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Generation of dialkyl phosphonodithioyl radicals and their addition onto alkenes. Synthesis of 3-phosphonodithiomethyl-3-deoxofuranosides

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Abstract

An efficient, three-step preparation of the new 2-phenylselanyl-[1,2,3]-dithiaphosphinane-2-oxide (**8**) from PCl_3 is described. The reagent is shown to behave as a precursor of the corresponding phosphonodithioyl radical, when placed in the presence of tin or silyl radicals. A novel synthesis of *S*,*S*-dialkyl phosphonodithioates is described based on these results. Application of this methodology to exocyclic 3-methylene-3-deoxofuranosides leads to the highly diastereoselective formation of 3-phosphonodithiomethyl-3-deoxofuranosides.

The implications of the phosphate group in biological processes and molecules have been the driving force of the decades-long search for isosters of that function. Thus, many analogs such as the phosphonates, the difluorophosphonates and the phosphinates, for instance, have been incorporated into molecules, with resultant potent bioactivities.[1] Phosphonothioates, dithioates and trithioates in particular have long been the focus of interest, due to their activities against various pest, or fungi, as well as antiwear additives in lubricating oils, and as material for resins with high refractive indexes.[2] Thus, for example *S*,*S*-diamyl phenylphosphonodithioate **1** was shown to be toxic in boll weevils, through inhibition of both acetylcholinesterase and aliesterase

1 **2** **3**

Figure 1.

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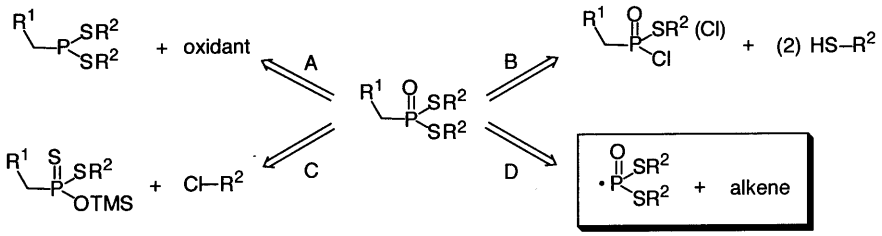
(Fig. 1).[3] In addition, the replacement of oxygen atom(s) with sulfur one(s) may induce changes in the chelating properties of these functional groups on various metal ions, thereby allowing to target more efficiently biological molecules.[4]

Previous work by us and others on the addition of phosphonyl radicals **2** onto alkenes led us to consider the reaction between phosphonodithioyl radicals **3** and alkenes as a way to developing a novel and useful access to phosphonodithioates.[5]

These compounds have been traditionally prepared by oxidation of trivalent *S*,*S*-dialkyl dithiophosphites, reaction of phosphonyl mono- or dichlorides with thiols under basic conditions and alkylation of *O*-silyl-*S*-alkyl phosphonodithioates (Scheme 1, paths A, B and C).[6] We reasoned that the presence of two sulfur atoms on the phosphorus would help stabilize the phosphorus-centered radical (when compared to the phosphonyl radical), which could result in an efficient addition reaction, when placed in the presence of an alkene (path D). To the best of our knowledge, these phosphonodithioyl radicals have not been generated or described in literature.



Scheme 1.

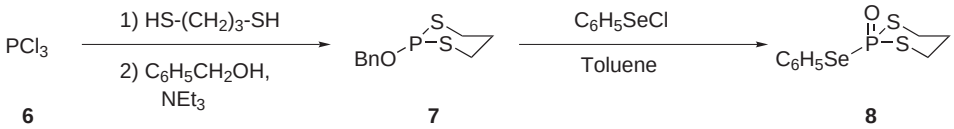
An approach relying on hydrogen abstraction from dithiophosphites (**4**) (Fig. 2) seemed thwarted by the physical properties of these potential radical precursors: indeed dithiophosphites are known to rapidly hydrolyze or react with nucleophiles, thus rendering their preparation difficult.[7] This is due to the weakness of the P–S bond.[7a] Even the more stable [1,2,3]-dithiaphosphinane-2-oxide (**5**) has been described as 'difficulty soluble in organic solvents'.[8]

4 **5**

Figure 2.

