product analysis [26]. Decomposition of simple aliphatic and aromatic polysulfides by phosphines has been studied previously, but only for the initial minutes of the reaction [26–29]. In addition, others [30, 31] have carried out calculational studies to model the process.

2. Results and discussion

2.1 *Probing the reaction*

Initially, we investigated the efficiency of desulfurization of bis(4-methylbenzene) trisulfide (**4**) and bis(4-methylbenzene tetrasulfide) (**5**) with Ph_3P in CH_2Cl_2 (table 1). Room temperature desulfurization of **4** reached 85% in 10 min and did not significantly change, even after 4 h, but under reflux (entry 4) we were able to recover near quantitative amounts of triphenylphosphine sulfide ($Ph_3P{=}S$). Increasing the number of sulfur atoms did not appreciably increase the yield of ($Ph_3P{=}S$).

$$\mathrm{ArSS}_n\mathrm{SAr} + \mathrm{Ph_3P} \xrightarrow{\mathrm{CH_2Cl_2}} \mathrm{ArSS}_{n-x}\mathrm{SAr} + \mathrm{Ph_3P{=}S} \qquad (1)$$

$$n = 1\ (\mathbf{4}), \quad n = 2\ (\mathbf{5}) \quad x \leq n$$

Table 1. Microscale desulfurization of **4** and **5** by equimolar Ph_3P in CH_2Cl_2.

Entry	Compd.	Time (min)	Yield[a] (%)
1	**4**	10	85
2	**4**	240	87
3	**5**	10	90
4[b]	**4**	10	90
5[b]	**4**	120	98

[a]Yield of $Ph_3P{=}S$ as isolated by silica gel chromatography. [b]Reaction was boiled under reflux in CH_2Cl_2.

2.2 *Desulfurization of trisulfide 4*

Having established that the desulfurization of **4** and **5** is facile and proceeds to near completion within minutes at room temperature in CH_2Cl_2, we then followed these reactions [26–29] *via* ^{1}H NMR. Trisulfides react with phosphines much faster than the corresponding disulfides,

[32, 33] but only three kinetic studies of aromatic trisulfides have been reported, [27, 28, 34] all of which arrive at the rate expression shown in equation (2).

$$\text{Rate} = k[\text{phosphine}][\text{trisulfide}] \tag{2}$$

Phosphine-catalyzed trisulfide exchange experiments [28, 34] similar to those with disulfides [35] establish both the existence of charged intermediates as well as the reversibility of their formation, suggesting that desulfurization proceeds *via* the formation

$$\text{Ar}-\text{S}-\text{S}-\text{Ar} + \text{Ph}_3\text{P} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \text{Ar}-\text{S}-\overset{+}{\text{P}}\text{Ph}_3 + \text{Ar}-\text{S}^- \tag{3}$$

of thiophosphonium salt adducts, *e.g.* equation (3).

The desulfurization of trisulfide **4** is shown in figure 1, yielding excellent agreement with first-order kinetics, table 2 ($R^2 > 0.98$).

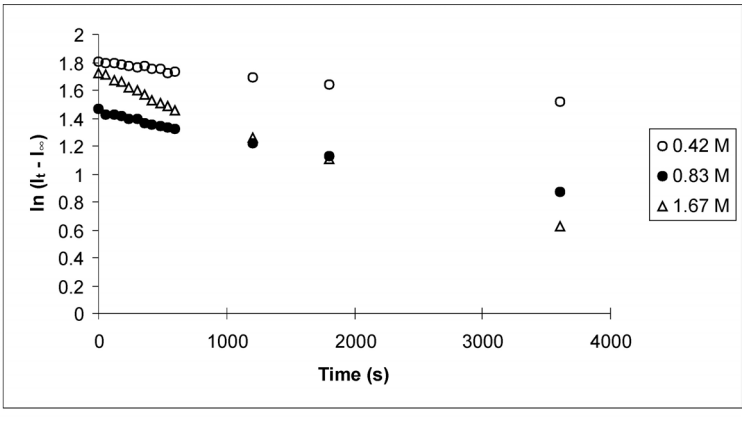


Figure 1. 1st order rate plot of the desulfurization of 0.025 M **4** at different concentrations of Ph_3P.

