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Synthesis of Thiazolines Linked to a Difluoromethylphosphonate Diester via Dithioester Chemistry

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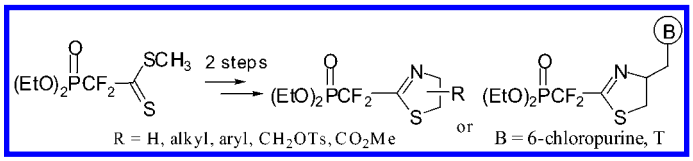
ABSTRACT



A two-step, high-yielding synthesis of Δ^2-thiazolines containing a difluoromethylphosphonate diester moiety has been devised using a building block approach. Racemic or chiral β-amino alcohols and diols were coupled with methyl difluoro(diethoxyphosphono)dithioacetate to give predominantly the corresponding β-hydroxythioamides, which were then cyclized to provide a series of novel substituted Δ^2-thiazolines.

Since the pioneering work of Blackburn,[1] a very wide range of structurally novel and biologically interesting difluoromethylenephosphonic acids and their phosphonate derivatives have been synthesized.[2] It has been demonstrated that the isoelectronic and isosteric CF_2/O transposition in phosphate analogues confers metabolic stability and imparts important features for receptor binding affinity or hydrogen bonding interactions. Many α,α-difluoroorganophosphorus (V) derivatives have been studied as potential enzyme inhibitors and as useful probes for the elucidation of biochemical processes.[3] Among the more potent nucleotidyl inhibitors are the Halazy's acyclic nucleoside phosphonate **I**,[4] together with its conformationally constrained analogues developed recently by Shimeno and Yokomatsu's groups,[5] and the ribonucleoside 5′-difluoromethyl phosphonates **II**[6] (Figure 1).

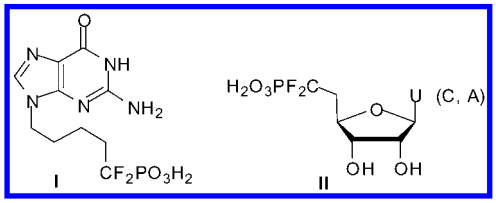


Figure 1. Structures of two representative nucleoside analogues as PNP (**I**) and RNA polymerase (**II**) inhibitors.

Peptides containing difluorophosphonomethyl amino acids[7] as well as difluoromethylene analogues of naturally occurring

(1) (a) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930. (b) Blackburn, G. M.; Eckstein, F.; Kent, D. E.; Perrée, T. D. *Nucleosides Nucleotides* **1985**, *4*, 165.

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(3) For recent leading references, see: (a) Halazy, S.; Ehrhard, A.; Eggenspiller, A.; Berges-Gross, V.; Danzin, C. *Tetrahedron* **1996**, *52*, 177. (b) Kawamoto, A. M.; Campbell, M. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1249. (c) Caplan, N. A.; Pogson, C. I.; Hayes, D. J.; Blackburn, G. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 421. (d) Yokomatsu, T.; Hayakawa, Y.; Kihara, T.; Koyanagi, S.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem.* **2000**, *8*, 2571.

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(5) Yokomatsu, T.; Hayakawa, Y.; Suemune, K.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2833.

(6) Matulic-Adamic, J.; Maerbili, P.; Usman, N. *J. Org. Chem.* **1995**, *60*, 2563.

(7) (a) Bigge, C. F.; Drummond, J. T.; Jonhson, G. *Tetrahedron Lett.* **1989**, *30*, 7013. (b) Wrobel, J.; Dietrich, A. *Tetrahedron Lett.* **1993**, *34*, 3543. (c) Berkowitz, D. B.; Shen, Q.; Maeng, J.-H. *Tetrahedron Lett.* **1994**, *35*, 6445. (d) Chetyrkina, S.; Estieu-Gionnet, K.; Laïn, G.; Bayle, M.; Déléris, G. *Tetrahedron Lett.* **2000**, *41*, 1923.

