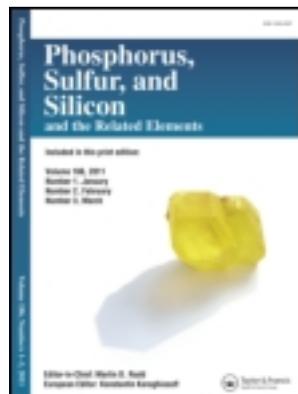


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AN EFFICIENT ROUTE TO NEW 1,2,4,3-TRIAZAPHOSPHOLE-3-OXIDE DERIVATIVES

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The condensation of hexamethylphosphorotriamide and bis-(dimethylamino) methylphosphonate with amidrazones 1 constitutes a new route to the synthesis of 1,2,4,3-triazaphosphole-3-oxide derivatives 3. Structures of all the synthesized compounds have been established by NMR (^1H , ^{13}C , ^{31}P) and IR spectroscopy, as well as by elemental analysis and MS spectral data for some products.

Keywords Amidrazones; bis-(dimethylamino) methylphosphonate; hexamethylphosphorotriamide; triazaphosphole

INTRODUCTION

The synthesis of phosphonitrogenous heterocycles^{1–3} is one of the aims of researchers in synthetic organic chemistry because of their large biological and pharmaceutical activities.^{3–6} Triazaphosphole derivatives are a family of heterocyclic compounds that has attracted the interest of chemists due to their various applications as antibacterials⁴ and cytotoxicity⁴ agents.

There are various methods^{7–12} for the synthesis of 1,2,4,3-triazaphospholes, but most of them suffer from one or more disadvantages, such as the triazaphosphole derivatives can exist in several different isomeric forms depending on the type of substitution. We report in this article the selective synthesis of new triazaphosphole derivatives **3** by the reaction of amidrazones **1** with hexamethylphosphorotriamide or bis-(dimethylamino) methyl phosphonate.

RESULTS AND DISCUSSION

2-Aminobenzamidrazones **1**, which are the starting material for this work, were prepared from the condensation of hydrazine with 2-aminobenzonitrile in the presence of a catalytic amount of acetic acid. The chemical structure of compound **1** is in agreement with its spectral data. The IR spectrum of compound **1** exhibited the absorption bands for NH_2

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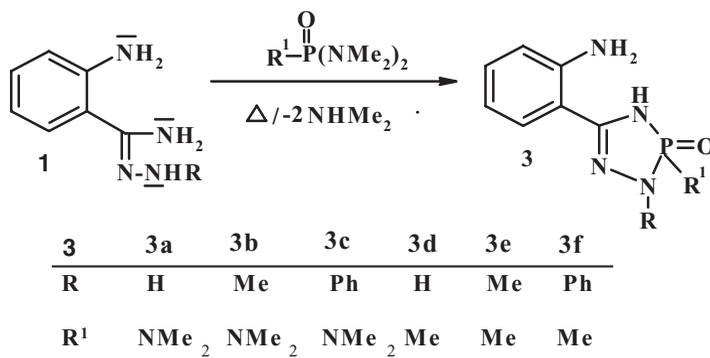


Figure 1 Synthetic route of the formation of compound 3.

and C=N (imine) and the absence of an absorption band of a CN group. ¹H NMR analysis confirmed the formation of compound **1** and showed the presence of new signals assigned to NH₂, NH, and protons of the methyl and phenyl introduced by the substituted hydrazine. ¹³C NMR spectra showed the total absence of a signal related to CN (nitrile) group.

The reaction of compound **1** with phosphorylated reagents in dry toluene under reflux afforded triazaphosphole **3** (Figure 1).

The formation of triazaphospholes **3** was confirmed by ¹H, ¹³C, and ³¹P NMR spectra and IR spectroscopy as well as elemental analysis for some products (**3c** and **3d**). The ³¹P NMR spectra showed the presence of a signal corresponding to phosphonate moiety (P=O) at 25 ppm when R¹ = NMe₂ and a signal at 38 ppm when R¹ = Me.

The IR spectrum of **3** showed absorption bands at 3230–3150 cm⁻¹ (NH₂), 3350 cm⁻¹ (NH), 1296–1308 cm⁻¹ (P=O bonded) and strong bands in the region of 1090–1100 cm⁻¹ indicating the presence of P-N groups. The ¹H NMR spectrum of **3** revealed the presence of two types of methyl group protons in NMe₂ with different chemical shifts. Furthermore, the Me group protons of NMe₂ groups coupled with phosphorus and were split into a doublet. The ¹³C NMR spectra of **3** displayed the characteristic signals of all carbons and revealed two signals attributable to the carbons of P-N(CH₃)₂ of the two non-equivalent methyls of the NMe₂ group.

