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Tetrahedron Letters 44 (2003) 8837–8840

TETRAHEDRON LETTERS

First synthesis of *S,S*-dialkyl difluorophosphonodithioates and difluorophosphonotrithioates

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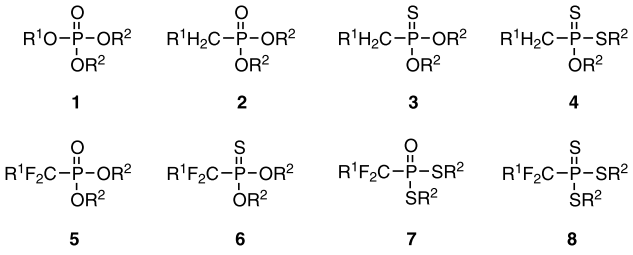
Received 15 July 2003; revised 16 September 2003; accepted 23 September 2003

Abstract—Several dialkyl difluoromethylphosphonodithioates and difluoromethylphosphonotrithioates have been prepared from difluoromethylphosphonyl dichloride and two equivalents of alkanethiols under basic conditions. Treatment of these species with LDA at low temperatures mainly resulted in decomposition, and to the low-yield isolation of difluorophosphinates or phosphine oxides, thus reflecting the lability of the P–S bond. The desired difluorophosphonodithioates and difluorophosphonotrithioates can be efficiently prepared by reversing the sequence of reactions.

The ubiquitous presence of the phosphate group **1** in biomolecules is the main reason behind the considerable amount of effort devoted to the search for the ideal mimic of this function (Fig. 1). Among the various molecular units that have been introduced in potentially bioactive molecules, the phosphonates **2**, phosphonothioates **3** and phosphonodithioates **4** have been much used in pharmaceuticals and agrochemicals, with various results.[1] The introduction of two fluorine



1 **2** **3** **4**

5 **6** **7** **8**

a: R^1 = H, R^2 = CH_2CH_3
b: R^1 = H, R^2 = $CH_2C_6H_5$
c: R^1 = H, R^2 = $C(CH_3)_3$
d: R^1 = H, R^2, R^2 = -$CH_2CH_2CH_2$-
e: R^1 = Li, R^2 = CH_2CH_3
f: R^1 = $CH_2C_6H_5$, R^2 = CH_2CH_3
g: R^1 = *n*-C_5H_{11}, R^2 = CH_2CH_3
h: R^1 = $Cl(CH_2)_4$-, R^2 = CH_2CH_3
i: R^1 = Br, R^2 = CH_2CH_3

Figure 1.

atoms α to the phosphorus by Blackburn in the early eighties gave a new impetus to the chemistry of phosphonates and resulted in an upsurge of interest for enzyme inhibitors featuring the difluorophosphonate unit **5**.[2] Thus, many synthetic methodologies have been worked out that allow either the construction of this functional group or its introduction into more complex structures.[3] We recently introduced a new variant, the difluorophosphonothioates **6**.[4] Beside being a new isostere to phosphate, reagents derived from molecules featuring a phosphorus–sulfur double bond often bear a clear synthetic advantage over their oxygenated counterparts. Thus, for instance, while the reported sensitive lithium reagent **5e** is stable at or below −78°C and readily decomposes at higher temperatures, its sulfur analogue **6e** is stable at temperatures of −40°C.[3d,4,5] In the course of a program dedicated to the search for new mimics of the phosphate group, we became interested in the, as yet, unreported difluorophosphonodithioates **7** and difluorophosphonotrithioates **8**, incorporating two and three sulfur atoms, respectively, and in the corresponding lithioderivatives **7e** and **8e**.

Dialkyl difluoromethylphosphonates and dialkyl difluoromethylphosphonothioates (e.g. **5a** and **6a**, respectively) are routinely prepared by interacting phosphites **9** or thiophosphites **10** with chlorodifluoromethane under basic conditions (Fig. 2).[3d,4a] A similar approach relying on the use of dithiophosphites **11** or trithiophosphites **12** was thwarted by the reported low stabilities of these species. Thus, the much less stable P–S bond (45–50 kCal/mol versus 90–100 kCal/

