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Synthesis of New Mercapto-Phosphono Substituted Heterocycles via a Thiophosphate - β-Mercaptophosphonate rearrangement

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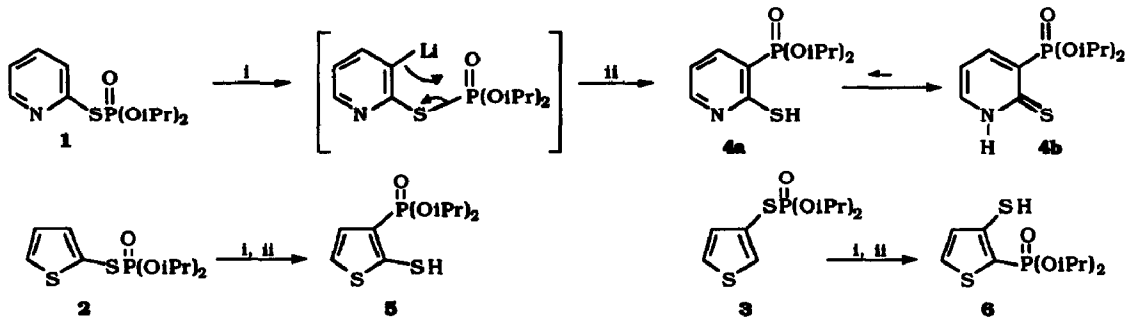
Abstract : Diisopropyl (1,2-dihydro-2-thioxo-3-pyridyl)-, (2-mercapto-3-thienyl)- and (3-mercapto-2-thienyl)- phosphonates were synthesized from the lithiated derivatives of the readily prepared O,O-diisopropyl S-(2-pyridyl)-, S-(2-thienyl)- and S-(3-thienyl)- thiophosphates through a S→C phosphonyl group migration.

Mercapto and phosphonyl derivatives of heterocyclic compounds arouse a great interest in metal-thiolate coordination chemistry and also in the field of biological research. In particular, 3- and 3,6-silylated 2-mercaptopyridines, readily prepared from the parent compounds by ortho lithiation-silylation procedures, form a variety of novel transition-metal complexes, and afford clusters with Cu^{I} and Ag^{I}.[1] In addition, substituted 2- and 4-pyridyl and quinolyl phosphonates are useful as corrosion inhibitors, bactericides, herbicides, and chelating agents.[2] (Mercaptoheteroaryl)phosphonates, also potentially interesting compounds for their biological and complexing properties, are, to our knowledge, not described. Recently, we reported the first example of phosphonyl S→C migration from the ortho-lithiated derivative of the readily prepared O,O-diisopropyl S-phenyl thiophosphate, leading to the phosphonic analogue of the mercaptosalicylic acid.[3] Similar O→C migration was previously described [4] but till now not studied from heterocyclic phosphates. The recently reported formation of hydroxypyridyl phosphonates from *o*-metallated pyridylphosphates [5] prompted us to publish our own results related to the synthesis of phosphono-substituted pyridinethione and mercaptothiophenes from their corresponding thiophosphates.



1 4a 4b

2 5 3 6

(i) LDA, THF, -78 to 0°C ; (ii) NH_4Cl / HCl, 0°C

O,O-Diisopropyl S-(2-pyridyl)- and S-(2-thienyl)- thiophosphates **1** and **2** were easily obtained by phosphorylation of sodium pyrid-2-thiolate and thiophene-2-thiolate (formed by the treatment of commercial pyrid-2-thiol and thiophene-2-thiol with sodium hydride [3]). O,O-Diisopropyl S-(3-thienyl)thiophosphate **3** was synthesized by treatment of lithium thiophene-3-thiolate (prepared by the lithium-halogen exchange reaction of 3-bromothiophene and sulfuration of the 3-lithiated thiophene [6]) with diisopropyl chlorophosphate.[7] Reaction of

S-heteroaryl thiophosphates **1** [8], **2** and **3** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) according to a previously described procedure [3] induces the [1,3]-S,C-rearrangement wherein the phosphonyl group migrates to the C-3 atom for compounds **1** and **2**, and to the C-2 atom for compound **3**, leading respectively to diisopropyl (1,2-dihydro-2-thioxo-3-pyridyl)phosphonate **4b** (75%), diisopropyl (2-mercapto-3-thienyl)- and (3-mercapto-2-thienyl)- phosphonates **5** (21%) and **6** (47%) after purification by flash column chromatography on silica gel (eluent : ethyl acetate for **4b** ; cyclohexane / ethyl acetate, 8 / 2 for **5** and **6**). The lower yields obtained with mercaptothiophenes **5** and **6** are partly due to their relative instability.[9] The structure of **4b**, **5** and **6** result from their NMR spectral data.[10] As previously observed with mercaptopyridines substituted by an electron-withdrawing group,[11] we observed, with the phosphonyl substituent, a quasi complete displacement of the 2-mercaptopyridine ⇌ pyrid-2-thione tautomeric equilibrium towards the thione form **4b**. The structure of **4b** is confirmed by UV spectrum (λ_{max} = 303 ; 387 nm in ethanol [12]) and by the similarity of the ^1H NMR signals with those of (1-hydro-3-bromo-2-pyridyl)thione :[13] compared with the disulfide **4'a** of **4a**, isolated as a by-product of **4b** (<10%), a shielding of proton H-5 (for **4'a**, δ= 7.11 ppm), an inversion of the chemical shifts for H-4 and H-6 signals (for **4'a**, $\delta(H_4)$= 8.17 ppm, $\delta(H_6)$= 8.40 ppm) and an increase of the coupling constant between H-5 and H-6 (for **4'a**, $^3J_{56}$= 4.7 Hz) are observed.