Table 2. Rate constants for the desulfurization of **4**.

	Loss of **4**[a]			Formation of **3**[b]		
$[Ph_3P_{(initial)}]$[c] (M)	$k_{obs} \times 10^{-3}$ (s^{-1})[d]	$k \times 10^{-3}$ $(M^{-1}s^{-1})$	$t_{1/2}$ (min)	$k_{obs} \times 10^{-3}$ (s^{-1})[d]	$k \times 10^{-3}$ $(M^{-1}s^{-1})$	$t_{1/2}$ (min)
0.42	0.3 ± 0.1	0.7 ± 0.3	17.5	0.2 ± 0.1	0.6 ± 0.2	20.7
0.83	0.4 ± 0.1	0.5 ± 0.2	24.0	0.4 ± 0.2	0.5 ± 0.2	23.0
1.67	0.9 ± 0.2	0.5 ± 0.1	22.3	1.1 ± 0.6	0.7 ± 0.4	16.8

[a]Partial order was determined to be 0.8. [b]Partial order determined to be 1.2. [c]Error on concentration is estimated to be 0.05 M. [d]1st order rate constant.

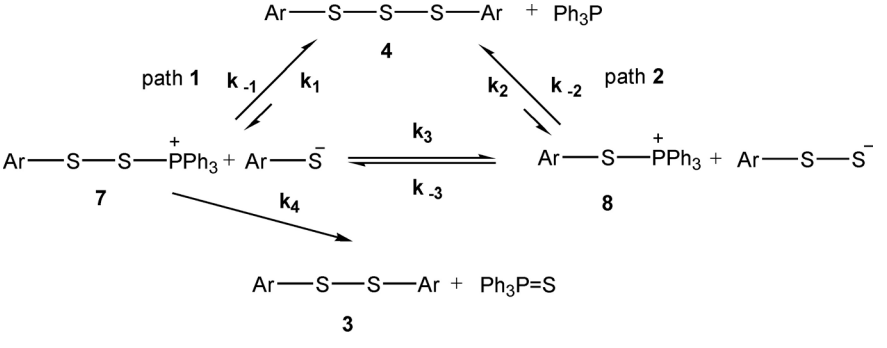
The measured first-order rate constant is reasonably close to the literature values {$5.4 \times 10^{-3}s^{-1}$ in benzene using $(Et_2N)_3P$ at 30 °C; [28] $1.25 \times 10^{-3}s^{-1}$ in toluene using $(Ph)_3P$ at 40 °C [27]}, the differences being attributed to the different solvent systems and phosphine used as well as to the slightly elevated temperatures of those studies.

The rate constant for formation of the disulfide product **3** was, within reasonable experimental error, equal to that of the decomposition of the trisulfide starting material **4**. Furthermore, the behavior in both the loss of **4** as well as the resulting formation of **3** remained first

order throughout the experiment. A small amount (ca. 10%) of 4-methylbenzenethiol (**6**) was observed in the ^{1}H NMR spectra but does not affect the rate-determining step of the reaction [36]. We conducted ^{31}P, ^{13}C and ^{1}H NMR experiments over a wide range of chemical shifts but were unable to detect any thiophosphonium salt intermediate. Unlike Wittig-type phosphonium salts, which are common and readily detectable [37, 38], there exist few reports of phosphonium species with Ph_3P, and then only when they are complexed with a suitable counterion [39].