2-Phenylselanyl-[1,2,3]-dithiaphosphinane-2-oxide (**8**) was envisioned as being a potentially efficient radical precursor, especially in view of the higher propensity of the selanyl group to undergo homolytic substitution reactions than the sulfides. This compound was readily prepared in multigram scale through a Mathis/Arbuzov sequence of reactions (Scheme 2), and was found to be stable at room temperature for months.[9,10]

Slow addition (10 hours) of a mixture of tri-*n*-butyltin hydride and AIBN (3 and 0.5 equivalents, respectively) in benzene to a benzene solution of precursor **3** (3 equivalents) and



6 7 8

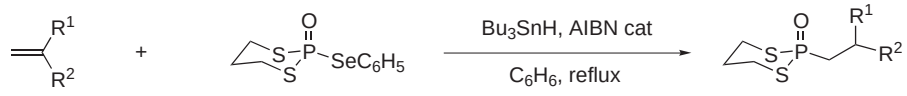
Scheme 2.

1-octene induced the formation of phosphonodithioate **10** in good yields (Table 1, entry 1).[11] Several aryl and alkyl substituted alkenes behaved in a similar fashion, affording the adducts in yields ranging from 50 to 75%. No trace of the regioisomer could be detected and total consumption of the starting alkene was observed in each case. Decreasing the ratio precursor/alkene or the addition time resulted in a lower yield in desired product (entries 2 and 3). Alkenes substituted by mesomeric electron-donating or electron-withdrawing substituents showed a different behavior, as revealed by experiments conducted in the presence of *n*-butyl vinyl ether or phenyl acrylate, respectively (entries 7 and 8). Thus, no addition product could be isolated with *n*-butyl vinyl ether, while phenyl acrylate afforded a 48% yield of the desired adduct[12] (Scheme 3) (Table 1).

Table 1
Yields and ^{31}P NMR chemical shifts of adducts **10**

Entry	R^1	R^2	Yield (%)[13]	δ ^{31}P (ppm)[c]
1	*n*-C_6H_{13}	H	60	62.3
2	*n*-C_6H_{13}	H	50[a]	62.3
3	*n*-C_6H_{13}	H	20[b]	62.3
4	–CH_2–CH_2–CH_2–CH_2–CH_2–		60	59.1
5	*n*-C_8H_{17}	CH_3	70	59.7
6	C_6H_5	CH_3	75	59.1
7	$COOC_6H_5$	H	48	61.7
8	O-*n*-C_4H_9	H	0	–

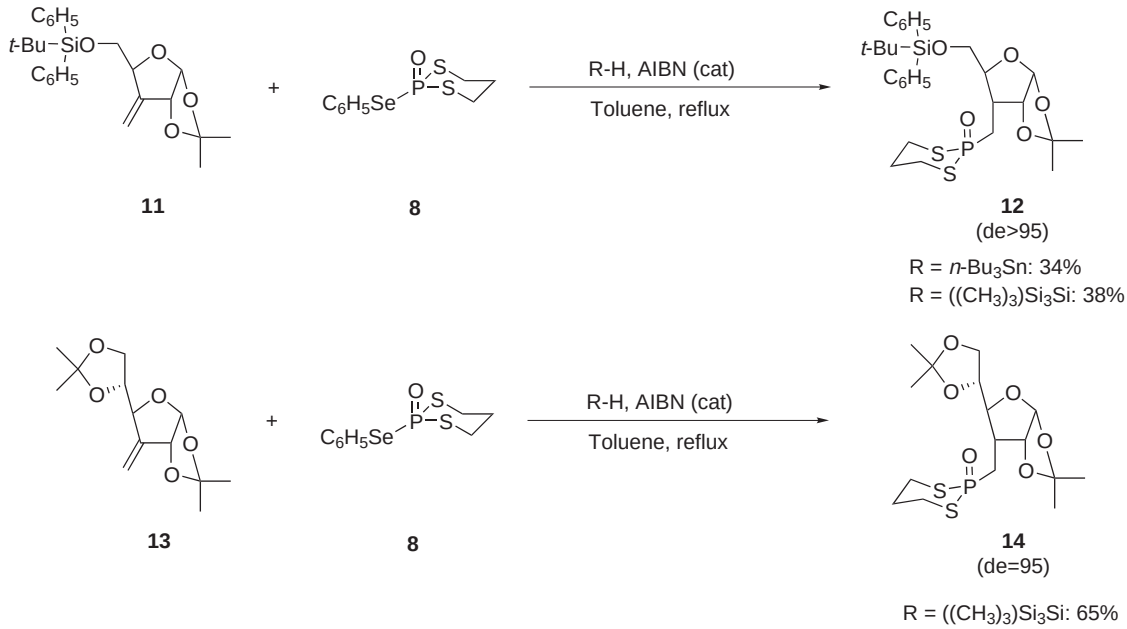
[a] Addition of the *n*-Bu_3SnH/AIBN solution was carried out over a period of 0.4 hours.
[b] A 10/1 ratio of 1-octene:radical precursor **8** was used.
[c] Reference: H_3PO_4.