The synthetic potential of this reaction for the preparation of new substituted heteroaryl phosphonates will be more extensively examined. In particular, the subsequent addition of electrophiles on the lithium thiolate group after the rearrangement and also the S-addition of electrophilic reagents on the pyridinethione **4b** will be studied.

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9. When protonation was replaced by methylation, better yields were obtained for the methylated analogues of **5** and **6** (36% and 63% respectively). However, together with **5**, formation of secondary products resulting from lithiation on C_4 or C_5 of the thiophene ring was observed. In particular, the nucleophilic attack of these lithiated species on the phosphonyl group of the thiophosphate **2** lead, by cleavage of the S-P bond and after protonation, to mercaptothiophene and 3,4- or 3,5-diphosphonylated mercaptothiophene.
10. Significant signals for **4b** : ^1H NMR ($CDCl_3$, 250 MHz, TMS) : δ= 6.77 (~ dt, $^3J_{54}$~ $^3J_{56}$~ 6.6 Hz, $^4J_{HP}$= 3.0 Hz, H_5), 7.72 (~ dt, $^3J_{65}$= 6.1 Hz, $^4J_{64}$~ $^5J_{HP}$~ 1.5 Hz, H_6), 8,22 (ddd, $^3J_{45}$= 7.3 Hz, $^4J_{46}$= 1.5 Hz, $^3J_{HP}$= 15.3 Hz, H_4) ; ^{13}C NMR ($CDCl_3$, 62.9 MHz, TMS) : δ= 112.22 (d, $^3J_{CP}$= 13.8 Hz, C_5), 132.86 (d, $^1J_{CP}$= 201.8 Hz, C_3), 140.74 (s, C_6), 146.34 (d, $^2J_{CP}$= 8.2 Hz, C_4), 178.34 (d, $^2J_{CP}$= 17.9 Hz, C_2) ; ^{31}P NMR ($CDCl_3$, 32.44 MHz, external H_3PO_4) : δ= 10.62 (s). Significant signals for **5** : ^1H NMR ($CDCl_3$, 250 MHz, TMS) : δ= 3.71 (s, SH), 7.07 (~ t, $^3J_{54}$~ $^4J_{HP}$~ 3.4 Hz, H_5), 7.45 (dd, $^3J_{45}$= 3.5 Hz, $^3J_{HP}$= 8.8 Hz, H_4) ; ^{13}C NMR ($CDCl_3$, 62.9 MHz, TMS) : δ= 134.88 (d, $^3J_{CP}$= 15.5 Hz, C_5) ; 136.29 (d, $^2J_{CP}$= 10.8 Hz, C_4) ; 136.39 (d, $^1J_{CP}$= 204.8 Hz, C_3) ; 143.82 (d, $^2J_{CP}$= 7.0 Hz, C_2) ; ^{31}P NMR ($CDCl_3$, 32.44 MHz, external H_3PO_4) : δ= 7.01 (s). Significant signals for **6** : ^1H NMR ($CDCl_3$, 250 MHz, TMS) : δ= 5.63 (s, SH), 6.96 (dd, $^3J_{54}$= 5.9 Hz, $^4J_{C\text{-}S\text{-}P}$= 3.5 Hz, H_5), 7.56 (~ t, $^3J_{45}$~ $^4J_{HP}$~ 5.0 Hz, H_4) ; ^{13}C NMR ($CDCl_3$, 62.9 MHz, TMS) : δ= 119.14 (d, $^1J_{CP}$= 210.9 Hz, C_2), 130.21 (d, $^3J_{C\text{-}S\text{-}P}$= 16.8 Hz, C_5), 132.23 (d, $^3J_{CP}$= 6.7 Hz, C_4), 137.79 (d, $^2J_{CP}$= 11.5 Hz, C_3) ; ^{31}P NMR ($CDCl_3$, 32.44 MHz, external H_3PO_4) : δ= 9.31 (s).
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