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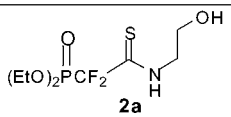
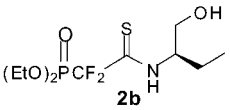
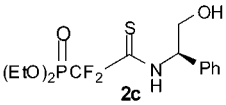
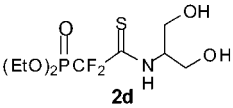
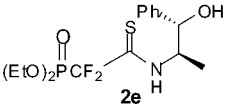
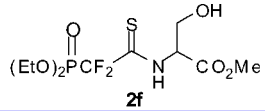
monosaccharide phosphates[8] have also been the subject of great interest as bioactive molecules.

The most common approaches to this class of phosphonates usually involve PCF_2-based nucleophilic synthons or radicals,[9] although the gem-difluorination and phosphonyl radical addition techniques may also offer alternative routes.[10] A number of difluorophosphonylated systems have also been prepared following the building block approach.[11] Representative examples using simple carbocyclic acids include phosphoenol pyruvate and sparfosic acid analogues; the latter, also referred to as PALA, is a potent inhibitor of ATCase.[12]

In connection with our studies on the chemistry of bifunctional organic compounds containing both phosphorus and dithioester moieties,[13] we anticipated that the methyl difluoro(diethoxyphosphono)dithioacetate **1** should provide a new synthesis of thiazolines appended with a PCF_2-function. Many biologically active natural products, including derived peptides, incorporate thiazoline (and/or thiazole) motifs in their structures,[14] and consequently, the construction of these rings has aroused considerable interest, as shown by the number of methods available.[15,16]

We report herein utilization of the methyl ester of difluoro(diethoxyphosphono)dithioacetic acid **1** as an efficient N-thioacylating reagent in order to open facile and flexible routes to thiazoline-based difluoromethylphosphonate diesters. To test this, dithioester **1** was conveniently prepared on a large scale (up to 15 g), according to a slightly modified procedure described by Blackburn et al.[17] and coupled with some achiral or enantiopure β-amino alcohols. A summary of these reactions is presented in Table 1.

Table 1. Synthesis of Difluoromethylphosphonate Diesters Linked to an *N*-β-Hydroxythioamido Group from Dithioester **1**

	β-Amino alcohol	Time (min)	Product	Yield $[\alpha]_D^{20}$
1	2-aminoethanol	10	 **2a**	68
2	(R)-(-)-2-amino butan-1-ol	10	 **2b**	64 +3,9
3	(R)-(+)-phenyl glycinol	10	 **2c**	85 -73,6
4	2-aminopropan-1,3-diol	15	 **2d**	76
5	(1S,2R)-(+)-norephedrin hydrochlorid	30[a]	 **2e**	67 +4.8
6	DL-serine methyl ester hydrochlorid	10 h[a]	 **2f**	64

[a] Reactions conducted with 1 equivalent of triethylamine.

The reactions were carried out routinely at room temperature by adding dithioester **1** dropwise to a stirred solution of commercially available β-amino alcohols in dried dichloromethane (THF is also a suitable solvent). The exceptional reactivity[18] of free amines was clearly evidenced by the color change from red to orange−yellow shortly after the addition was completed (entries 1−4, Table 1). Use of triethylamine as a dehydrohalogenating agent allowed β-hydroxyamine hydrochlorides to be similarly coupled, albeit in longer reaction times (entries 5 and 6). The reaction rates

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(9) (a) Otaka, A.; Miyoshi, K.; Burke, T. R., Jr.; Roller, P. P.; Kubota, H.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **1995**, *36*, 927. (b) Berkowitz, D. B.; Sloss, D. G. *J. Org. Chem.* **1995**, *60*, 7047. (c) Lequeux, T. P.; Percy, J. M. *Synlett* **1995**, 361. (d) Berkowitz, D. B.; Eggen, M.; Shen, Q. R.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666. (e) Piettre, S. R.; Cabanas, L. *Tetrahedron Lett.* **1996**, *37*, 5881. (f) Blades, K.; Lapôtre, D.; Percy, J. M. *Tetrahedron Lett.* **1997**, *38*, 5895.

