Unusual Course of the Reaction of Lawesson's Reagent with β -Phosphoryl- β '-carbethoxyhydrazones: First Synthesis of 5-Mercapto-3-(methylthio-phosphoryl)pyrazoles

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Abstract: It is well known that Lawesson's reagent (LR) reacts with hydrazone derivatives at 80 °C to yield 3-thioxo-1,2,3-diazaphospholine derivatives. We show, in the present investigation, that the reaction of LR with β -phosphoryl- β '-carbethoxyhydrazones under the same conditions, took an entirely different course and gave a new type of pyrazole derivatives, the 5-mercapto-3-(methylthiophosphoryl)pyrazoles.

Keywords: Hydrazones, Lawesson's reagent, mercaptopyrazoles, pyrazoles, thiophosphorylpyrazoles.

INTRODUCTION

The use of 2,4-bis(p-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide [Lawesson's reagent (LR)] in heterocyclic synthesis has been well documented [1-4]. One of its important applications involves the synthesis of 1,2,3diazaphospholine derivatives by reaction with hydrazones It is worth noting that pyrazole derivatives are an important class of compounds in medicinal chemistry with a wide range of biological properties including anticancer [9, 10], antimicrobial [11, 12], antiviral [13] and antiinflammatory [14, 15] activities. Some of these compounds are also known for their applications in agrochemistry as herbicide [16] fungicide [17] and insecticide [18] agents.



Scheme 1. Synthesis of diazaphospholine derivatives by reaction of LR with hydrazones.

[5] (Scheme 1). In this area, we have previously shown that phosphoryl- and esterhydrazones react with LR to give 3-thioxo-1,2,3-diazaphospholine derivatives bearing a phosphoryl or an ester group [6-8]. We report, in the present investigation, the extension of this reaction to β -phosphoryl- β '-carbethoxyhydrazones 2. Our initial objective was to study the effect of the phosphoryl and ester groups on the course of the reaction, and to access new 1,2,3-diazaphospholine derivatives. Contrary to our expectation, the reaction took an entirely different course and gave the novel 5-mercapto-3-(methylthiophosphoryl)pyrazoles 3.

Experimentally [19], hydrazones 2 were easily obtained from the reaction of β -keto- δ -carbethoxyphosphonates and phosphineoxides 1 [20] with phenylhydrazine in ethanol at 0 °C (Scheme 2). The reaction times range from 2 to 4 h depending on the nature of the substrate. The isolated yield of the reaction is about 90% (Table 1).

Compounds **2** were characterized on the basis of their IR, NMR (1 H, 31 P, 13 C) and mass spectral data [21], which indicate that they are obtained as a mixture of Z and E isomers. Their relative proportions were estimated from the 31 P NMR spectra where a singlet for each isomer is present (Table **1**).

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Scheme 2. Synthesis of β -phosphoryl- β '-carbethoxyhydrazones **2**.

Table 1. Synthesis of β-phosphoryl-β'-carbethoxyhydrazones 2

| Entry | R or R ₂ P | Product | Yield ^a (%) | Reaction time (h) ^b | $\delta^{31} P(Z)^{c,d}$ | δ ³¹ P (E) | % Z ^e | % E ^e |
|-------|-----------------------|---------|------------------------|-----------------------------------|--------------------------|-----------------------|------------------|------------------|
| 1 | Ph | 2a | 96 | 2 | 31.5 | 29.9 | 79 | 21 |
| 2 | EtO | 2b | 83 | 2 | 25.2 | 24.1 | 60 | 40 |
| 3 | MeO | 2c | 91 | 3 | 23.7 | 21.0 | 72 | 28 |
| 4 | | 2d | 88 | 4 | -14.7 | -7.6 | 67 | 33 |
| 5 | C P | 2e | 87 | 4 | 4.1 | -2.3 | 59 | 41 |

^aIsolated yield.

^bThe progress of the reactions was monitored by TLC. ^c121.5 MHz, CDCl₃.

^dδ in ppm.

^eDetermined from the ³¹P NMR spectra.

The Z and E configurations were attributed on the basis of the ¹³C chemical shift values for the CH₂-P carbon. Indeed, according to some literature data [22-25] concerning the stereochemistry of hydrazones, the carbon adjacent to the C=N double bond resonates at higher field when it is in syn position to the NHPh group.