9 8 10

Scheme 3.

We next turned our attention to the addition of such radicals onto exocyclic 3-methylene furanoses. The resultant furanosides bearing a phosphonodithiomethyl moiety in position 3 are useful in the context of modified oligonucleotides.[14,15] Scheme 4 depicts the first results obtained from such radical addition.



Scheme 4.

The expected adducts are isolated in fair to good yields. The use of tris(trimethylsilyl)silane in place of the more toxic tri-*n*-butyltin hydride bears the additional advantage of a much simpler purification procedure.[16] The lower yields in adduct **12** presumably result from a competitive desilylation reaction. Very high diastereoselectivities were observed in favor of the 2,3 *cis* stereoisomer. This can be attributed to the well-known shielding effect of the 1,2 isopropylidene group on the α-face, thus inducing stereoselective hydrogen quenching from the less congested face of the furanosyl radical-adduct **15a**.[17] The fact that the phosphonodithioyl group itself does not play any role in this stereoselectivity was demonstrated by the addition of decyl radical (generated from iododecane, *n*-Bu_3SnH and AIBN) onto methylene furanoside **13** to give radical **15b**: here again a diastereoselectivity of 95% was observed in the products. Interestingly, the literature reports the generation of a secondary radical **16** (from the corresponding haloderivative) on the same position 3 and its trapping with acrylonitile: a 1:4 mixture of α/β stereoisomers is produced[18] (Fig. 3).

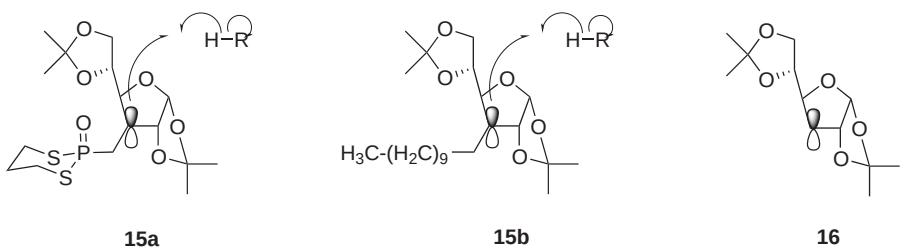


Figure 3.

In summary, we have prepared a new reagent **8** and shown that it is a substitute for the unstable dithiophosphite. This reagent can be used to generate the hitherto undescribed phosphonodithioyl radicals **3**, which add onto alkenes via a chain process, thereby establishing a new synthesis of phosphonodithioates. In particular, exocyclic 3-methylene furanoses furnished the expected adducts with a very high diastereoselectivity in favor of the α isomer. Application of this methodology to the preparation of modified oligonucleotides is currently under investigation and will be reported in due course.