(10) (a) Differding, E.; Duthaler, R. O.; Krieger, A.; Rüegg, G. M.; Schmit, C. *Synlett* **1991**, 395. (b) Burke, T. R.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. P. *J. Org. Chem.* **1993**, *58*, 1336. (c) Smyth, M. S.; Burke, T. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 551. (d) Herpin, T. F.; Motherwell, W. B.; Roberts, B. P.; Roland, S.; Weibel, J. M. *Tetrahedron* **1997**, *53*, 15082. (e) Lequeux, T.; Lebouc, F.; Lopin, C.; Yang, H.; Gouhier, G.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 185.

(11) (a) Phillion, D. P.; Cleary, D. G. *J. Org. Chem.* **1992**, *57*, 2763. (b) Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. A. *Tetrahedron* **1996**, *52*, 165. (c) Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Zappala, C. *Synthesis* **1998**, 1511. (d) Boivin, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 6877. (e) Blades, K.; Butt, A. H.; Cockerill, G. S.; Easterfield, H. J.; Lequeux, T. P.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3609. (f) Butt, A. H.; Percy, J. M.; Spencer, N. S. *Chem. Commun.* **2000**, 1691. (g) Yokomatsu, T.; Katayama, S.; Shibuya, S. *Chem. Commun.* **2001**, 1878.

(12) (a) Coutrot, Ph.; Grison, C.; Charbonnier-Gérardin, C. *Tetrahedron* **1992**, *48*, 9841. (b) Ben-Bari, M.; Dewynter, G.; Aymard, C.; Jei, T.; Montero, J.-L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *105*, 129. (c) Morris, A. D.; Cordi, A. A. *Synth. Comm.* **1997**, *27*, 1259.

(13) (a) Masson, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95*−*96*, 127. (b) Leflemme, N.; Marchand, P.; Gulea, M.; Masson, S. *Synthesis* **2000**, 1143.

(14) (a) McGowan, D. A.; Jordis, U.; Minster, D. K.; Hecht, S. M. *J. Am. Chem. Soc.* **1977**, *99*, 8078. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbet, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566. (d) Bayer, A.; Freund, S.; Nicholson, G.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1336. (e) Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733. (f) Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556. (g) Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron* **1996**, *52*, 14543. (h) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1. (i) White, J. D.; Kim; T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1997**, *119*, 103. (j) Kuriyama, N.; Akaji, K.; Kiso, Y. *Tetrahedron* **1997**, *32*, 8323. (k) Akaji, K.; Kiso, Y. *Tetrahedron* **1999**, *55*, 10685. (l) Ramasamy, K. S.; Bandaru, R.; Averett, D. *J. Org. Chem.* **2000**, *65*, 5849. (m) Ritter, T. K.; Wong, C.-H. *Tetrahedron Lett.* **2001**, *42*, 615.

(15) (a) North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267. (b) Fukuyama. T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449. (c) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron*, **1995**, *51*, 7321. (d) Charrette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908. (e) Ino, A.; Murabayashi, A. *Tetrahedron* **1999**, *55*, 10271. (f) Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289. (g) Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223. (h) Fernandez, X.; Fellous, R.; Dunach, E. *Tetrahedron Lett.* **2000**, *41*, 3381.

(16) (a) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397. (b) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Synlett* **1995**, 171. (c) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (d) Muir, J. C.; Pattenden, G.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 2861.

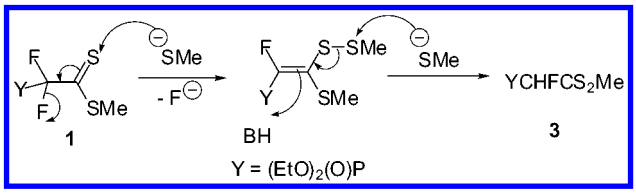
(17) Blackburn, G. M.; Brown, D.; Martin, S. J. *J. Chem. Res.* **1985**, 92.