With these hydrazone derivatives in hand, we next focused our efforts to investigate their behaviour towards

Lawesson's reagent. Thus, treatment of compounds 2 with an equimolar amount of LR, performed in toluene, at 80 °C, for 5-8 h, afforded the novel 5-mercapto-3-(methylthiophosphoryl)pyrazoles 3 [26] rather than the expected 1,2,3diazaphospholine derivatives A or B (Scheme 3). This can be attributed to the poor nucleophilicity of the carbons at the α and α ' positions relative to the C=N double bond, because of the conjugation with the phosphoryl and ester groups [8]. This poor nucleophilicity would render the α and α ' carbons



Scheme 3. Synthesis of 5-mercapto-3-(methylthiophosphoryl)pyrazoles 3.



Scheme 4. Loss of reactivity of the α and α ' carbons because of the conjugation with the ester and phosphoryl groups.



Scheme 5. Reaction mechanism for the synthesis of pyrazoles 3.

unable to initiate cyclization to give the diazaphospholine derivatives **A** and **B** (Scheme 4).

A plausible mechanism for the formation of compounds **3** is depicted in scheme **5**. It is believed that the reaction begins with a thionation of the phosphoryl group followed by an intramolecular cyclization. The obtained pyrazolone intermediate undergoes a second thionation with LR to lead, after tautomerization, to the aromatic pyrazole derivative **3**. This mechanism can be confirmed by some literature data [3] which indicate that LR thionates readily the phosphoryl, ketone, amide and ester functions, and that the relative reactivity order of these functional groups toward LR is as follows: phosphoryles > amides > ketones > esters.

The formation of compounds **3** was confirmed by IR, NMR (1 H, 31 P, 13 C) and mass spectral data [27]. The IR spectra revealed the presence of absorption bands towards

700 and 2500 cm⁻¹ corresponding respectively to the P=S and S-H vibrators. The ¹H NMR spectrum of each compound **3** showed, in particular, a doublet at 3.6-3.9 ppm, ascribable to the CH₂-P=S protons. Such a doublet is characteristic of the coupling with phosphorus with a ${}^{2}J_{PH}$ coupling constant of about 15 Hz. We also observed a singlet (in some cases a doublet with a small ${}^{4}J_{\rm PH}$ coupling constant) towards 6 ppm assignable to the pyrazolic CH. The S-H proton resonates as a broad singlet at 8-9 ppm. The ³¹P NMR shift recorded for compounds 3 was $\delta = 40-80$ ppm which is consistent with the thiophosphoryl chemical shift values. The ¹³C NMR spectra display the characteristic signals of all carbons and particularly those corresponding to the pyrazole ring. Of particular note is the CH₂-P=S carbon which resonates as a doublet (${}^{1}J_{CP} = 53.6-143.4 \text{ Hz}$) around 30 ppm. Structure of compounds 3 was supported additionally by the mass spectra which showed the correct molecular ion peaks.

Table 2. Synthesis of 5-mercapto-3-(methylthiophosphoryl)pyrazoles 3

| Entry | R or R ₂ P | Product | Yield ^a (%) | Reaction time (h) ^b | δ ³¹ P (ppm) ^c |
|-------|-----------------------|---------|------------------------|--------------------------------|--------------------------------------|
| 1 | Ph | 3a | 89 | 7 | 40.7 |
| 2 | EtO | 3b | 79 | 8 | 71.2 |
| 3 | MeO | 3c | 84 | 6 | 79.9 |
| 4 | | 3d | 75 | 7 | 43.9 |
| 5 | O, P | 3e | 81 | 5 | 46.8 |

^aIsolated yield.

^bThe progress of the reactions was monitored by TLC.

°121.5 MHz. CDCl₃.

In conclusion, we have shown in the present investigation, that the introduction of electron-withdrawing phosphoryl and ester groups at the β and β ' positions relative to the hydrazone function, significantly changes the reactivity towards Lawesson's reagent and provides the novel 5-mercapto-3-(methylthiophosphoryl)pyrazoles rather than the expected 1,2,3-diazaphospholine derivatives.

CONFLICT OF INTEREST

Declared none.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers web site along with the published article.

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for 2-4 h (Table 1). The reaction mixture was then concentrated *in vacuo*. The solid obtained was washed with petroleum ether.