EXPERIMENTAL

IR spectra were recorded on Perkin Elmer Paragon 1000 PC spectrometer using a solution of CHCl₃. The spectra resolution was 4 cm⁻¹.

¹H, ¹³C, and ³¹P NMR spectra were recorded in CDCl₃ as solvent containing TMS (tetramethylsilane) on a Brüker 300 spectrometer (¹H: 300 MHz, ¹³C: 75.47 MHz, ³¹P: 121.49 MHz). The chemical shifts (δ) are reported in ppm relative to TMS (internal reference) for ¹H and ¹³C and relative to 85% H₃PO₄ (external reference) for ³¹P.

Melting points were determined using a Büchi melting point apparatus and are uncorrected. Elemental microanalysis was performed on a Perkin-Elmer CHN-2400 analyzer apparatus.

Synthesis of 2-Aminobenzamidrazones 1

To a solution of anthranilonitrile (0.01 mol) in ethanol (10 mL), hydrazine (0.015 mol) and a few drops of acetic acid were added. The reaction mixture was refluxed for 12 h and then allowed to reach room temperature. The solvent was evaporated from the vacuum pump, and the resulting solid was filtered, washed several times with diethyl ether, and recrystallized from ethanol. Compound **1a** obtained was chromatographed on a silica gel column using a mixture of ethyl acetate and petroleum ether (4:6) as eluent.

1a: Mp = 50°C. Yield = 93%. IR (CHCl₃), ν (cm⁻¹): ν (NH₂) = 3320–3400; ν (NH) = 3460. ¹H NMR (CDCl₃): δ 4.38 (s, 6H, NH₂); 6.60–7.28 (m, 4H, H_{arom}). ¹³C NMR (CDCl₃): δ 115.23; 117.75; 117.90; 132.32; 134.04; 149.78.

1b: Mp = 52°C. Yield = 94%. IR (CHCl₃), ν (cm⁻¹): ν (NH₂) = 3320–3400, ν (NH) = 3455. ¹H NMR (CDCl₃): δ 4.60 (broad s, 5H, NH, NH₂); 3.10 (s, 3H, CH₃); 6.40–7.25 (m, 4H, H_{arom}). ¹³C NMR (CDCl₃): δ 38.60; 117.34; 118.48; 128.50; 129.29; 131.98; 146.85; 150.78.

1c: Oil. Yield = 90%. IR (CHCl₃), ν (cm⁻¹): ν (NH₂) = 3325–3400, ν (NH) = 3465. ¹H NMR (CDCl₃): δ 4.30 (broad s, 5H, NH, NH₂); 6.40–7.25 (m, 9H, H_{arom}). ¹³C NMR (CDCl₃): δ 115.34, 118.00, 119.43, 119.77, 128.50, 129.29, 131.98, 134.56, 146.85, 151.42.

Synthesis of 1,2,4,3-Triazaphosphole-3-oxide Derivatives

A mixture of aminobenzamidrazone **1** (1.0 mmol) and hexamethylphosphorotriamide or bis-(dimethylamino) methylphosphonate (1.0 mmol) dissolved in anhydrous toluene (10 mL) was heated under reflux for 24 h. After evaporating off the solvent in vacuum, the resulting solid product was recrystallized from CCl₄ (**3c**, **3d**, **3e**, **3f**), and the oil obtained (**3a** and **3b**) was purified by column chromatography using silica gel (60–120 mesh) with ethyl acetate:petroleum ether (3:7) as eluent.

3a: Oil. Yield = 60%. IR (CHCl₃), ν (cm⁻¹): ν (C=N) = 1635; ν (NH₂) = 3230–3150; ν (NH) = 3350; ν (P=O) = 1296. ¹H NMR (CDCl₃): δ 2.35 (d, ³J_{PH} = 5.5 Hz, 3H, N-CH₃); 2.52 (d, ³J_{PH} = 5.5 Hz, 3H, N-CH₃); 4.81 (broad s, 4H, NH, NH₂); 6.50–7.16 (m, 4H_{arom}). ¹³C NMR (CDCl₃): δ 35.88 (d, ²J_{PC} = 9.2 Hz, NCH₃); 36.22 (d, ²J_{PC} = 6.0 Hz, NCH₃); 115.22; 116.11; 117.53; 131.42; 133.30; 150.74; 169.96. ³¹P NMR (CDCl₃): δ 25.09. Calcd for C₉H₁₄N₃PO: %C: 45.18; %H: 5.85; %N: 29.28; found: %C: 45.10; %H: 5.80; %N: 29.15.