References

1. (a) Blackburn, G. M.; Brown, D.; Martin, S. J.; Parrat, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 181–186. (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913–917. (c) Blackburn, G. M.; Brown, D.; Martin, S. J. *J. Chem. Res.* **1985**, 92–93. (d) McKenna, C. E.; Shen, P. *J. Org. Chem.* **1981**, *46*, 4573–4576. (e) Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991**, *113*, 315–317. (f) Matulic-Adamic, J.; Usman, N. *Tetrahedron Lett.* **1994**, *35*, 3227–3230. (g) Martin, S. F.; Wong, Y.-L.; Wagmann, A. S. *J. Org. Chem.* **1994**, *59*, 4821–4831. (g) Zhang, J.; Matteucci, M. D. *Tetrahedron Lett.* **1995** *36*, 8375–8378. (h) Saadi, M.; Lebeau, L.; Mioskowski, C. *Synlett* **1995**, 643–644. (i) Ross, F. C.; Botting, N. P.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2643–2646. (j) Endova, M.; Masojidova, M.; Budesinsky, M.; Rosenberg, I. *Tetrahedron* **1998**, *54*, 11187–11208. (k) Vayron, P.; Renard, P.-Y.; Valleix, A.; Mioskowski, C. *Chem. Eur. J.* **2000**, *6*, 1050–1063.
2. See for instance: (a) Kazama, H.; Matsuoka, S. *JP Patent* **1992**, 04,330,083 [92,330,383]. (b) Kazama, H.; Matsuoka, S. *JP Patent* **1993**, 05 39,296 [93 39,296]. (c) Nakanishi, H.; Kuribayashi, T. *JP Patent* **1993**, 05 09,490 [93 09,490]. (d) Tang, C. C.; Ma, F. P.; Zhang, K.; He, Z. J.; Jin, Y. C. *Heteroat. Chem.* **1995**, *6*, 413–417. (e) Rodriguez, O. P.; Thompson, C. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *117*, 101–110.
3. Jingzen, Y.; Chambers, H. W. *Pestic. Biochem. Physiol.* **1996**, *54*, 210–219.
4. Räsänen, J. P.; Pohjala, E.; Pakkanen, T. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2485–2490.
5. (a) Davies, A. G.; Griller, D.; Roberts, B. P. *J. Am. Chem. Soc.* **1972**, *94*, 1782–1783. (b) Finke, M.; Kleiner, H. *J. Liebigs Ann. Chem.* **1974**, 741–750. (c) Dingwall, J. G.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2081–2089. (d) Brel, A. K.; Tyurenkov, I. N.; Strel'tsova, G. V.; Matyukhova, N. P.; Nazarenko, V. N.; Agarkova, N. S. *Khim.-Farm. Zh.* **1988**, *22*, 167–170. (e) Piettre, S. R. *Tetrahedron Lett.* **1996**, *37*, 2233–2236. (f) Herpin, T. F.; Motherwell, W. B.; Roberts, B. P.; Roland, S.; Weibel, J.-M. *Tetrahedron* **1997**, *53*, 15085–15100.
6. (a) Zalesova, N. N.; Butorina, L. S.; Nifant'ev, E. E.; Masteryukova, T. A. *Zh. Obshch. Kim.* **1990**, *60*, 1735–1739. (b) Kim, S.; Mimikakis, J. L.; Roundhill, D. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *68*, 119–128. (c) Martin, S. F.; Wagman, A. S. *J. Org. Chem.* **1996**, *61*, 8016–8023.
7. (a) Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1956**, 3269–3271. (b) Nifant'ev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Blagoveshchenskii, V. S.; Yakovleva, O. P.; Esenina, E. V. *Zh. Obshch. Khim.* **1974**, *44*, 1694–1697. (c) Al'fonsov, V. A.; Trusenev, A. G.; Batyeva, E. S.; Pudovik, A. N.; Pudovik, M. A. *Izv. Akad. Nauk. SSSR* **1991**, 2103–2111.
8. Nifant'ev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Chernyak, S. M. *Dokl. Akad. Nauk. SSSR* **1972**, *203*, 593–595.
9. Boudjebel, H.; Goncalves, H.; Mathis, F. *Bull. Soc. Chim. Fr.* **1974**, 1671–1674. Reaction with other thiols (ethanethiol; benzylthiol; ethanedithiol) resulted in untractable mixtures in the first or second step.
10. A solution of 2-benzyloxy-[1,2,3]-dithiaphosphinane (**7**) (1.86 g, 7.6 mmol) in anhydrous toluene (5 ml) was added dropwise to an ice-cold solution of phenylselanyl chloride (1.51 g, 7.88 mmol) in anhydrous toluene under argon. The resultant mixture was stirred for 2 hours at 0°C, warmed up to room temperature and evaporated under reduced pressure. Filtration and washing of the solid with heptane (3×15 ml) afforded the colorless, crystalline product. The filtrate was evaporated and the crude remaining sample was chromatographed and eluted with a 98:2 mixture of heptane/dichloromethane. Total yield is 1.65 g (70%), mp 112°C. ^{1}H NMR ($CDCl_3$/ref. TMS) δ: 1.95–2.24 (m, 2H), 3.04–3.26 (m, 4H), 7.30–7.42 (m, 3H), 7.67–7.73 (m, 2H). ^{13}C NMR ($CDCl_3$/ref. $CDCl_3$) δ: 25.0 (d, $J_{C-P}=4.3$ Hz), 33.8 (d, $J_{C-P}=4.1$ Hz), 126.2 (d, $J_{C-P}=7.3$ Hz), 130.1, 130.1, 136.7 (d, $J_{C-P}=4.0$ Hz). ^{31}P NMR ($CDCl_3$/ref. H_3PO_4): 51.9. HRMS $C_9H_{11}OPS_2Se$ calc. 309.9154. Found 309.9147. Anal. C, H, S.

