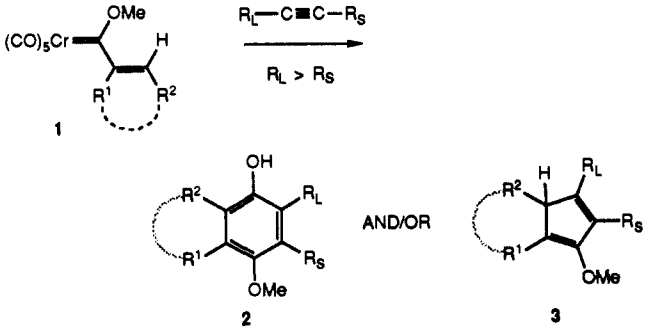
Heteroannulation of Chromium Carbene Complexes. A Novel and Efficient Pyrrole Synthesis

Vera Dragisich, Christopher K. Murray, Benjamin P. Warner, William D. Wulff,* and Dominic C. Yang[1]

Department of Chemistry, Searle Chemistry Laboratory The University of Chicago, Chicago, Illinois 60637

Received September 6, 1989

The annulations of α,β-unsaturated carbene complexes of chromium with acetylenes have become the most synthetically useful reactions of Fischer carbene complexes, as indicated by their demonstrated applications in organic synthesis.[2] When the unsaturated substituent of the carbene ligand in **1** is an aryl group, either the five- or six-membered-ring annulation products are possible;[3] however, for alkenyl complexes of the type **1**, only six-membered-ring products have been reported.[4] Given the established synthetic importance of the annulation of chromium carbene complexes for the production of carbocycles, the development of this reaction for the synthesis of heterocycles has remained an alluring yet heretofore elusive goal.[5]

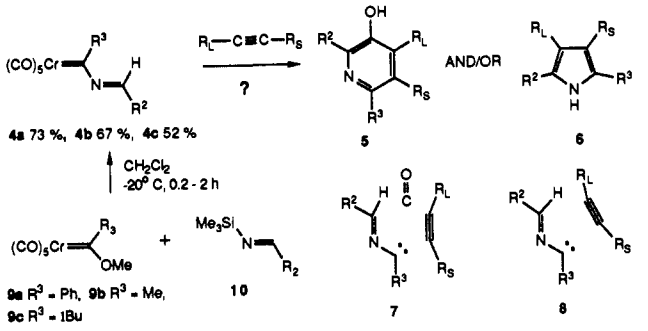


In considering the adaptation of these annulations to the construction of nitrogen heterocycles, the only known aza analogue of **1** is the imine class of complexes of the type **4**.[11d] Although several methods have been reported for their preparation, they all suffer from low yields.[11c,12] These complexes can be prepared much more efficiently from the addition of *N*-silyl imines, generated in situ from aldehydes and lithium hexamethyldisilazide,[13] to methoxy and acyloxy carbene complexes.[14,15] The imino complexes **4** are quite stable and (like the alkoxy complexes **9**) can be handled in air and purified on silica gel. They can be prepared in two steps from chromium hexacarbonyl and in most cases in good overall yield since the alkoxy complexes **9** are generally obtainable in high to excellent yields.[16] On the basis of the known carbocyclic annulations of the complexes **1**, the heteroannulations of the imino complexes **4** can be anticipated to give either 3-hydroxypyridine **5** or the pyrrole **6**.

Table I. Pyrroles from the Heteroannulation of Imino Complexes **4**[a]

entry	complex	R_2	R_3	R_L	R_S	product series	% yield of **13**
1	**4a**	Ph	Ph	Et	Et	**a**[b]	97
2	**4a**	Ph	Ph	*n*-Pr	OEt	**b**	94
3	**4a**	Ph	Ph	Et	$(C{=}O)CH_3$	**c**	98
4	**4b**	Ph	CH_3	Et	Et	**d**[b]	81
5	**4c**	Ph	*t*-Bu	*n*-Pr	H	**e**[c,d]	94
6	**4c**	Ph	*t*-Bu	Et	Et	**f**[d]	85
7	**4d**	CH_3	Ph	Et	Et	**d**[b,d]	84

[a] Unless otherwise specified, all reactions were carried out in hexane at 70 °C under argon at 0.014 M in carbene complex with 2.3–3.0 equiv of alkyne for 2–3 days. Workup involves filtration, concentration, and direct purification on silica gel. [b] Temperature 85–90 °C. [c] 1% **13e** detected; 5% **5e** also isolated. [d] Reaction time, 1 day.