3b: Oil. Yield = 70%. IR (CHCl₃), ν (cm⁻¹): ν (C=N) = 1630; ν (NH₂) = 3235–3120; ν (NH) = 3350; ν (P=O) = 1296. ¹H NMR (CDCl₃): δ 2.38 (d, ³J_{PH} = 4.9 Hz, 3H, N-CH₃); 2.50 (d, ³J_{PH} = 4.9 Hz, 3H, N-CH₃); 3.20 (s, 3H, N-CH₃); 4.80 (broad s, 3H, NH₂, NH); 6.05–7.16 (m, 4H_{arom}). ¹³C NMR (CDCl₃): δ 35.70 (d, ²J_{PC} = 3.0 Hz, NCH₃); 36.12 (d, ²J_{PC} = 7.0 Hz, NCH₃); 39.70 (NCH₃); 116.25; 116.59; 116.92; 130.65; 133.31; 149.44; 169.00. ³¹P NMR (CDCl₃): δ 25.60. m/e (Relative intensity): 253 (5); 193 (50); 165 (20); 150 (30); 135(47); 109(35); 92(42); 76(14).

3c: Mp: 175°C. Yield = 73%. IR (CHCl₃), ν (cm⁻¹): ν (C=N) = 1635; ν (NH₂) = 3230–3140; ν (NH) = 3330; ν (P=O) = 1296. ¹H NMR ((CDCl₃): δ 2.22 (d, ³J_{PH} = 5.0 Hz, 3H, N-CH₃); 2.10 (d, ³J_{PH} = 4.9 Hz, 3H, N-CH₃); 5.00 (broad s, 3H, NH₂, NH); 6.10–7.20 (m, 4H_{arom}). ¹³C NMR (CDCl₃): δ 36.07 (d, ²J_{PC} = 6.0 Hz, NCH₃); 36.12 (d, ²J_{PC} = 7 Hz, NCH₃); 111.59; 116.11; 117.63; 122.34; 128.04; 128.53; 129.17; 140.42; 147.06; 164.72. ³¹P NMR (CDCl₃): δ 25.10. Calcd for C₁₅H₁₈N₃PO: %C: 57.14; %H: 5.71; %N: 22.22; found: %C: 57.00; %H: 5.68; %N: 22.00.

3d: Mp: 180°C. Yield = 80%. IR (CHCl₃), ν (cm⁻¹): ν (C=N) = 1635; ν (NH) = 3354; ν (NH₂) = 3230–3150; ν (P=O) = 1308. ¹H NMR (CDCl₃): δ 1.30 (d, ²J_{PH} = 11.0 Hz, 3H, P-CH₃); 4.72 (broad s, 3H, NH₂, NH); 6.60–7.70 (m, 4H_{arom}). ¹³C NMR (CDCl₃): δ 13.12 (NCH₃); 114.82; 117.77; 118.98; 119.30; 131.70; 134.33; 145.00; 150.27. ³¹P NMR (CDCl₃): δ 38.08. Calcd for C₈H₁₁N₄PO: %C: 45.71; %H: 5.23; %N: 26.66; found: %C: 45.60; %H: 5.20; %N: 26.56.

3e: Mp: 200°C. Yield = 80%. IR (CHCl₃), ν (cm⁻¹): ν (C=N) = 1630; ν (NH) = 3354; ν (NH₂) = 3230–3140; ν (P=O) = 1308. ¹H NMR (CDCl₃): δ 1.30 (d, ²J_{PH} = 10.0 Hz, 3H, P-CH₃); 2.60 (s, 3H, N-CH₃); 4.90 (broad s, 3H, NH₂, NH); 6.50–7.60 (m, 4H_{arom}). ¹³C NMR (CDCl₃): δ 11.72 (NCH₃); 28.98; 115.17; 117.83; 121.12; 131.90; 133.90; 143.77; 150.54. ³¹P NMR (CDCl₃): δ 38.80. MS: m/e (Relative intensity) %: 224(1); 209 (55); 162(10); 150(30); 135(37); 109(30); 92(48); 76(24).

3f: Mp: 192°C. Yield = 82%. IR (CHCl₃), ν (cm⁻¹): ν (C=N) = 1632; ν (NH) = 3350; ν (NH₂) = 3225–3130; ν (P=O) = 1307. ¹H NMR (CDCl₃): δ 1.32 (d, ²J_{PH} = 12.0 Hz, 3H, P-CH₃); 4.68 (broad s, 3H, NH₂, NH); 6.62–7.31 (m, 9H_{arom}). ¹³C NMR (CDCl₃): δ 14.24 (NCH₃); 116.80; 119.71; 121.36; 128.81; 131.3; 133.35; 142.01; 148.78. ³¹P NMR (CDCl₃): δ 34.20.

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