11. Typical procedure: Under inert atmosphere, a degassed solution of tri-*n*-butyltin hydride (324 mg, 1.11 mmol) and azobis*iso*butyronitrile (23 mg, 0.14 mmol) in benzene (1.2 ml) is added to a refluxing, degassed solution of 2-phenylselanyl-[1,2,3]-dithiaphosphinane-2-oxide (**8**) (259 mg, 0.84 mmol) and octene (32 mg, 0.28 mmol) in benzene (2 ml) over a period of time of 10 hours. After the addition is complete, the solution is refluxed for another 4 hours, then cooled down to room temperature and evaporated under reduced pressure. The crude residue is chromatographed on silica and eluted with a mixture of heptane/ethyl acetate to afford 43 mg (60%) of the desired adduct as a colorless oil. ^{1}H NMR ($CDCl_3$/ref. TMS) δ: 0.83 (t, $^{3}J = 6.2$ Hz, 3H), 1.20–1.38 (m, 12H), 1.65–1.73 (m, 2H), 2.00–2.27 (m, 4H), 2.89–3.07 (m, 2H), 3.26–3.40 (m, 2H). ^{13}C NMR ($CDCl_3$/ref. $CDCl_3$) δ: 13.99, 22.03, 22.14, 22.51, 25.18 (d, $J_{C-P} = 3.0$ Hz), 27.88 (d, $J_{C-P} = 3.0$ Hz), 28.88, 30.32 (d, $J_{C-P} = 16.7$ Hz), 31.13, 36.85 (d, $J_{C-P} = 72.8$ Hz). MS (m/z): 266 (18), 224 (32), 191 (98), 154 (100), 106 (56), 74 (88). Anal. C, H, S.
12. In the case of *n*-butyl vinyl ether, $C_6H_5SeSn(C_4H_9)_3$ was the only product that could be isolated.
13. All yields refer to pure products, isolated by flash chromatography (eluents: 10/1 to 1/1 mixtures of heptane/AcOEt). Analytical samples gave satisfactory combustion or high resolution mass spectrometry data.
14. (a) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543–584. (b) Milligan, J. F.; Matteuci, M. D.; Martin, J. C. *J. Med. Chem.* **1993**, *36*, 1923–1937. (c) De Mesmaeker, A.; Häner, R.; Martin, P.; Moser, H. E. *Acc. Chem. Res.* **1995**, *28*, 366–374. (d) Crooke, S. T.; Leleu, B. *Antisense Research and Applications;* CRC Press: Boca Raton, 1993. (d) In *Antisense Therapeutics*; Agrawal, S., Ed.; Humana Press: Totawa, 1996.
15. The only example of a 3-deoxofuranose substituted in position 3 by a methyl bearing a phosphorus-based substituent has been reported in: Albrecht, H. P.; Jones, G. H.; Moffatt, J. G. *Tetrahedron* **1984**, *40*, 79–85.
16. Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678–683.
17. This feature has already been exploited in the context of diastereoselective transformations: (a) Bjoersne, M.; Classon, B.; Kers, I.; Samuelsson, B.; Kvarnstroem, I. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 43–46. (b) Schmeichel, M.; Redlich, H. *Synthesis* **1996**, 1002–1006. (c) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179.
18. Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69–70. For a review on diastereoselectivity of free radical reactions see: Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–980.