The heteroannulations of the imino complexes **4** are remarkably efficient and general (Table I). They are very highly chemoselective, giving only pyrrole products, and also highly regioselective, giving only a single pyrrole with terminal acetylenes. The yields are excellent with both terminal and internal acetylenes, and furthermore, the pyrroles can be obtained from these heteroannulations in high yields with both electron-rich and electron-deficient acetylenes, a feat that is not possible with the carbocyclic annulations of carbene complexes.[2-4] This new pyrrole synthesis has several advantages to offer over existing methods[17] and compares favorably with the best of other transition-metal-mediated approaches.[18]

(1) National Institutes of Health Predoctoral Fellow.

(2) For recent reviews, see: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984. (b) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (c) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (d) Casey, C. P. *React. Intermed.* **1985**, *3*, 109. (e) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9. (f) Dötz, K. H.; In *Organometallics in Organic Synthesis: Aspects of a Modern Interdisciplinary Field*; tom Dieck, H., de Meijere, A., Eds.; Springer: Berlin, 1988. (g) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1989; Vol. 1. (h) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, in press.

(3) For recent references, see: (a) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9. (b) Yamashita, A.; Toy, A.; Watt, W.; Muchmore, C. R. *Tetrahedron Lett.* **1988**, *29*, 3403. (c) Dötz, K. H.; Erben, H. G.; Harms, K. *J. Chem. Soc., Chem. Commun.* **1989**, 692. For a complete list of citations, see ref 9a.

(4) (a) Dötz, K. H.; Kuhn, W. *J. Organomet. Chem.* **1983**, *252*, C78. (b) Wulff, W. D.; Chan, K. S.; Tang, P. C. *J. Org. Chem.* **1984**, *49*, 2293.

(5) (a) The only other heteroannulations of carbene complexes that are known are those with phosphaalkynes[6] and with pyrazole complexes.[7] (b) Reactions with nitriles do not lead to cyclic products.[8] (c) Furans[9] and pyrones[10] have been observed as carbon monoxide derived products. (d) For failed attempts, see refs 8 and 11a.

(6) (a) Dötz, K. H.; Tiriliomis, A.; Harms, K.; Regitz, M.; Annen, U. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 713. (b) Dötz, K. H.; Tiriliomis, A.; Harms, K. *J. Chem. Soc., Chem. Commun.* **1989**, 788.

(7) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229.

(8) Yang, D. C.; Dragisich, V.; Wulff, W. D.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 307.

(9) (a) McCallum, J. S.; Kunng, F. A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346. (b) Dötz, K. H.; Dietz, R.; Neugebauer, D. *Chem. Ber.* **1979**, *112*, 1486.

(10) Semmelhack, M. F.; Tamura, R.; Schnatter, W.; Springer, J. *J. Am. Chem. Soc.* **1984**, *106*, 5363.

(11) (a) Wulff, W. D.; Dragisich, V.; Huffman, J. C.; Kaesler, R. W.; Yang, D. C. *Organometallics* **1989**, *8*, 2196. (b) Hegedus, L. S.; Shultze, L. M.; Montgomery, J. *Organometallics* **1989**, *8*, 2189. (c) Aumann, R.; Hinterding, P. *Chem. Ber.* **1989**, *122*, 368. (d) An aldimine complex has been cited in a review: Aumann, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1456.

