Heteroatom Chemistry
Volume 19, Number 5, 2008

Studies on Organophosphorus Compounds: Synthesis and Reactions of [1,2,4,3]Triazaphospholo[4,5-*a*]Quinoxaline Derivative

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Received 12 May 2007; revised 7 December 2007, 8 March 2008

ABSTRACT: *2,4-Bis-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) (***1***) reacted with 2-hydrazino-3-methylquinoxaline (***2***) to give [1,2,4,3]-triazaphospholo[4,5-a]quinoxaline derivative* **3**. *The Mannich reaction using different amines on compound* **3** *gave Mannich bases* **4a–d**. *Also, compound* **3** *reacted with formaldehyde to give the corresponding 2-hydroxymethyl derivative* **5**, *which upon reaction with thionyl chloride gave the corresponding chloromethyl derivative* **6**. *Treatment of compound* **6** *with some thiols yielded the corresponding sulfides* **7a–d**. *Acylation of compound* **3** *gave acylated compounds* **8a,b**. *Compound* **9,** *which was prepared through the reaction of compound* **3** *with ethyl cyanoacetate, was investigated as a starting material for the synthesis of some new heterocyclic systems* **10–13**. *Also, reaction of compound* **9** *with carbon disulfide and 2 equivalents of methyl iodide in a one-pot reaction yielded the corresponding ketene-S,S-acetal* **14**, *which in turn reacted with bidentates to give some new heterocycles* **15–17**. Heteroatom Chem 19:520–529, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20473

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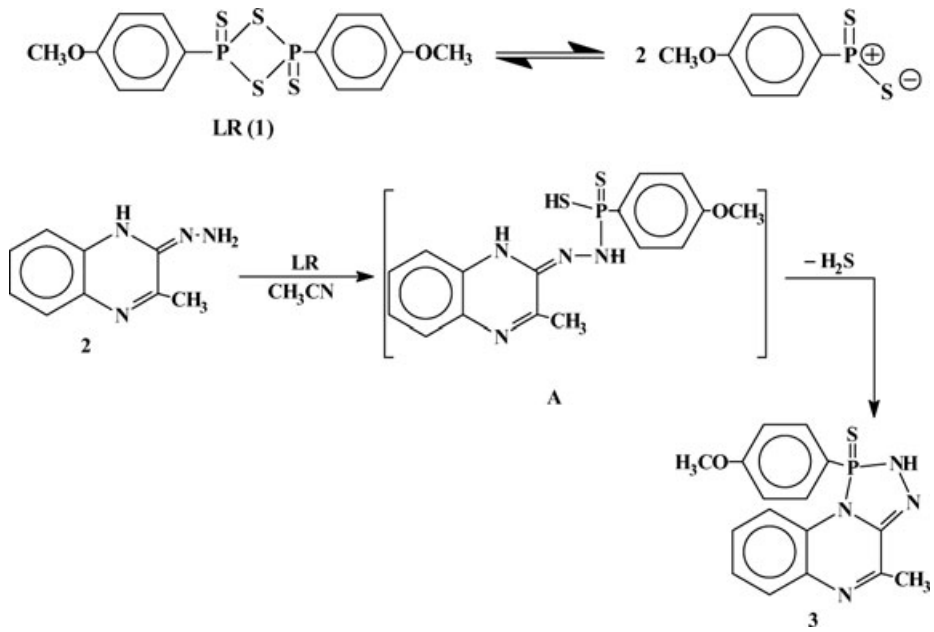
INTRODUCTION

Quinoxalines have been found to be biologically active compounds having antiviral [1], antimicrobial [2], and anticancer [3] properties. Also, organophosphorus compounds possess a large variety of interesting pharmacological and biological activities that include herbicidal [4], insecticidal [5,6], antibacterial [7,8], antifungal [7,9], and anticancer [10] properties. In view of the above observations and in continuation of our studies in the same area [11–14], it was of interest to fuse P-heterocycles with the quinoxaline nucleus, with the hope that the newly synthesized compounds might exhibit enhanced biological properties. 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, LR, **1**) has been shown to be quite versatile in thiation of different carbonyl compounds [15–17], and it is also known that nucleophiles attack compound **1** at the phosphorus atom. In certain cases, where the substrate contains two functional groups or can react in different ways, P-heterocycles are formed [18–22]. As an extension of our general studies on the reagent **1**, its reaction with quinoxaline derivatives is reported in this work.