Notwithstanding the absence of an observable intermediate, we may construct a possible reaction mechanism (scheme 1) in which the equilibrium positions of k_1 and k_2 are very likely in favor of the starting material (no higher order polysulfides were detected). Nucleophile displacement at sulfur ultimately results in displacement of the thermodynamically more stable mercaptide, or hydrodisulfide, ion [30, 31, 40, 41]. Although the pK_a for phenylhydrodisulfide (PhSSH) has not been measured in solution, gas phase calculations [42] predict it to be lower than that of 4-methylbenzene thiol (**6**), in accord with the calculated relative acidities of polysulfanes (HS_nH) in the gas phase [43]. The aromatic hydrodisulfide anion may therefore be considered as the better leaving group, thus favoring path 2 over path 1 (scheme 1) (polarization of the sulfur atom will also stabilize the intermediate thiophosphonium ion **8**). This type of intermediate has been reported in the desulfurization of calicheamicin γ_1^I [41].

However, to obtain **3**, the reaction presumably proceeds via intermediate **7**, assuming that the only sulfur that can be extruded is the central one, *i.e.* nucleophilic attack on the 4-methylbenzene ring does not occur. The final step and the driving force of the reaction would therefore involve the formation of $Ph_3P{=}S$ through attack of ArS^- at the sulfenyl sulfur of **7**. The fact that the rate of formation of **3** is the same as that of the loss of **4** argues for k_4 being the rate-determining step. We thus arrive at the same mechanistic conclusions for aromatic trisulfides as those previously reported for aliphatic trisulfides [29], these latter being based on a second step attack on *carbon* rather than sulfur in the formation of $Ph_3P{=}S$.



SCHEME 1 Mechanism for the desulfurization of aromatic trisulfides.

2.3 *Desulfurization of tetrasulfide 5*

The rate of reaction of **5** with Ph_3P is considerably greater than that of **4**, resulting in a typical time profile of reaction as shown in figure 2. It was more difficult to ascertain rate constants for the loss of **5** due to the speed of the reaction. However, the initial cleavage rates of the desulfurization of tetrasulfide **5** demonstrate a relative increase in the rate (compared with **4**) by a factor of ca. 12 for $[Ph_3P] = 0.83$ M (table 3). A modest amount of **3** (ca. 17%

of desulfurization products after 3 min regardless of Ph_3P concentration) forms in the initial stages of the reaction and continues to form at rates comparable to those observed during the desulfurization of **4**. The presence of **3** in the initial stages of the reaction is a result of the subsequent desulfurization of formed trisulfide **4** [44]. We were also able to determine the kinetics for the loss of trisulfide **4** and the gain of product **3** (table 3).

Within reasonable error, the rate constants for the formation of **3** are of the same order of magnitude as those for the loss of intermediate **4**, and approximate to those observed in the direct desulfurization of **4** (table 2). Notably, utilizing ^{1}H NMR methods, it is now possible to track intermediate and/or product formation as well as starting material loss, unlike in previously reported kinetic studies on related systems [27, 28, 34].

While the mechanistic scheme for desulfurization of **5** is potentially much more complex than that for **4**, some tentative conclusions may be drawn from our data. As no higher order polysulfides were observed in carefully monitored experiments with **5** and Ph_3P, and trithiomercaptide ions are thermally unstable [47], attack of Ph_3P at the terminal sulfur to yield $ArSSS^-$ as leaving group is unlikely to be a significant contributor to the loss of **5**. Thus, attack at a central sulfur to yield $ArSS^-$ and/or ArS^-, followed by reaction of the sulfur nucleophile(s) on the thiophosphonium ion to yield **4** is the more probable reaction pathway. We are unable to distinguish between the two possible nucleophiles, but attack at a central sulfur atom in polysulfides is not without precedent [48], and extrusion of a central sulfur atom in **4** and **5** is expected. This is in accord with the results of the other two studies we are aware on the desulfurization of aromatic tetrasulfides [48, 49], and allows a simplified reaction scheme to be postulated (scheme 2).