Keywords: difluorophosphonodithioate; difluorophosphonotrithioate; Lawesson's reagent.
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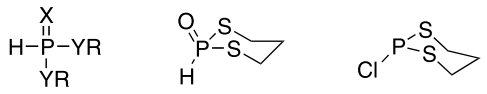
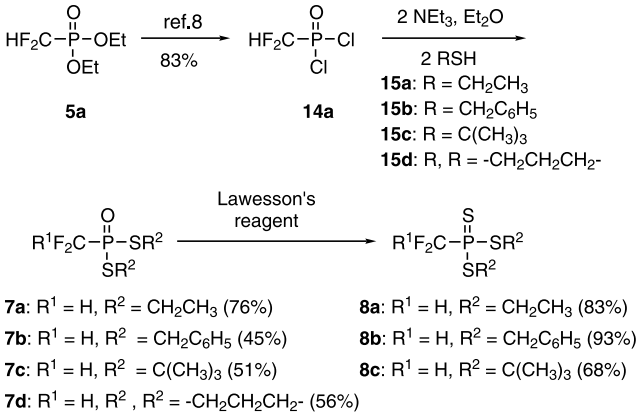
doi:10.1016/j.tetlet.2003.09.195



9: X=Y=O
10: X=S, Y=O
11: X=O, Y=S
12: X=Y=S

11a **13**

Figure 2.



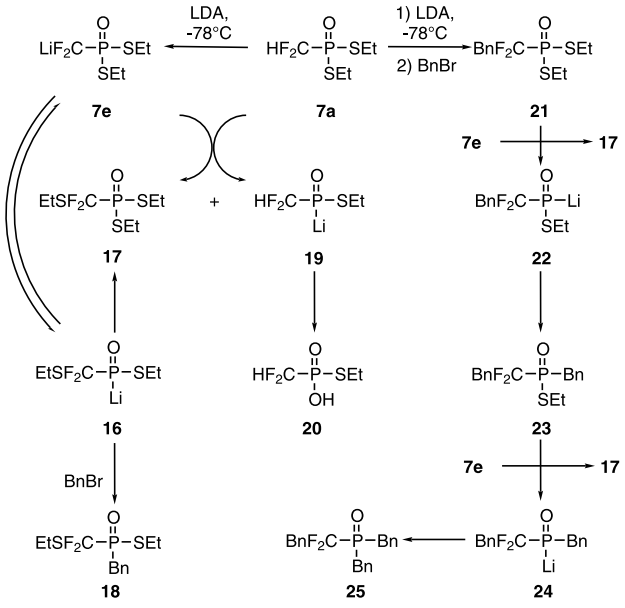
5a **14a**

15a: R = CH_2CH_3
15b: R = $CH_2C_6H_5$
15c: R = $C(CH_3)_3$
15d: R, R = $-CH_2CH_2CH_2-$

7a: R^1 = H, R^2 = CH_2CH_3 (76%)
7b: R^1 = H, R^2 = $CH_2C_6H_5$ (45%)
7c: R^1 = H, R^2 = $C(CH_3)_3$ (51%)
7d: R^1 = H, R^2 , R^2 = $-CH_2CH_2CH_2-$ (56%)

8a: R^1 = H, R^2 = CH_2CH_3 (83%)
8b: R^1 = H, R^2 = $CH_2C_6H_5$ (93%)
8c: R^1 = H, R^2 = $C(CH_3)_3$ (68%)

Scheme 1.



Scheme 2.

mol for the P–O bond) results in the rapid hydrolysis of dithiophosphites **11**, rendering their preparation difficult.[6] Attempts to synthesize the reportedly more stable 1,2,3-dithiaphosphinane-2-oxide **11a** were conducted by hydrolysing the chloride **13** (1 equiv. H_2O, 1 equiv. triethylamine) or interacting it with an equimolar amount of *tert*-butanol and triethylamine, but were unsuccessful. In addition, both dithiophosphites **11** and trithiophosphites **12** have been reported to readily disproportionate, dimerize or oligomerize.[7]

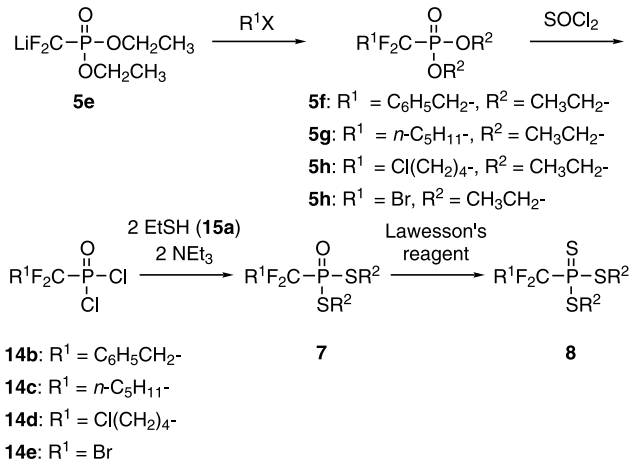
A second approach based on heteroatomic manipulation on phosphorus proved to be more successful. Transformation of diethyl difluoromethylphosphonate (**5a**) into the corresponding phosphonyl dichloride **14a** can be achieved efficiently in excess refluxing thionyl chloride (Scheme 1).[8] Treatment of **14a** with two equivalents of thiols **15a–c** or one equivalent of propan-1,3-dithiol **15d** under basic conditions delivered the desired difluorophosphonothioates **7a–d** in fair to good isolated yields. Exposure of difluoromethylphosphonodithioates **7a–c** to Lawesson's reagent allowed the clean conversion of the P=O bond into a P=S bond and delivered the corresponding difluoromethylphosphonotrithioates **8a–c** in good to excellent yields.[9] Interestingly, the interaction of diethyl difluoromethylphosphonothioate (**6a**) with an excess of thionyl chloride under similar conditions resulted in the formal replacement of the sulfur atom with an oxygen and led exclusively to the isolation of phosphonyl dichloride **14a**.[10]