RESULTS AND DISCUSSION

2-Hydrazino-3-methylquinoxaline (**2**) [23,24] was prepared in good yields by the reaction of the corresponding methyl sulfone with hydrazine hydrate. Compound **2** was allowed to react with LR (**1**)



SCHEME 1

in boiling acetonitrile to give 1-(4-methoxyphenyl)-4-methyl-1,2-dihydro-[1,2,4,3]-triazaphospholo[4,5-*a*]quinoxaline-1-sulfide (**3**). It was suggested that the amino group of the hydrazone attacks LR giving the intermediate A followed by ring closure through elimination of H_2S to give compound **3** (cf. Scheme 1)

The structure of compound **3** was confirmed on the basis of its elemental and spectral analysis (cf. Table 1).

The IR spectrum of compound **3** showed the absence of the absorption bands corresponding to the NH_2 group while exhibiting characteristic bands corresponding to P=S at 652 cm^{-1}. The ^1H NMR spectrum of compound **3** showed the absence of the signal corresponding to the NH_2 group while exhibiting a signal corresponding to three aliphatic protons at 3.9 (—OCH_3, s).

The Mannich reaction on compound **3** using formaldehyde and different amines namely benzylamine, aniline, morpholine, and diethylamine afforded the corresponding Mannich bases **4a–d** (cf. Scheme 2). The IR and ^1H NMR spectra of these compounds confirm their proposed structures (cf. Table 1).

Also, compound **3** reacted with formaldehyde to give the corresponding 1-hydroxymethyl derivative **5**, which in turn reacted with thionyl chloride to give the corresponding 1-chloromethyl derivative **6**. Treatment of compound **6** with aliphatic, aromatic, or heterocyclic thiols acting as a sulfur nucleophile in boiling ethanol in the presence of sodium ethoxide yielded the corresponding sulfides **7a–d** in good yields (cf. Scheme 2).

Acetylation and benzoylation of compound **3** gave N-acylated compounds **8a,b**, respectively (cf. Scheme 2).

The reaction of compound **3** with ethyl cyanoacetate in the presence of sodium *t*-butoxide afforded N-cyanoethyl derivative **9**. Refluxing of compound **9** with LR (**1**) in toluene gave the corresponding thiocompound **10**. Treatment of compound **10** with benzylidene malononitrile yielded thiopyrane derivative **11**. The reaction pathway was assumed to follow a preliminary formation of cabanion of the active methylene compound **10** followed by a nucleophilic addition at the ethylenic bond and cyclization via the nucleophilic addition of the mercapto group at the cyano group to give compound **11**. Also, compound **9** was allowed to react with acetylacetone and/or ethyl acetoacetate in the presence of sulfur in the ethanolic triethylamine solution to give the corresponding thienyl derivatives **12a,b**, respectively. Furthermore, the reaction of compound **9** with carbon disulfide and 1,2-dibromoethane or 2 equivalents of methyl iodide in a one-pot reaction using phase-transfer catalysis conditions [K_2CO_3/dioxan/TBAB] afforded compounds **13** and **14**, respectively in good yields. The structure of products **9–14** was proved by elemental analysis and spectral data (cf. Scheme 3, Table 1).