(12) (a) Knauss, L.; Fischer, E. O. *Chem. Ber.* **1970**, *103*, 3744. (b) Knauss, L.; Fischer, E. O. *J. Organomet. Chem.* **1971**, *31*, C68.

(13) (a) Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539. (b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 5369.

(14) Murray, C. K.; Warner, B. P.; Dragisich, V.; Wulff, W. D.; Rogers, R. D., manuscript in preparation.

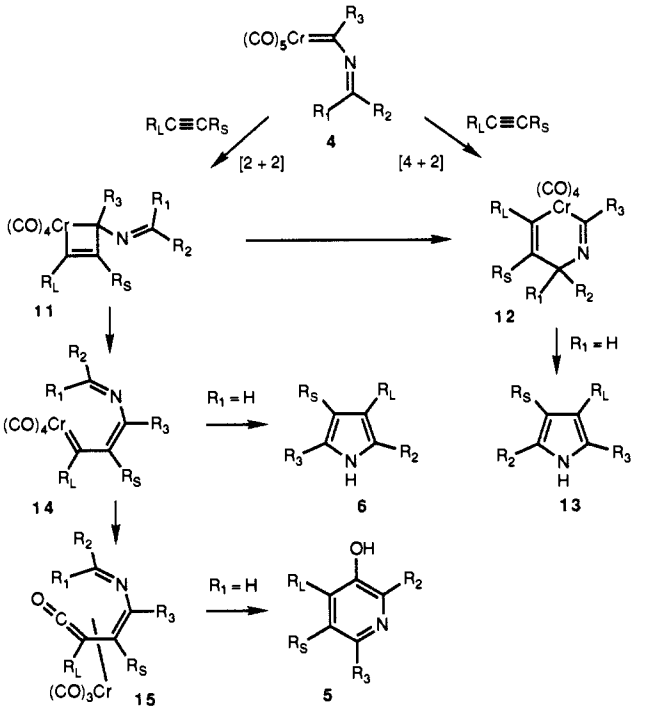
(15) (a) The formation of **4c** is slow, and the yield is based on unrecovered starting material at 50% conversion. (b) Complex **4d** was prepared in 42% yield from an in situ generated acetoxy carbene complex.[14]

(16) (a) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth.* **1987**, *65*, 140. (b) Fischer, E. O.; Schubert, U.; Kleine, W.; Fischer, H. *Inorg. Synth.* **1979**, *19*, 165. It is not necessary to perform the chromatography at low temperatures or under an inert atmosphere as described in ref 16b.

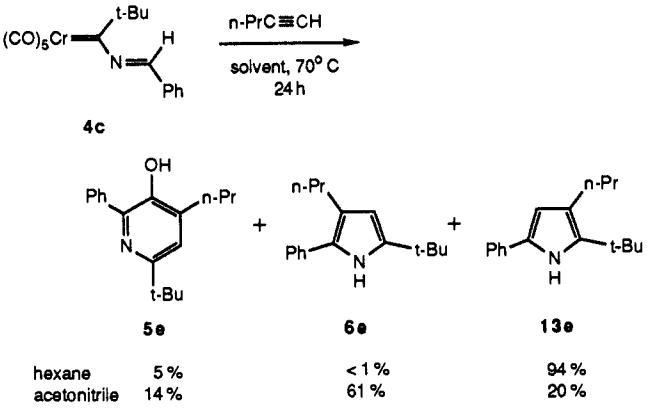
(17) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 4, pp 313–76. (b) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1977.