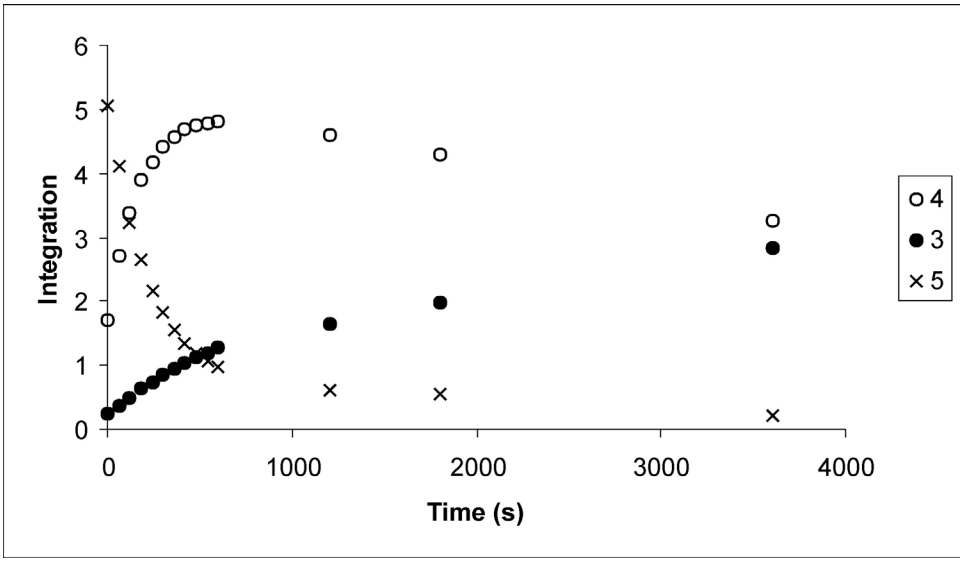


Figure 2. Time profile of the desulfurization of 0.025 M **5** by 0.42 M Ph_3P.

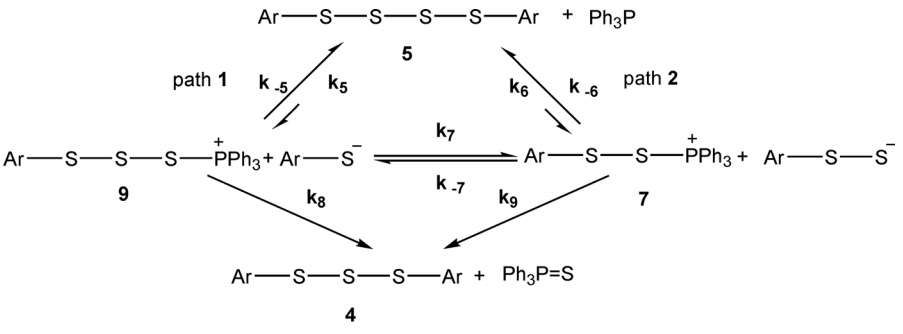
The 12-fold increase in reaction rate of **5** as compared with that of **4** is likely due to the statistical doubling of the number of removable sulfurs and the probability of rapid attack by $ArSS^-$ at the more electrophilic exo-aromatic sulfur atom of **7**.

This preliminary evaluation of **5** as a phosphorothionation reagent indicates that, when treated with an oligodeoxyribonucleotide substrate, it will not be sufficiently reactive to classify as an effective sulfurizing reagent.

Table 3. Rate constants for the desulfurization of **4** and **5** and formation of **3** in the reaction of 0.025 M **5** with Ph_3P.