Compound **14** reacted with some bidentates, namely hydrazine hydrate, ethylene diamine,

TABLE 1 Analytical and Spectral Data of the New Compounds

Compound	MP (°C) Crystal Solvent	Yield (%)	Molecular Formula (Molecular weight)	Analytical Data Calcd/Found C	H	N	S	IR (cm^{-1})	^1H NMR, δ (ppm)
3	223 Ethanol	81	$C_{16}H_{15}N_4OPS$ (342.35)	56.13 55.81	4.41 4.33	16.36 16.17	9.36 9.21	3212 (NH), 1246 (C—O), 652 (P═S)	11.2 (br, 1H, NH), 7.95–7.80 (dd, 2H, $J_{HH} = 9$ Hz, ortho to P); 7.45–7.40 (m, 4H, quinoxaline protons), 6.9 (dd, 2H, $J_{HH} = 9$ Hz, meta to P); 3.9 (s, 3H, OCH_3), 2.2 (s, 3H, CH_3)
4a	192 Ethanol	63	$C_{24}H_{24}N_5OPS$ (461.52)	62.45 62.15	5.24 5.09	15.17 14.95	6.94 6.83	3259 (NH), 1239 (C–O), 650 (P═S)	11.9 (br, 1H, NH),7.96–7.85 (dd, 2H, $J_{HH} = 9$ Hz, ortho to P); 7.40–7.10 (m, 9H, quinoxaline protons + Ph); 6.92 (dd, 2H, $J_{HH} = 9$ Hz, meta to P); 5.1 (s, 2H, N–CH_2–N); 4.1 (s, 2H, CH_2); 3.9 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3)
4b	184 Ethanol	71	$C_{23}H_{22}N_5OPS$ (447.49)	61.73 61.48	4.95 4.81	15.65 15.46	7.16 6.99	3259 (NH), 1239 (C–O), 650 (P═S)	11.9 (br, 1H, NH), 7.92–7.84 (dd, 2H, $J_{HH} = 9.2$ Hz, ortho to P); 7.35–7.05 (m, 9H, quinoxaline protons + Ph); 6.90 (dd, 2H, $J_{HH} = 9.5$ Hz, meta to P); 5.1 (s, 2H, N–CH_2–N); 3.9 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3)
4c	199–201 Dioxan	69	$C_{21}H_{24}N_5O_2PS$ (441.49)	57.13 56.82	5.48 5.29	15.86 15.65	7.26 7.09	1243 (C–O), 655 (P═S)	7.94–7.80 (dd, 2H, $J_{HH} = 9.2$ Hz, ortho to P); 7.4–7.30 (m, 4H, quinoxaline protons), 6.95 (dd, 2H, $J_{HH} = 9.5$ Hz, meta to P); 5.1 (s, 2H, N–CH_2–N); 3.9 (s, 3H, OCH_3); 3.7–3.4 (m, 4H, CH_2–OCH_2); 2.9–2.6 (m, 4H, CH_2–N–CH_2); 2.3 (s, 3H, CH_3)