0002-7863/90/1512-1251$02.50/0

Scheme I



In addition to the high yields realized with both electron-rich and -deficient acetylenes, there are several other features of these heteroannulations that are unprecedented in the carbocyclic annulations of the complexes **1**. First, the annulations of the alkenyl complexes of the type **1** occur exclusively with carbon monoxide incorporation to give only six-membered-ring annulation products,[4] whereas the annulations of the imino complexes **4** give only five-membered-ring annulation products. In one case, a 5% yield of the six-membered-ring annulation product (3-hydroxypyridine) was observed (Table I, entry 5). A second difference is that the regioselectivity of alkyne incorporation is reversed for the heteroannulation of the imino complexes **4**. On the basis of the regioselectivity of the carbocyclic annulations,[19] the expected pyrrole is **6**, where the alkyne is incorporated as illustrated in **8**. The formation of the unexpected regioisomer **13**[20] occurs with a ≥71:1 selectivity and is quite remarkable since this regioisomer has never been observed as the major product for any carbocyclic annulation.[19] Equally as fascinating and unprecedented is the dependence of the regioselectivity on the solvent.[21] The pyrrole **13e** is the exclusive isomer in hexane, whereas in acetonitrile the formation of **6e** occurs preferentially by a factor of 3:1.



	5e	**6e**	**13e**
hexane	5%	<1%	94%
acetonitrile	14%	61%	20%

A mechanistic accounting of these heteroannulation reactions is presented in Scheme I. The mechanisms proposed for the carbocyclic annulations[2] are not satisfying in accounting for the formation of the pyrrole **13**. While it is possible that **13** could be formed from the regioisomer of the [2 + 2] cycloadduct **11** (not shown) which is formed from a reversal in alkyne incorporation, it is also possible that **13** could arise from the [4 + 2] cycloadduct **12** as shown. The formation of two regioisomeric five-membered products has not been observed for carbocyclic annulations, but the intermediacy of a [4 + 2] cycloadduct of the type **12** has been suggested[22] and may be involved in certain two-alkyne annulations.[23] The formation of the pyrrole **6** and the 3-hydroxypyridine **5** from **16** may occur via mechanisms analogous to those proposed for carbocyclic annulations.[2,24] Further experiments will be needed before the mechanism for the formation of the regioisomeric pyrroles **6** and **13** and the dependence of their distribution on the solvent can be better understood.

Previously we and others have reported[8,11] the preparation of *O*-alkyl and *O*-acyl imidate carbene complexes of the type **16**, which are closely related to the imino complexes **4**. The heteroannulations of **16a** and **16b** both give higher selectivities for 3-hydroxypyridine formation as compared with the imino complexes **4**, as illustrated for their reactions with 1-pentyne.[25] It is also quite interesting that, unlike the imino complex **4c**, the *O*-acyl imidate complex **16d** gives pyrrole **6e** as the major regioisomer. The heteroannulation of the *O*-alkyl imidate complex **16c** with 1-pentyne fails due to nitrile deinsertion.[8,11a]

The demonstrated utility for pyrrole synthesis, the potential for 3-hydroxypyridine synthesis, and the unique mechanistic issues raised by the initial results described herein should serve to stimulate the further development of the heteroannulations of chromium carbene complexes.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (PHS-GM 33589). A predoctoral training grant has been provided for D.C.Y. by the National Institutes of Health (GM 07151). Some of the mass