Clean alkylation of **5a** and **6a** have been reported to occur at −78°C and −40°C, respectively, upon sequential treatment with LDA and various alkyl halides.[3d,4a] When *S*,*S*-diethyl difluoromethylphosphonodithioate (**7a**) was reacted with LDA and benzyl bromide, two compounds, identified as **17** and **18**, were formed in variable amounts (Scheme 2). Modification of the reaction conditions did not lead to any improvement in yield.[11] Purification by chromatography allowed the isolation of the two compounds in low yields (**17**: 3–15%; **18**: 4–5%).[12] Evaporation of the aqueous phase resulting from the work-up furnished *S*-ethyl difluoromethylphosphonothioic acid (**20**).

These experiments clearly show that the intermediate lithium reagent **7e** is formed at −78°C, but seems to undergo a rapid transformation into **16**, followed by a fast reaction with unreacted **7a** (competitive with deprotonation by LDA) to produce **17** and **19**; the latter would generate **20** upon hydrolysis and air oxidation of the tautomeric P(III) intermediate during the work-up. Alternatively, **7a** and **7e** could also react together to give **17** and **19**. Neither the desired derivative **21**, nor any of the possible compounds resulting from a polyalkylation process (**23** or **25**) were detected. Additional experiments conducted at –100°C led to analogous results.

Difluoromethylphosphonodithioates **7b**, **7c** and **7d**, and difluoromethylphosphonotrithioate **8a** behaved similarly under analogous conditions. Thus, the low stabilities of lithium reagents **7e** and **8e**, as well as of other related dialkyl analogues, led us to consider a new approach.

Reversing the sequence of reactions, i.e. alkylating phosphonate **5a** first, then applying the above described protocol, successfully led to the isolation of the desired α,α-difluorophosphonodithioates **7** and α,α-difluorophosphonotrithioates **8** (Scheme 3). Thus, generation of diethyl difluorophosphonates **5f**, **5g** and **5h** from lithium salt **5e** and benzyl bromide, *n*-pentyl bromide or 1-bromo-4-chlorobutane, respectively, and



Scheme 3.

treatment of the resultant alkylated compounds first with thionyl chloride, then with two equivalents of ethanethiol in the presence of triethylamine led to the isolation of the desired difluorophosphonodithioates **7f–h** in fair to good yields (Table 1). Reacting these species with Lawesson's reagent efficiently achieved their conversion into the corresponding difluorophosphonotrithioates **8f–h**. Even diethyl bromodifluoromethylphosphonate (**5i**) ($R^1 = Br$, $R^2 = CH_3CH_2$) was converted into the dichloride and the difluorophosphonodithioate **7i**, albeit in low overall yield, presumably because of the sensitivity of both the intermediate bromodifluoromethylphosphonyl dichloride and the product itself (Entry 4).[13] Conversion to the phosphonotrithioate **8i** occurred smoothly to deliver the desired compound in very good yield. Both families of compounds are reasonably stable, and can be easily chromatographed on silica without undergoing noticeable decomposition.[14]

Conclusion

Difluorophosphonates can be transformed into difluorophosphonodithioates and difluorophosphonotrithioates by applying to the substrates a sequence of reactions involving (i) chlorination; and (ii) the interaction with two equivalents of alkanethiol under basic conditions, and, for the difluorophosphonotrithioates; (iii) treatment with Lawesson's reagent. The lithium salts of diethyl difluoromethylphosphonodithioate and difluorophosphonotrithioate appear to be unstable, even at −100°C, and undergo transformations into a variety of compounds.