4d	183 Ethanol	81	$C_{21}H_{26}N_5OPS$ (427.50)	58.99 58.69	6.13 5.96	16.38 16.11	7.50 7.31	1239 (C–O), 644 (P═S)	7.80–7.70 (dd, 2H, $J_{HH} = 9.2$ Hz, ortho to P); 7.60–7.30 (m, 4H, quinoxaline protons), 6.95 (dd, 2H, $J_{HH} = 9.5$ Hz, meta to P); 5.1 (s, 2H, N–CH_2–N); 3.9 (s, 3H, OCH_3), 2.6 (q, 4H, 2NCH_2); 2.3 (s, 3H, CH_3); 1.1 (t, 6H, 2CH_3)
5	151 Ethanol	66	$C_{17}H_{17}N_4O_2PS$ (372.38)	54.82 54.49	4.61 4.48	15.04 14.81	8.59 8.37	3412 (OH), 1233 (C–O), 659 (P═S)	8.9 (br, 1H, OH); 7.82–7.70 (dd, 2H, $J_{HH} = 9$ Hz, ortho to P); 7.60–7.25 (m, 4H, quinoxaline protons), 6.95 (dd, 2H, $J_{HH} = 9$ Hz, meta to P); 5.4 (s, 2H,CH_2); 3.9 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3)
6	173 Ethanol	69	$C_{17}H_{16}N_4OPSCl$ (390.82)	52.24 51.89	4.12 4.01	14.33 14.21	8.20 8.07	770 (C–Cl), 649 (P═S)	7.85–7.70 (dd, 2H, $J_{HH} = 9.2$ Hz, ortho to P); 7.55–7.30 (m, 4H, quinoxaline protons), 6.98 (dd, 2H, $J_{HH} = 9.3$ Hz, meta to P); 6.2 (s, 2H, CH_2); 3.9 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3)
7a	143 Ethanol	71	$C_{20}H_{23}N_4OPS_2$ (430.53)	55.79 55.49	5.38 5.22	13.01 12.81	14.89 14.77	1233 (C–O), 692 (C–S–C), 659 (P═S)	7.80–7.65 (dd, 2H, $J_{HH} = 9.1$ Hz, ortho to P); 7.40–7.30 (m, 4H, quinoxaline protons), 6.97 (dd, 2H, $J_{HH} = 9.1$ Hz, meta to P); 5.2 (s, 2H, N–CH_2–S); 3.9 (s, 3H, OCH_3), 2.7 (t, 2H, SCH_2); 1.7 (m, 2H, CH_2); 2.3 (s, 3H, CH_3); 1.1 (t, 3H, CH_3)