(18) Metzner, P. *Synthesis* **1992**, 1185.

appeared to correlate, as shown in the last entry, with the nucleophilicity of the amino group. After careful flash chromatography on silica, the desired N-β-hydroxylated difluorophosphonoethanethioamides **2a**−**f** were isolated in satisfactory yields.

In most cases, however, the yields of **2** were significantly depressed by competing formation of the monofluoro dithioester **3** (5−12% yield). A plausible mechanism to account for this side product is shown in Scheme 1 and

Scheme 1. Proposed Mechanism for the Formation of the Monofluorophosphono Dithioacetate **3**

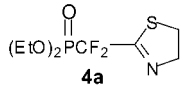
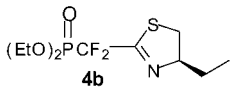
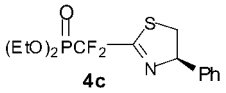
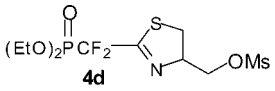
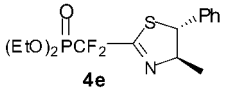
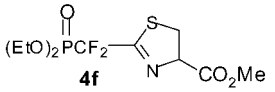


involves presumably initial thiophilic addition of methanethiol (or its anion) liberated during the reaction onto the starting difluoro dithioester **1**[19] followed by elimination of hydrogen fluoride. Subsequent displacement of the methylthio group upon an intermediately formed ketenedithioacetal disulfide with methanethiol would afford the unwanted **3** and dimethyl disulfide. Further investigations to confirm this hypothesis are currently underway.[20]

At this stage, the reagents and reaction conditions necessary to effectively mediate the formal cyclodehydration process were examined. Over the years, a number of β-hydroxythioamide-based syntheses of Δ^2-thiazolines have been reported.[16] Initial application of the Mitsunobu conditions[21] (PPh_3, DEAD, THF) to thioamido alcohol **2a** as a model substrate showed that the byproducts of this reaction have R_f values similar to those of thiazoline **4a**, thus preventing an easy final purification.

Therefore, we turned our attention to inducing the intramolecular cyclodehydration with alternative protocols such as thionyl chloride.[22] As evident from Table 2, method A ($SOCl_2$/pyridine) provides a mild access within 30−60 min to thiazolines **4** and the yields were good to excellent. Remarkably, primary thioamido alcohols **2** (entries 1−3 and 6) cyclize as well as a secondary one (entry 5) and no 1,2-dehydration of the α-thioamido β-hydroxy ester **2f** is observed. In addition, the norephedrin adduct **2e** was easily cyclized without detectable epimerization or racemization. However, in the case of the 2-thioamido-1,3-diol **2d**, this method failed to produce the expected thiazoline and instead

Table 2. Dehydrocyclization of N-β-Hydroxylated Thioamides to Thiazolines at 20 °C in CH_2Cl_2

	Substrate (method)[a]	Time	Product	Yield $[\alpha]_D^{20}$
1	**2a** (A)	30 min	 **4a**	82
2	**2b** (A)	30 min	 **4b**	85 +54.7
3	**2c** (A)	30 min	 **4c**	80 -15.4
4	**2d** (B)	48h	 **4d**	79
5	**2e** (A)	1h	 **4e**	82 +60.2
6	**2f** (A)	1h	 **4f**	77

[a] (A) 1.1 equiv of $SOCl_2$ and pyridine; (B) 2 equiv of MsCl and Et_3N.

led to a cyclic sulfite derivative.[23] Nevertheless, the desired cyclization of **2d** was achieved with MsCl/Et_3N (method B, entry 4), and the expected thiazoline was recovered as its mesylate **4d** after the reaction.

Having fully characterized all compounds listed in Tables 1 and 2 and noticed that thioamido alcohols **2** proved to be somewhat difficult to purify, we further carried out the two-step sequence in the same flask. The N-thioacylation followed by cyclodehydration in a "one-pot" procedure was found to provide a rapid access and an efficient route to chiral thiazolines **4b**,**c**,**e** with overall yields ranging from 75 to 80% after standard flash chromatography performed on silica gel. Interestingly, the resulting thiazolines preserved the high enantiomeric purity of the starting β-amino alcohols substrates, as demonstrated by HPLC analysis (97.4% ee).