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- Spectral data of compound 2a (Table 1, entry 1). White solid; mp = [21] 178-180 °C; ¹H NMR (300 MHz, CDCl₃): $\delta = 1.15$ (t, 3H, ³ $J_{HH} =$ 6.0 Hz, C<u>H</u>₃-CH₂-O, Z); 1.16 (t, 3H, ${}^{3}J_{HH} = 6.0$ Hz, C<u>H</u>₃-CH₂-O, E); 2.78 (d, 2H, ${}^{4}J_{PH} = 3.0$ Hz, CH₂-C=O, Z); 3.44 (d, 2H, ${}^{2}J_{PH} = 15.0$ Hz, CH₂-P=O, E); 3.53 (d, 2H, ⁴J_{PH}= 3.0 Hz, CH₂-C=O, E); 3.60 (d, 2H, ${}^{2}J_{PH} = 15.0$ Hz, CH₂-P=O, Z); 4.01 (q, 2H, ${}^{3}J_{HH} = 6.0$ Hz, CH₃-C<u>H</u>₂-O, Z); 4.06 (q, 2H, ${}^{3}J_{HH} = 6.0$ Hz, CH₃-C<u>H</u>₂-O, E); 6.76-7.80 (m, 15H, arom-H); 8.23 (br s, 1H, N-H, E); 9.89 (br s, 1H, N-H, Z); ¹³C NMR (75.5 MHz, CDCl₃): $\delta = 14.1$ (s, CH₃-CH₂-O, Z); 18.4 (s, <u>CH</u>₃-CH₂-O, E); 34.3 (d, ${}^{1}J_{CP}$ = 64.9 Hz, CH₂-P, Z); 40.0 (d, ${}^{1}J_{CP} = 66.4$ Hz, CH₂-P, E); 43.2 (s, <u>C</u>H₂-C=O, E); 43.7 (s, <u>C</u>H₂-C=O, Z); 61.0 (s, CH₃-<u>C</u>H₂-O, Z); 61.7 (s, CH₃-<u>C</u>H₂-O, E); 145.1 (s, C=N, E); 146.2 (s, C=N, Z); 168.7 (s, C=O, E); 170.3 (s, C=O, Z); phenyl carbons: $\delta = 113.2$, 113.7, 118.9, 120.0, 121.9, 125.2, 125.9, 128.5, 128.6, 128.7, 128.9, 129.0, 129.1, 130.5, 130.6, 130.8, 130.9, 131.0, 131.9, 132.2, 134.4, 134.6; IR (neat): $v_{P=0}$ = 1233 cm⁻¹; $v_{c=N}$ = 1601 cm⁻¹; $v_{c=0}$ = 1732 cm⁻¹; v_{NH} = 3311 cm⁻¹; EI-HRMS: calculated for $C_{24}H_{25}N_2O_3P$, 420.1603 (M⁺); found: 420.1607
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- [26] General procedure for the synthesis of 5-mercapto-3-(methylthiophosphoryl)pyrazoles 3. A mixture of hydrazone 2 (0.01 mol), LR (0.01 mol) and dry toluene (30 mL) was heated at 80 °C with stirring for 5-8 h (Table 2). The reaction mixture was then concentrated *in vacuo*. The residue obtained was chromatographed on a silica gel column using a mixture of Et₂O and hexane (9:1) as eluent.
- [27] Spectral data of compound **3a** (Table **2**, entry 1). White solid; mp = 152-153 °C; ¹H NMR (300 MHz, CDCl₃): δ = 3.91 (d, 2H, ²J_{PH} = 15.0 Hz, CH₂-P); 6.50 (d, 1H, ⁴J_{PH} = 2.2 Hz, CH=C-S); 7.06-7.83 (m, 15H, arom-H); 8.07 (br s, 1H, S-H); ¹³C NMR (75.5 MHz, CDCl₃): δ = 34.7 (d, ¹J_{CP} = 53.6 Hz, CH₂-P); 116.5 (d, ³J_{CP} = 2.3 Hz, CH=C-S); 138.8 (s, C-S); 144.0 (d, ²J_{CP} = 6.0 Hz, C=N); phenyl carbons: 125.58, 128.15, 128.50, 128.66, 128.71, 131.54, 131.58, 131.62, 131.67, 131.74, 132.80, 133.64; IR (neat): v_{P=S} = 698 cm⁻¹; v_{S-H} = 2551 cm⁻¹; E1-HRMS: calculated for C₂₂H₁₉N₂PS₂, 406.0727 (M⁺); found: 406.0725.