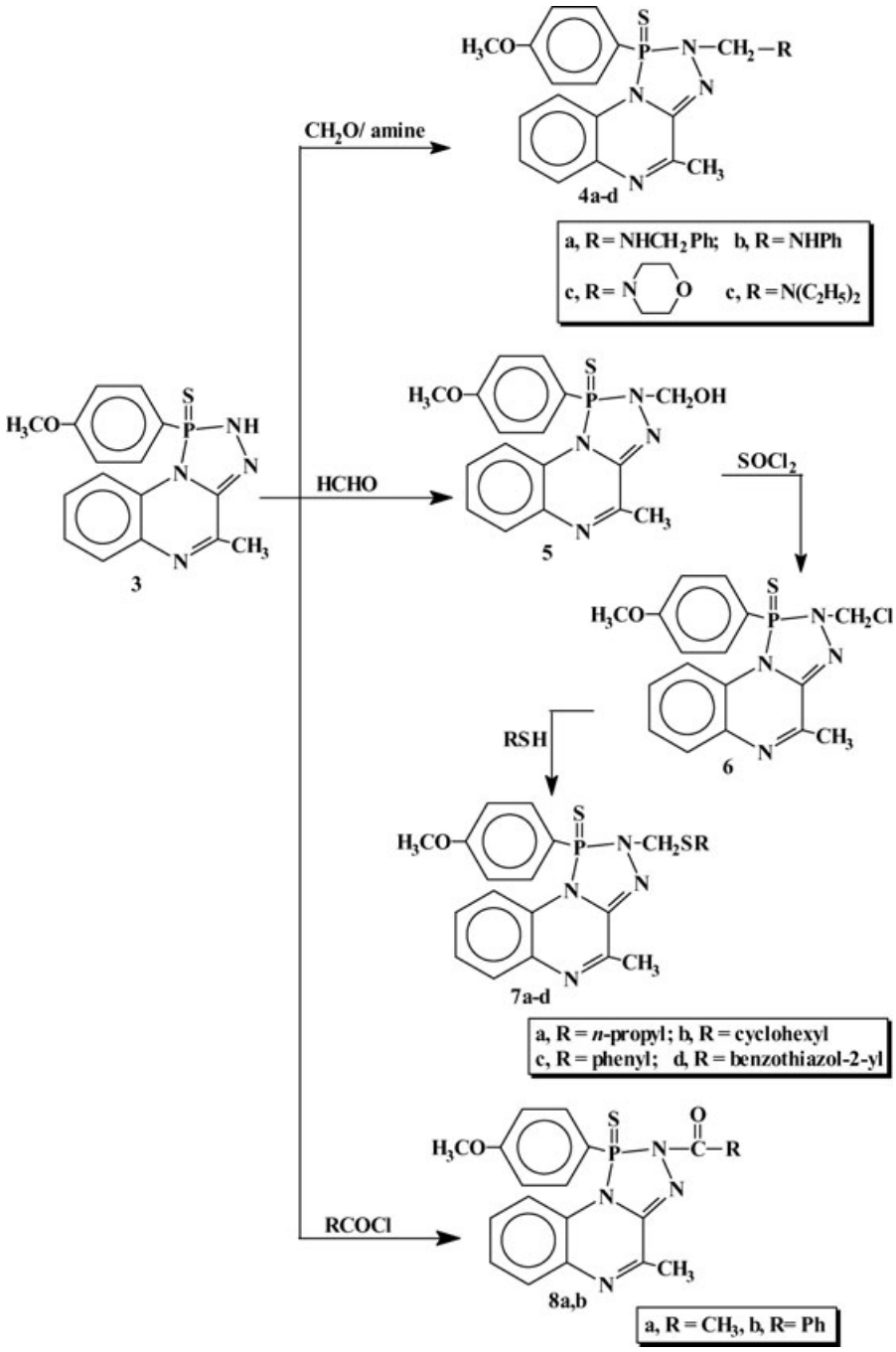
TABLE 1 Continued

Compound	MP (°C) Crystal Solvent	Yield (%)	Molecular Formula (Molecular weight)	Analytical Data Calcd/Found C	H	N	S	IR (cm^{-1})	^1H NMR, δ (ppm)
7b	132 Ethanol	80	$C_{23}H_{27}N_4OPS_2$ (470.59)	58.69 58.41	5.78 5.59	11.90 11,71	13.62 13.51	1248 (C–O), 696 (C–S–C), 659 (P=S)	7.80–7.65 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.40–7.30 (m, 4H, quinoxaline protons), 6.95 (dd, 2H, J_{HH} = 9 Hz, meta to P); 5.2 (s, 2H, N–CH_2–S); 3.9 (s, 3H, OCH_3), 3.3 (m, 1H, SCH); 2.3 (s, 3H, CH_3); 1.7–1.2 (m, 10H, cyclic CH_2)
7c	173 Ethanol	75	$C_{23}H_{21}N_4OPS_2$ (464.54)	59.46 59.09	4.55 4.40	12.06 11.91	13.80 13.59	1236 (C–O), 696 (C–S–C), 659 (P=S)	7.90–7.78 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.65–7.15 (m, 9H, quinoxaline protons + Ph); 6.95 (dd, 2H, J_{HH} = 9 Hz, meta to P); 5.7 (s, 2H, N–CH_2–S); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3)
7d	187 Ethanol	59	$C_{24}H_{20}N_5OPS_3$ (521.61)	55.25 54.86	3.86 3.70	13.48 13,29	18.44 18.22	1243 (C–O), 696 (C–S–C), 662 (P=S)	7.92–7.83 (dd, 2H, J_{HH} = 9.2 Hz, ortho to P); 7.35–7.05 (m, 8H, quinoxaline + bezothiazole protons); 6.90 (dd, 2H, J_{HH} = 9 Hz, meta to P); 6.1 (s, 2H, N–CH_2–S); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3)
8a	210 Chloro-form	86	$C_{18}H_{17}N_4O_2PS$ (384.39)	56.24 55.86	4.45 4.27	14.57 14.29	8.34 8.20	1690 (C=O), 1261 (C–O), 649 (P=S)	7.85–7.75 (dd, 2H, J_{HH} = 9.3 Hz, ortho to P); 7.41–7.34 (m, 4H, quinoxaline protons), 6.95 (dd, 2H, J_{HH} = 9.5 Hz, meta to P); 3.9 (s, 3H, OCH_3), 2.4 (s, $COCH_3$); 2.3 (s, 3H, CH_3)