(18) For other transition-metal-mediated pyrrole syntheses, see: (a) Buchwald, S. L.; Wannamaker, M. W.; Wilson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776. (b) Hong, P.; Yamazaki, H. *J. Organomet. Chem.* **1989**, *373*, 133. (c) Roskamp, E. J.; Dragovich, P. S.; Hartung, J. B., Jr.; Pedersen, S. F. *J. Org. Chem.* **1989**, *54*, 4736. (d) Igarashi, S.; Haruta, Y.; Ozawa, M.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737. (e) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570. (f) Danks, T. N.; Thomas, S. E. *Tetrahedron Lett.* **1988**, *29*, 1425. (g) Tsuji, Y.; Yokoyama, Y.; Huh, K. T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456. (h) Aumann, R.; Kuckert, E.; Krüger, C.; Angermund, K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 563. (i) Aumann, R.; Heinen, H. *Chem. Ber.* **1986**, *119*, 3801. (j) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (k) Inada, A.; Heimgartner, H. *Helv. Chim. Acta* **1982**, *65*, 1489. (l) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, 4277. (m) Bäckvall, J. E.; Nyström, J. E. *J. Chem. Soc., Chem. Commun.* **1981**, 59. (n) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1980**, *45*, 2741. (o) Bellamy, F. *J. Chem. Soc., Chem. Commun.* **1978**, 998. (p) Bellamy, F.; Schuppiser, J. L.; Streith, J. *Heterocycles* **1978**, *11*, 461. (q) Alper, H.; Prickett, J. E.; Wollowitz, S. *J. Am. Chem. Soc.* **1977**, *99*, 4330. (r) Alper, H.; Prickett, J. E. *Inorg. Chem.* **1977**, *16*, 67. (s) Müller, E.; Luppold, E.; Winter, W. *Chem. Ber.* **1975**, *108*, 237. (t) Murahasi, S. I.; Shimamura, T.; Moritani, J. *J. Chem. Soc., Chem. Commun.* **1974**, 931. (u) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549. (v) Chalk, A. J. *Tetrahedron Lett.* **1972**, 3487. (w) Jautlat, M.; Ley, K. *Synthesis* **1970**, 593. (x) Schute, K. E.; Reisch, J.; Walker, H. *Chem. Ber.* **1965**, *98*, 98. (y) Braye, E. H.; Hoogzand, C.; Hübel, W.; Krüerke, U.; Merenyi, R.; Weiss, E. *Advances in the Chemistry of Coordination Compounds*; Kirschner, S., Ed.; Macmillan: New York, 1961; p 191.

(19) (a) Wulff, W. D.; Tang, P. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677. (b) Dötz, K. H.; Muhlemeier, J.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187. (c) Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471.

(20) The structural assignments for pyrroles **6e** and **13e** were made on the basis of NOE experiments (supplementary material).

(21) For an additional example, see: Brandvold, T. A.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.*, in press.

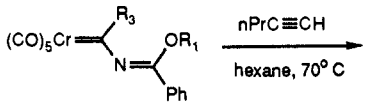
(22) Collman, J. P., Hegedus, L. S., Norton, J. R., Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 792.

(23) Xu, Y. C.; Challener, C. A.; Dragisich, V.; Brandvold, T. A.; Peterson, G. A.; Wulff, W. D.; Williard, P. G. *J. Am. Chem. Soc.* **1989**, *111*, 7269.

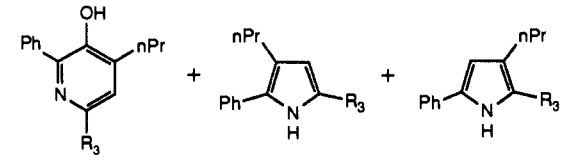
(24) Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915.

(25) (a) The reaction of **16a** also gives 31% of *N*-(4-(2-*n*-propyl-1-naphthol)) *O*-methylphenyl imidate (**23**). (b) The products from the reactions with **16** are the result of a reduction of a carbon–oxygen bond in the ultimate intermediate.[26]

(26) Wulff, W. D.; Kaesler, R. W.; Peterson, G. A.; Tang, P. C. *J. Am. Chem. Soc.* **1985**, *107*, 1060.



16a R_3 = Ph, R_1 = Me
16b R_3 = Ph, R_1 = C(O)CH_3
16c R_3 = tBu, R_1 = Me
16d R_3 = tBu, R_1 = C(O)CH_3



complex			
16a	5g 51%	6g 4%	
16b	5g 31%	6g 9%	
16d	5e 37%	6e 26%	13e 13%

spectral data were obtained at the Midwest Center for Mass Spectrometry, an NSF Regional Instrument Facility (CHE-8211164). The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA-14599).

Supplementary Material Available: ^1H and ^{13}C NMR, IR, and mass spectral data for all new compounds (**4a-d**, **5e,g**, **6e,g**, **13a-f**, and **23**) (7 pages). Ordering information is given on any current masthead page.