	Loss of **5**[a]			Formation of **4**[b]			Formation of **3**[c]		
$[Ph_3P_{(initial)}]$[d] (M)	$k_{obs} \times 10^{-3}$ (s^{-1})[e]	$k \times 10^{-3}$ ($M^{-1}s^{-1}$)	$t_{1/2}$ (min)	$k_{obs} \times 10^{-3}$ (s^{-1})[e]	$k \times 10^{-3}$ ($M^{-1}s^{-1}$)	$t_{1/2}$ (min)	$k_{obs} \times 10^{-3}$ (s^{-1})[e]	$k \times 10^{-3}$ ($M^{-1}s^{-1}$)	$t_{1/2}$ (min)
0.42	4.8 ± 0.9	11.5 ± 2.6	1.0	0.2 ± 0.1	0.4 ± 0.1	28.8	0.5 ± 0.1	1.2 ± 0.3	9.9
0.83	4.8 ± 1.4	5.8 ± 1.7	2.0	0.8 ± 0.5	0.9 ± 0.6	12.5	0.6 ± 0.2	0.7 ± 0.3	15.9
1.67	3.2 ± 2.1	1.9 ± 1.3	6.1	1.1 ± 0.4	0.7 ± 0.3	17.0	1.2 ± 0.5	0.7 ± 0.3	16.3

[a]Partial order was determined to be −0.3. [b]Partial order determined to be 1.4. [c]Partial order determined to be 0.6. [d]Error on concentration is estimated to be 0.05 M. [e]1st order rate constant.



SCHEME 2 Mechanism for the desulfurization of aromatic tetrasulfides.

3. Experimental

3.1 *General experimental*

Triphenylphosphine, 1,3,5-tri-*t*-butylbenzene, bis(4-methylbenzene) disulfide (**3**) and 4-methylbenzene thiol (**6**) were all commercially available. All experiments were performed under an inert (N_2) atmosphere. Deuterated chloroform ($CDCl_3$) was dried over molecular sieves. Flash chromatography [50] was performed using 230–400 mesh silica gel. Melting points were obtained on a Gallenkamp block apparatus (Mp) and are uncorrected.

3.2 *Instrumentation and measurement techniques*

NMR spectra were recorded in $CDCl_3$ at 300, 400 or 500 MHz for ^{1}H, 75, 101 or 125 MHz for ^{13}C and 81 MHz for ^{31}P. Kinetic studies were performed at 23.4 ± 0.8 °C on a 500 MHz machine. Stock solutions of bis(4-methylbenzene) disulfide **3**, bis(4-methylbenzene) trisulfide **4** and bis(4-methylbenzene) tetrasulfide **5** in $CDCl_3$, each at 0.100 ± 0.002 M concentration, were kept in sealed volumetric glass flasks. A stock solution of triphenylphosphine (Ph_3P) at 4.90 ± 0.08 M was used as the phosphine source. A stock solution of 1,3,5-tri-*t*-butylbenzene at 0.100 ± 0.002 M was used as the internal standard. The total volume per sample was 600 μL, which included 100 μL of 1,3,5-tri-*t*-butylbenzene solution as the internal standard [^{1}H NMR ($CDCl_3$) δ (ppm): 1.34 (s, 27H), 7.26 (m, 3H)]. To ensure pseudo-first-order kinetics with respect to Ph_3P, the ratio of Ph_3P to the substrate was either 16.3:1, 32.7:1 or 65.3:1, the substrate concentration being 0.025 M in all experiments.

The delay time was set to 10 s [51]. The machine was shimmed with a dummy sample to afford a peak resolution of less than 2 Hz. Data were acquired at 1 min intervals for the first 10 min followed by measurements at 20, 30 and 60 min. The methyl signals were entirely resolvable [52] and integratable, the precision of the chemical shifts of the methyl signals from experiment to experiment being on average, ±0.002 ppm. An infinity value for rate constant determination was estimated based on the extent of desulfurization after 60 min.

3.3 *Kinetics methodology*

Pseudo-first-order plots of $\ln(I_t - I_\infty)$ *vs.* time (where I_t, I_∞ are the ^{1}H NMR integrations of the methyl peaks at times $t = t$, $t = t_\infty$, respectively) were determined for the decomposition of **3** as well as the desulfurization of **4** and **5**. The initial $t = 0$ s point was taken as the time of the first NMR acquisition (usually 4–5 min after the reagents were mixed). The pseudo-first-order rate constants, k_{obs}, were calculated using the least-squares method. Each experiment was repeated three times and the average rate constant was used.