8b	159 Ethanol	86	$C_{23}H_{19}N_4O_2PS$ (446.46)	61.87 61.56	4.29 4.13	12.55 12.40	7.18 7.07	1672 (C=O), 1240 (C–O), 643 (P=S)	7.90–7.78 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.65–7.15 (m, 9H, quinoxaline protons + Ph); 6.95 (dd, 2H, J_{HH} = 9 Hz, meta to P); 3.9 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3)
9	188 Ethanol	78	$C_{19}H_{16}N_5O_2PS$ (409.40)	55.73 55.36	3.94 3.77	17.10 16.91	7.83 7.64	2207 (CN), 1691 (C=O), 1249 (C–O), 644 (P=S)	7.85–7.75 (dd, 2H, J_{HH} = 9.3 Hz, ortho to P); 7.44–7.34 (m, 4H, quinoxaline protons), 6.90 (dd, 2H, J_{HH} = 9.5 Hz, meta to P); 4.8 (s, 2H, CH_2); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3)
10	203 Ethanol	69	$C_{19}H_{16}N_5OPS_2$ (425.46)	53.63 53.22	3.79 3.87	16.46 16.30	15.07 14.83	2211 (CN), 1233 (C–O), 1190 (C=S), 649 (P=S)	7.90–7.78 (dd, 2H, J_{HH} = 9.3 Hz, ortho to P); 7.45–7.35 (m, 4H, quinoxaline protons), 6.90 (dd, 2H, J_{HH} = 9.5 Hz, meta to P); 4.2 (s, 2H, CH_2); 3.9 (s, 3H, OCH_3); 2.2 (s, 3H, CH_3)
11	203 Ethanol	72	$C_{29}H_{22}N_7OPS_2$ (579.63)	60.08 59.72	3.82 3.61	16.91 16.67	11.06 10.83	3366, 3302 (NH_2), 2211 (2CN), 664 (P=S)	7.90–7.80 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.65–7.25 (m, 9H, quinoxaline protons + Ph); 6.90 (dd, 2H, J_{HH} = 9 Hz, meta to P); 5 (br, 2H, NH_2) 3.9 (s, 3H, OCH_3); 3.5 (s, 1H, CH); 2.3 (s, 3H, CH_3)
12a	249 DMF	81	$C_{24}H_{22}N_5O_3PS_2$ (523.56)	55.05 54.68	4.23 4.08	13.37 13.11	12.24 12.05	3352, 3286 (NH_2), 1683, 1659 (2C=O) 661 (P=S)	7.92–7.78 (dd, 2H, J_{HH} = 9.1 Hz, ortho to P); 7.45–7.35 (m, 4H, quinoxaline protons), 6.92 (dd, 2H, J_{HH} = 9.6 Hz, meta to P); 5.4 (br, 2H, NH_2) 3.9(s, 3H, OCH_3); 2.5 (s, 3H, $COCH_3$); 2.2 (s, 3H, N=CCH_3); 2.0 (s, 3H, CH_3)