3*H*-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizing Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates

Radhakrishnan P. Iyer, William Egan, Judith B. Regan, and Serge L. Beaucage*

Division of Biochemistry and Biophysics
Center for Biologics Evaluation and Research
Food and Drug Administration
8800 Rockville Pike, Bethesda, Maryland 20892

Received October 5, 1989

Oligodeoxyribonucleoside phosphorothioates are isoelectronic analogues of natural phosphodiesters in which one of the oxygen atoms that does not participate in the internucleotidic linkage is replaced by a sulfur atom.[1] Unlike natural oligomers, phosphorothioate oligodeoxyribonucleotides are resistant to degradation by nucleases[1] and, hence, have demonstrated their usefulness as "antisense" molecules by inhibiting gene expression in vitro.[2] The inhibitory mechanism is presumed to occur by binding specific messenger RNAs (the "sense" molecules) as DNA-RNA duplexes thereby impairing the translation of the messages by the ribosomes[3] and/or from the degradation of the heteroduplexes by RNase H.[4]

In experiments using "antisense" DNA fragments as potential therapies against AIDS,[5] it has been shown that phosphorothioate oligomers inhibited the cytopathic effect of HIV-1 in chronically infected H9 cells.[6] These results suggest that oligonucleoside phosphorothioates may represent a new class of therapeutic agents. Consequently, the availability of these analogues is urgent and crucial for clinical evaluation. Our efforts at improving their preparation are reported herein.

The automated synthesis of phosphorothioate DNA[7-11] according to the "phosphoramidite" approach[12] involves a stepwise sulfurization reaction effected by a solution of elemental sulfur (S_8). This relatively slow (7.5 min)[8] sulfur-transfer reaction has, in our laboratory, led to instrument failure as a result of the insolubility of S_8 in most organic solvents.[13] To circumvent these problems, a novel sulfurizing agent was designed according to the following criteria: (i) The reagent must be readily prepared and easily handled under laboratory conditions. (ii) The stability and solubility of the reagent in various solvents and concentrations must be compatible with automated oligonucleotide synthesis. (iii) The reagent must exhibit fast sulfurization reaction kinetics, and most importantly, it must quantitatively convert phosphite triesters into phosphorothioate triesters without nucleosidic modifications to ensure the genetic integrity of the synthetic DNA.

Conceptually, thiosulfonates[14-16] are attractive reagents for sulfur-transfer reactions. These compounds are susceptible to nucleophilic attack by phosphite triesters at the sulfenyl sulfur leading to the cleavage of the polarized sulfur-sulfur bond and the generation of a sulfinate anion[15] (Figure 1). This anion would then trigger an intramolecular cyclization[16] to complete the sulfur-transfer reaction with enhanced kinetics.[17] Selected thiosulfonates were therefore prepared and evaluated with respect to the criteria outlined above (data not shown). Thiosulfonate **1**[18] fulfilled all requirements. The compound, isolated in large quantities (20 g), was prepared in 50% yield by the oxidation of 3*H*-1,2-benzodithiole-3-one[19] using trifluoroperoxyacetic acid.[20]

The efficacy of the sulfurizing reagent was tested during the automated solid-phase synthesis of the dinucleoside phosphorothioate **3** (Figure 1). A 0.2 M solution of **1** in acetonitrile[21] was used to sulfurize **2** during a period of 30 s. To assess the extent of the reaction, excess **1** was immediately washed away with