3.4 *Compounds synthesized according to literature procedures [25]*

3.4.1 ***Bis(4-methylbenzene) trisulfide, 4.*** Yellow powder, yield: 97%; recrystallization from *n*-pentane at −15 °C afforded light yellow needles: mp 78–79 °C. (lit. [26] 82–84 °C); ^{1}H NMR δ (ppm): 2.32 (s, 3H), 7.25 (AB, 4H $J = 8.0$ Hz); ^{13}C NMR δ (ppm): 21.3, 129.7, 130.9, 132.8, 138.5; MS (EI) m/z (rel intensity) 278 (12.6), 246 (100) [−S], 214 (4.8) [−2S], 123 (93.8) [$-S_2C_7H_7$], 91 (27.2) [$-S_3C_7H_7$].

3.4.2 ***Bis(4-methylbenzene) tetrasulfide, 5.*** Yellow powder, yield: 99%; recrystallization from *n*-pentane at −15 °C afforded bright yellow needles: mp 62–64 °C; ^{1}H NMR δ (ppm): 2.35 (s, 3H), 7.28 (AB, 4H $J = 7.8$ Hz); ^{13}C NMR δ (ppm): 21.4, 129.8, 130.9, 132.7, 138.7; MS (FAB) m/z (rel intensity) 310 (47.4), 278 (24.0) [−S], 246 (22.5) [$-S_2$], 123 (29.5) [$-S_3C_7H_7$]; Anal. calcd (%) for $C_{14}H_{14}S_4$: C, 54.14; H, 4.45; S, 41.30. Found: C, 53.89; H, 4.10; S, 41.75.

3.4.3 ***Desulfurization of 4 or 5.*** The following is a general example of the experimental procedure for the experiments detailed in table 1. A solution of Ph_3P (262 mg, 1 mmol, 1 equiv.) and **4** (278 mg, 1 mmol, 1 equiv.) in CH_2Cl_2 (20 ml) was allowed to stir at room temperature (see table 1 for reaction times). The solvent was then removed under reduced pressure and the residue dried *in vacuo*. The resulting crude solid was chromatographed [50] (10% $CHCl_3$-hexanes slowly increasing to 80% $CHCl_3$-hexanes). For entry 2 in table 1 a yellow oil identified as a mixture of polysulfides **3** and **4**, $R_f = 0.64$ (50% $CHCl_3$-hexanes), and a white powder identified as $Ph_3P{=}S$, $R_f = 0.47$ (50% $CHCl_3$-hexanes), were the only recovered products. Yield of $(Ph)_3P{=}S$: 87% [53]; ^{1}H NMR δ (ppm): 7.45 (m, 10H), 7.70 (m, 5H); ^{31}P NMR δ 44.48.

Acknowledgments

We thank NSERC for support. EZ-C thanks FCAR for a personal scholarship. We are especially grateful to Dr R. Bruce Lennox (McGill University) for helpful discussions regarding the kinetics analysis. Helpful discussions with Dr Harry R. Hudson (University of North London) regarding ^{31}P NMR detection of intermediates are also acknowledged. We also thank Dr Ekaterina Viazovkina for preliminary testing of **5** with oligodeoxyribonucleotides.