TABLE 1 Continued

Compound	MP (°C) Crystal Solvent	Yield (%)	Molecular Formula (Molecular weight)	Analytical Data Calcd/Found C	H	N	S	IR (cm^{-1})	^1H NMR, δ (ppm)
12b	221 Ethanol	59	$C_{25}H_{24}N_5O_4PS_2$ (553.59)	54.23 53.92	4.37 4.19	12.65 12.45	11.58 11.37	3319, 3299 (NH_2), 1723 (C=O ester), 1689 (C=O), 661 (P=S)	7.90–7.80 (dd, 2H, J_{HH} = 9.1 Hz, ortho to P); 7.44–7.35 (m, 4H, quinoxaline protons), 6.91 (dd, 2H, J_{HH} = 9.5 Hz, meta to P); 5.4 (br, 2H, $-NH_2$); 4.1 (q, 2H, CH_2); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H N=CCH_3); 2.0 (s, 3H, CH_3); 1.1 (t, 3H, CH_3)
13	153 Ethanol	85	$C_{22}H_{18}N_5O_2PS_3$ (511.57)	51.64 51.35	3.54 3.33	13.69 13.40	18.80 18.61	2209 (CN), 1665 (C=O), 659 (P=S)	7.91–7.80 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.42–7.35 (m, 4H, quinoxaline protons), 6.88 (dd, 2H, J_{HH} = 9.3 Hz, meta to P); 3.3 (t, 4H, J_{HH} = 6.1 Hz, $2SCH_2$); 3.9 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3)
14	132 Ethanol	79	$C_{22}H_{20}N_5O_2PS_3$ (513.59)	51.44 51.08	3.92 3.77	13.63 13.41	18.72 18.55	2200 (CN), 1661 (C=O), 659 (P=S)	7.90–7.77 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.48–7.41 (m, 4H, quinoxaline protons), 6.91 (dd, 2H, J_{HH} = 9.4 Hz, meta to P); 3.9 (s, 3H, OCH_3) 3.2 (s, 6H, $2SCH_3$); 2.3 (s, 3H, CH_3)
15	179 Ethanol	74	$C_{21}H_{20}N_7O_2PS_2$ (497.53)	50.69 50.31	4.05 3.90	19.70 19.40	12.88 12.67	3372, 3321, 3246 ($NH + NH_2$), 1661 (C=O); 663 (P=S)	12.0 (br, 1H, NH); 7.90–7.78 (dd, 2H, J_{HH} = 9.3 Hz, ortho to P); 7.46–7.38 (m, 4H, quinoxaline protons), 6.88 (dd, 2H, J_{HH} = 9.2 Hz, meta to P); 4.8 (br, 2H, NH_2); 3.9 (s, 3H, OCH_3); 3.3 (s, 3H, SCH_3); 2.3 (s, 3H, CH_3)
16	166 Ethanol	76	$C_{22}H_{20}N_7O_2PS$ (477.48)	55.33 54.95	4.22 4.09	20.53 20.38	6.71 6.51	3211 (NH), 2203 (CN), 1660 (C=O), 651 (P=S)	12.0 (br, 1H, NH); 11.2 (br, 1H, NH); 7.90–7.78 (dd, 2H, J_{HH} = 9.1 Hz, ortho to P); 7.46–7.36 (m, 4H, quinoxaline protons), 6.90 (dd, 2H, J_{HH} = 9.5 Hz, meta to P); 3.9 (s, 3H, OCH_3); 3.2 (t, 4H, J_{HH} = 4.6 Hz, $2CH_2$); 2.3 (s, 3H, CH_3)
17a	211 DMF	89	$C_{26}H_{19}N_6O_2PS_2$ (542.57)	57.55 57.31	3.53 3.43	15.48 15.39	11.81 11.67	2209 (CN), 1669 (C=O), 653 (P=S)	7.92–7.83 (dd, 2H, J_{HH} = 9 Hz, ortho to P); 7.40–7.05 (m, 8H, quinoxaline + benzo-thiazole protons); 6.90 (dd, 2H, J_{HH} = 9 Hz, meta to P); 6.1 (s, 1H, CH); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3)
17b	221 DMF	78	$C_{26}H_{19}N_6O_3PS$ (526.51)	59.30 58.91	3.63 3.49	15.96 15.79	6.09 5.99	2201 (CN), 1663 (C=O), 660 (P=S)	7.90–7.83 (dd, 2H, J_{HH} = Hz, ortho to P); 7.38–7.06 (m, 8H, quinoxaline + benzoxazole protons); 6.88 (dd, 2H, J_{HH} = 9 Hz, meta to P); 6.2 (s, 1H, CH); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3)
17c	194 Ethanol	81	$C_{26}H_{20}N_7O_2PS$ (525.52)	59.41 59.00	3.83 3.68	18.65 18.45	6.10 5.98	3269 (NH), 2201 (CN), 1662 (C=O), 650 (P=S)	11.1 (br, 1H, NH); 7.92–7.83 (dd, 2H, J_{HH} = 9.2 Hz, ortho to P); 7.39–7.04 (m, 8H, quinoxaline + benzimidazole protons); 6.90 (dd, 2H, J_{HH} = 9 Hz, meta to P); 6.1 (s, 1H, CH); 3.9 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3)

[a]Uncorrected.
[b]Satisfactory microanalysis obtained (C: ±0.44, H: ±0.19, N: ±0.39, S: ±0. 35).
[c]Measured by Nicolet FT-IR 710 spectrophotometer.
[d]Measured by ^{1}H-NMR LA 400 MHz (Jeol) at the Assiut University.