(1) Eckstein, F. *Annu. Rev. Biochem.* **1985**, *54*, 367-402.
(2) Cazenave, C.; Stein, C. A.; Loreau, N.; Thuong, N. T.; Neckers, L. M.; Subasinghe, C.; Helene, C.; Cohen, J. S.; Toulme, J.-J. *Nucleic Acids Res.* **1989**, *17*, 4255-4273.
(3) Liebhaber, S. A.; Cash, F. E.; Shakin, S. H. *J. Biol. Chem.* **1984**, *259*, 15597-15602.
(4) Walder, R. Y.; Walder, J. A. *Proc. Natl. Acad. U.S.A.* **1988**, *85*, 5011-5015.
(5) Matsukura, M.; Shinozuka, K.; Zon, G.; Mitsuya, H.; Reitz, M.; Cohen, J. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7706-7710.
(6) Matsukura, M.; Zon, G.; Shinozuka, K.; Robert-Guroff, M.; Shimada, T.; Stein, C. A.; Mitsuya, H.; Wong-Staal, F.; Cohen, J. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 4244-4248.
(7) Stec, W. J.; Zon, G.; Egan, W.; Stec, B. *J. Am. Chem. Soc.* **1984**, *106*, 6077-6079.
(8) Stein, C. A.; Subasinghe, C.; Shinozuka, K.; Cohen, J. S. *Nucleic Acids Res.* **1988**, *16*, 3209-3221.
(9) The preparation of phosphorothioate DNA according the the "deoxynucleoside H-phosphonate" approach has also been reported.[10] In our hands, however, the solid-phase synthesis of these oligonucleotides has not been, as yet, as efficient with the "phosphonate" approach[11] as the "phosphoramidite" methodology.[12]
(10) Froehler, B. C. *Tetrahedron Lett.* **1986**, *27*, 5575-5578.
(11) Garegg, P. J.; Regberg, T.; Stawinski, J.; Stromberg, R. *Chem. Scr.* **1985**, *25*, 280-282. (b) Garegg, P. J.; Lindh, I.; Regberg, T.; Stawinski, J.; Stromberg, R. *Tetrahedron Lett.* **1986**, *27*, 4051-4054. (c) Froehler, B. C.; Matteucci, M. D. *Tetrahedron Lett.* **1986**, *27*, 469-472. (d) Froehler, B. C.; Ng, P. G.; Matteucci, M. D. *Nucleic Acids Res.* **1986**, *14*, 5399-5407.
(12) (a) Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859-1862. (b) McBride, L. J.; Caruthers, M. H. *Tetrahedron Lett.* **1983**, *24*, 2953-2956. (c) Adams, S. P.; Kavka, K. S.; Wykes, E. J.; Holder, S. B.; Galluppi, G. R. *J. Am. Chem. Soc.* **1983**, *105*, 661-663. (d) Sinha, N. D.; Biernat, J.; McManus, J.; Koster, H. *Nucleic Acids Res.* **1984**, *12*, 4539-4557.
(13) Alternatively, the sulfurization of "H-phosphonate" oligomers can be manually achieved outside the instrument by using a solution of S_8. This approach, however, suffers from the inherent limitation that oligonucleotides carrying predetermined combinations of natural and phosphorothioate linkages cannot easily be prepared.
(14) Michalski et al.[15] reported that the reaction of certain thiosulfonates with trialkylphosphites led to *O,O,S*-trialkyl phosphorothiolates. These observations prompted us to design thiosulfonates which upon reaction with trialkylphosphites would generate the desired *O,O,O*-trialkyl phosphorothioates.
(15) Michalski, J.; Modro, T.; Wieczorkowski, J. *J. Chem. Soc.* **1960**, 1665-1670.
(16) Harpp, D. N.; Gleason, J. G.; Ash, D. K. *J. Org. Chem.* **1971**, *36*, 322-326.
(17) Abell, K. W. Y.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. II* **1983**, 1171-1174.
(18) Hortmann, A. G.; Aron, A. J.; Bhattacharya, A. K. *J. Org. Chem.* **1978**, *43*, 3374-3378.
(19) McKibben, M.; McClelland, E. W. *J. Chem. Soc.* **1923**, 170-173.
(20) Venier, C. G.; Squires, T. G.; Chen, Y.-Y.; Hussmann, G. P.; Shei, J. C.; Smith, B. F. *J. Org. Chem.* **1982**, *47*, 3773-3774.
(21) For optimum results, **1** is dissolved in dry acetonitrile prior to use and the solution kept in an amber "siliconized" glass bottle.