Difluorophosphonodithioates and difluorophosphonotrithioates constitute new isosteres of the phosphate group and may find applications in the context of analogues of natural phosphates as inhibitors of biochemical processes.

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Table 1.

Entry	R^1	R^2		Yields (%)[a]		Yields (%)
1	$C_6H_5CH_2$–	CH_3CH_2–	**7f**	87	**8f**	99
2	*n*-C_5H_{11}–	CH_3CH_2–	**7g**	42	**8g**	92
3	$Cl(CH_2)_4$–	CH_3CH_2–	**7h**	52	**8h**	97
4	Br	CH_3CH_2–	**7i**	19[b]	**8i**	86

[a] Isolated yields from **5f–i** and **15a**.
[b] See Ref. 13.

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11. These included temperatures, number of equivalents of base and electrophile or addition of HMPA (see: Ref. 3kk).
12. Complete consumption of the starting phosphonodithioate was observed (^{1}H, ^{19}F and ^{31}P NMR spectrometries).
13. ^{19}F NMR spectroscopic data of **14e** and **7i** indicated 70% and 48% yields, respectively, for the two steps.
14. Representative procedure for compounds **7f** and **8f**: To a stirring mixture of diethyl 2-phenyl-1,1-difluoroethylphosphonate (**5f**) (1 g, 3.6 mmol) and freshly distilled pyridine (0.045 mL, 0.55 mmol) under argon was added thionyl chloride (2.7 mL, 36 mmol). The resultant solution was refluxed for 72 h, cooled down to room temperature, and the excess thionyl chloride was distilled off under reduced pressure (50–60°C/50 mbar; Kugelrohr) to give the desired phosphonyl chloride **14b**. ^{19}F NMR (188 MHz, $CDCl_3$) $\delta = 55.96$ (dt, 2F, $J = 20.3$ Hz, $J = 138.8$ Hz). This material was used in the next step without further purification. A solution of **14b** (0.93 g, 3.6 mmol) in dry ether (7.3 mL) was added dropwise to a cooled solution (0°C) of triethylamine (0.9 g, 1.24 mL, 8.87 mmol) and ethanethiol (0.445 g, 0.533 mL, 7.17 mmol) in dry ether (14 mL). Stirring was continued at room temperature for 16 h, after which period of time the volatiles were removed under vacuum. A Kugelrohr distillation afforded **7f** as a colorless oil (0.96 g, 87%, 2 steps). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.15 (m, 5H), 3.49 (td, 2H, $J = 20.5$, 2.9 Hz), 3.10–2.90 (m, 4H), 1.41 (t, 6H, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 131.39$, 128.80, 128.15 (3s, 5C), 39.05 (dt, 1C, $J = 20.1$, 16.2 Hz), 25.83 (d, 2C, $J = 3.5$ Hz), 16.89 (d, 2C, $J = 4.9$ Hz). ^{19}F NMR (188 MHz, $CDCl_3$) δ 54.42 (dt, 2F, $J = 20.3$, 105.1 Hz). ^{31}P NMR (81 MHz, $CDCl_3$) δ 59.93 (t, 1P, $J = 102.3$ Hz). Exact mass (CI, 200 eV) m/z calcd for $C_{12}H_{17}F_2OPS_2$. M^+ 310.0427. Found 310.0423. A stirring solution of phosphonodithioate **7f** (0.96 g, 3.1 mmol) and Lawesson's reagent (1.26 g, 3.1 mmol) in dry toluene (13 mL) was refluxed under argon for 2 h. The mixture was then cooled to room temperature and evaporated. The residual oil was diluted in heptane (20 mL) and filtered, and the filtrate was evaporated. Purification on silica gel eluting with heptane/ethyl acetate (7:3) furnished **8f** as a yellowish oil (1 g, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 3.60 (dt, 2H, $J = 19.7$, 2.9 Hz), 3.10–2.90 (m, 4H), 1.39 (t, 6H, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.93, 127.33, 126.63 (3s, 5C), 36.85 (dt, 1C, $J = 20.4$, 18.4 Hz), 26.59 (d, 2C, $J = 3.5$ Hz), 14.82 (d, 2C, $J = 5.6$ Hz). ^{19}F NMR (188 MHz, $CDCl_3$) δ 55.90 (dt, 2F, $J_{F\text{-}H} = 16.9$, 101.7 Hz). ^{31}P NMR (81 MHz, $CDCl_3$) δ 88.00 (t, 1P, $J = 98.7$ Hz). Exact mass (CI, 200 eV) m/z calcd for $C_{12}H_{17}F_2PS_3$. M^+ 326.0198. Found 326.0188.