In view of the current interest focused on the syntheses of novel types of nucleoside analogues, we next sought to study the possibility of introducing nucleobase derivatives onto either our primary mesylate-containing thiazoline **4d** or, even better, its thioamido-1,3-diol precursor **2d**. Recent literature reports[24] dealing with the synthesis of pseudoazanucleosides and thionucleosides suggest that primary alcohols are or would be superior substrates for our purpose. On the other hand, Mitsunobu-type procedures have been reported to cyclize 2-thioamido alcohols[16,25] and to link nucleic acid

(19) (a) Viola, H.; Hartenhauer, H.; Mayer, R. *Z. Chem.* **1988**, 269. (b) Bulpin, A.; Masson, S. *J. Org. Chem.* **1992**, *57*, 4507.

(20) For example, the following ketenedithioacetal disulfide $(EtO)_2P(O)CF{=}C(SMe)S{-}S$-*t*-Bu was prepared in high yield and fully characterized from a CH_2Cl_2 solution containing difluorodithioester **1** and *t*-BuSH in the presence of triethylamine. Its further conversion to the monofluorodithioester **3** was easily achieved by using lithium ethylthiolate in THF.

(21) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

(22) (a) Crawhall, J. C.; Elliott, D. F. *J. Chem. Soc.* **1951**, 2071, 2075. (b) Tomalia, D. A.; Paige, J. N. *J. Org. Chem.* **1973**, *38*, 3949.

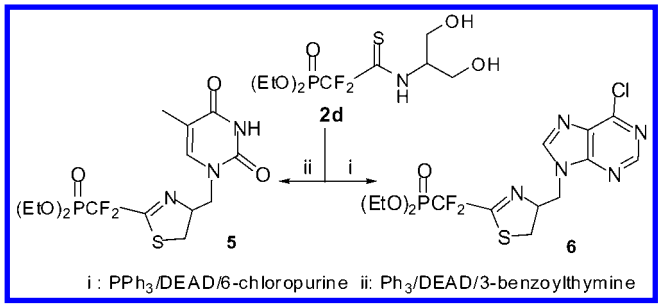
(23) Review: Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7052.

(24) (a) Deng, L.; Schärer, O. D.; Verdine, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 7865. Reviews: (b) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541. (c) Yokoyama, M. *Synthesis* **2000**, 1637.

bases to skeletons bearing a free hydroxyl group.[5,26] Therefore, this approach was applied to the thioamido-1,3-diol **2d**.

As outlined in Scheme 2, Mitsunobu cyclization and condensation with 3-benzoylthymine[27] and 6-chloropurine

Scheme 2. Synthesis of 2-(Difluorophosphonomethyl)Thiazoline-Based Nucleotide Analogues under Mitsunobu Conditions



in a one-pot process afforded compounds **5** and **6**, respectively. The likely intermediates for these transformations are related to oxyphosphonium species. Experimentally, the two thiazolines appended with a methylene base unit were produced in yields ranging from 58 to 66% by simply treating a suspension of the diol **2d**, the nucleobase derivative, and Ph_3P in THF with DEAD (dropwise addition in THF at 0 °C) for 4 days. Deprotection of the thymine adduct occurred during the purification.

Here we have reported a new building block approach for the synthesis of racemic or enantiomerically pure 2-(difluorophosphonomethyl)-Δ^2-thiazolines using β-amino alcohols. This method has the advantages of simplicity and brevity and provides the possibility of linking preformed nucleic base derivatives to the thiazoline backbone if a β-amino-1,3-diol is employed. The principles of the approach delineated here should find further applications in modified nucleotide synthesis, and other ring systems should also be accessible via dithioester chemistry in a near future.

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Supporting Information Available: Detailed description of experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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