References

[1] Zamecnik, P. C., 1991, Prospects for antisense nucleic acid therapy for cancer and AIDS (New York: Wiley Liss).
[2] Mirabelli, C. K. and Crooke, S. T., 1993, Antisense research and applications (Ann Arbor: CRC).
[3] Eckstein, F., 1985, *Annu. Rev. Biochem.*, **54**, 367.
[4] Liebhaber, S. A., Cash, F. E. and Shakin, S. H., 1984, *J. Biol. Chem.*, **259**, 15597.
[5] Crooke, S. T., 1998, *Antisense Nucleic A*, **8**, vii.
[6] De Smet, M. D., Meenken, C. and Van Den Horn, G. J., 1999, *Ocul. Immunol. Inflamm.*, **7**, 189.
[7] Cheruvallath, Z. S., Carty, R. L., Moore, M. N., Capaldi, D. C., Krotz, A. H., Wheeler, P. D., Turney, B. J., Craig, S. R., Gaus, H. J., Scozzari, A. N., Cole, D. L. and Ravikumar, V. T., 2000, *Org. Process Res. Dev.*, **4**, 199.
[8] Xu, Q., Musier-Forsyth, K., Hammer, R. P. and Barany, G., 1996, *Nucleic Acids Res.*, **24**, 1602.
[9] Xu, Q., Barany, G., Hammer, R. P. and Musier-Forsyth, K., 1996, *Nucleic Acids Res.*, **24**, 3543.
[10] Ma, M. Y.-X., Dignam, J. C., Fong, G. W., Li, L., Gray, S. H., Jacob-Samuel, B. and George, S. T., 1997, *Nucleic Acids Res.*, **25**, 3590.
[11] Tang, J.-Y., Han, Y., Tang, J. X. and Zhang, Z., 2000, *Org. Process Res. Dev.*, **4**, 194.
[12] Brill, W. K.-D., Tang, J.-Y., Ma, Y.-X. and Caruthers, M. H., 1989, *J. Am. Chem. Soc.*, **111**, 2321.
[13] Iyer, R. P., Phillips, L. R., Egan, W., Regan, J. B. and Beaucage, S. L., 1990, *J. Org. Chem.*, **55**, 4693.

[14] Iyer, R. P., Egan, W., Regan, J. B. and Beaucage, S. L., 1990, *J. Am. Chem. Soc.*, **112**, 1253.
[15] Vu, H. and Hirschbein, B. L., 1991, *Tetrahedron Lett.*, **32**, 3005.
[16] Stec, W. J., Uznanski, B., Wilk, A., Hirschbein, B. L., Fearon, K. L. and Bergot, B. J., 1993, *Tetrahedron Lett.*, **34**, 5317.
[17] Liu, X. and Reese, C. B., 1995, *J. Chem. Soc., Perkin. Trans. 1*, **13**, 1685.
[18] Stec, W. J., Grajkowski, A., Kobylanska, A., Karwowski, B., Koziolkiewicz, M., Misiura, K., Okruszek, A., Wilk, A., Guba, P. and Boczkowska, M., 1995, *J. Am. Chem. Soc.*, **117**, 12019.
[19] Almer, H., Stawinski, J. and Stromberg, R., 1996, *Nucleic Acids Res.*, **24**, 3811.
[20] Wyrzykiewicz, T. K. and Ravikumar, V. T., 1994, *Bioorg. Med. Chem. Lett.*, **4**, 1519.
[21] Zhang, Z., Nichols, A., Tang, J. X., Alsbeti, M. and Tang, J.-Y., 1997, *Nucleosides Nucleotides*, **16**, 1585.
[22] Eleuteri, A., Cheruvallath, Z. S., Capaldi, D. C., Cole, D. L. and Ravikumar, V. T., 1999, *Nucleosides Nucleotides*, **18**, 1893.
[23] Cheruvallath, Z. S., Wheeler, P. D., Cole, D. L. and Ravikumar, V. T., 1999, *Nucleosides Nucleotides*, **18**, 1195.
[24] Efimov, V. A., Kalinkina, A. L., Chakhmakhcheva, O. G., Hill, T. S. and Jayaraman, K., 1995, *Nucleic Acids Res.*, **23**, 4029.
[25] Harpp, D. N. and Zysman-Colman, E., 2003, *J. Org. Chem.*, **68**, 2487.
[26] Harpp, D. N. and Smith, R. A., 1979, *J. Org. Chem.*, **44**, 4140.
[27] Féher, F. and Kurz, D., 1968, *Z. Naturforsch.*, **23B**, 1030.
[28] Harpp, D. N., Ash, D. K. and Smith, R. A., 1980, *J. Org. Chem.*, **45**, 5155.
[29] Harpp, D. N. and Smith, R. A., 1982, *J. Am. Chem. Soc.*, **104**, 6045.
[30] Mulhearn, D. C. and Bachrach, S. M., 1996, *J. Am. Chem. Soc.*, **118**, 9415.
[31] Greer, A., 2001, *J. Am. Chem. Soc.*, **123**, 10379.
[32] Gleason, J. G., 1970, The chemistry of organic disulfides, desulfurizations with aminophosphines. PhD thesis, McGill University.
[33] Ash, D. K., 1973, The chemistry of organic trisulfides. PhD thesis, McGill University.
[34] Hall, C. D., Tweedy, B. R., Kayhanian, R. and Lloyd, J. R., 1992, *J. Chem. Soc., Perkin. Trans. 2*, 775.
[35] Harpp, D. N., Gleason, J. G. and Snyder, J. P., 1968, *J. Am. Chem. Soc.*, **90**, 4181.
[36] Besides the expected desulfurized product **3**, only one other product was detected, which was identified as **6** (SH-peak not present). The absence of alcoholic hydroxyl or water signals detected by ^{1}H NMR combined with the absence of an SH peak for **6** suggests that a competing reaction may convert some of the assumed thiophosphonium intermediate into **6** and that the reduction source is deuterated.
[37] Bangerter, F., Karpf, M., Meier, L. A., Rys, P. and Skrabal, P., 1998, *J. Am. Chem. Soc.*, **120**, 10653.
[38] Puke, C., Erker, G., Wibbeling, B. and Fröhlich, R., 1999, *Eur. J. Org. Chem.*, **8**, 1831.
[39] Tebby, J. C., Maierm, L. and Diel, P. J., 2000, Handbook of phosphorus-31 nuclear magnetic resonance data (Boston: CRC Press).
[40] Parker, A. J. and Kharasch, N., 1960, *J. Am. Chem. Soc.*, **82**, 3071.
[41] Ellestad, G. A., Hamann, P. R., Zein, N., Morton, G. O., Siegal, M. M., Pastel, M., Borders, D. B. and McGahren, W. J., 1989, *Tetrahedron Lett.*, **30**, 3033.
[42] Snyder, J. P., 2002, personal communication.
[43] Steudel, R. and Otto, A. H., 1999, *Eur. J. Inorg. Chem.*, 2057.
[44] In contrast, Hayashi [45] reported that it was easier and faster to desulfurize **3** compared with **4** with Ph_3P. This appears to be an erroneous conclusion since the desulfurization of aromatic disulfides is possible only at high temperatures.
[45] Hayashi, S., Furukawa, M., Yamamoto, J. and Hamamura, K., 1967, *Chem. Pharm. Bull.*, **15**, 1310.
[46] Harpp, D. N., Kader, H. A. and Smith, R. A., 1982, *Sulfur Lett.*, **1**, 59.
[47] Langer, H. J. and Hyne, J. B., 1973, *Can. J. Chem.*, **51**, 3403.
[48] Ganesh, K. and Kishore, K., 1995, *Macromolecules*, **28**, 2483.
[49] Démarcq, M. C., 1993, *J. Chem. Res., (M)*, 3052.
[50] Still, W. C., Kahn, M. and Mitra, A., 1978, *J. Org. Chem.*, **43**, 2923.
[51] Control experiments were conducted with known ratios of **1**, **2** and **3** to reproduce these ratios through the integration of their respectively resolved methyl groups by ^{1}H NMR.
[52] van Wazer, J. R. and Grant, D., 1964, *J. Am. Chem. Soc.*, **86**, 1450.
[53] In control experiments, it was possible to elute and then isolate 100% of $Ph_3P{=}S$ pre-loaded on a column.