SCHEME 2

o-aminothiophenol, *o*-aminophenol, and *o*-phenylenediamine in refluxing dimethyl-formamide for about 38 h, to give compounds **15,16** and **17a–c**, respectively. The reaction with hydrazine hydrate was assumed to proceed via a Michael addition of one amino group at the ethylenic bond with the elimination of methyl mercaptan followed by a nucleophilic addition of the other amino group at the cyano group to give compound **15**, whereas the reaction with the other amino compounds proceed via a nucleophilic attack of both the nucleophilic groups at the ethylenic bond with elimination of

two molecules of methyl mercaptan to give compounds **16** and **17a–c**, respectively (cf. Scheme 4 and Table 1).

EXPERIMENTAL

Synthesis of Compound **3**

Lawesson's reagent (2.02 g, 0.005 mol) was added to a solution of the hydrazone (0.01 mol) in 50 mL acetonitrile and refluxed until the evolution of hydrogen sulfide was ceased (12 h). The reaction mixture was concentrated. After cooling, the formed precipitate was filtered off and recrystallized from the appropriate solvent, yield 81% (cf. Table 1).

Synthesis of Compounds **4a–d***: General Procedure*

Formaldehyde (1.5 mL, 40% solution) was added to a solution of compound **3** (0.001 mol) in absolute ethanol (10 mL). The reaction mixture was refluxed for 1 h. After cooling to room temperature, the appropriate amine (0.001 mol) was added. The reaction mixture was refluxed for 4 h. After cooling, the formed precipitate was filtered and recrystallized from the appropriate solvent to give the corresponding Mannich bases **4a–d**, yielding 63%–81% (cf. Table 1).

Synthesis of Compound **5**

Formaldehyde (1.5 mL, 40% solution) was added to a solution of compound **3** (0.001 mol) in absolute ethanol (10 mL). The reaction mixture was refluxed for 1 h, the solvent was evaporated to dryness. The formed solid was recrystallized from ethanol to give compound **5**, yield 66% (cf. Table 1).

Synthesis of Compound **6**

Thionyl chloride (10 mL) was added dropwise to compound **5** (0.005 mol), and the reaction mixture was warmed on a water bath for 1 h. After cooling, the reaction mixture was poured on petroleum ether (100 mL, 40/60°C). The formed precipitate was filtered and recrystallized from ethanol to give compound **6**, yield 69% (cf. Table 1).

Synthesis of Compounds **7a–d***: General Procedure*

The appropriate thiol (0.01 mol) was added to an alcoholic solution of sodium ethoxide (Na, 0.23 g, 0.01 mol in 25 mL ethanol), then compound **6** (0.01 mol) was added in small portions over 10 min. The reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure. The residual solid was washed with cold water, filtered, and recrystallized from ethanol to give the corresponding sulfides **7a–d**, yield 59%–80% (cf. Table 1).

Synthesis of Compounds **8a,b***: General Procedure*

To a solution of compound **3** (0.005 mol) and triethylamine (0.005 mol) in dimethyl-formamide (30 mL), appropriate acid chloride was added in small portions over 5 min. The reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure. The formed precipitate was filtered, washed with cold water, and recrystallized from ethanol to give compounds **8a,b**, yield 86% (cf. Table 1).

Synthesis of Compound **9**

A mixture of compound **3** (0.01 mol), ethyl cyanoacetate (0.01 mol), and sodium *t*-butoxide [Na (0.23 g, 0.01 mol) in 40 mL *t*-butanol] was refluxed for 3 h, evaporated in vacuo, and the separated solid was collected by filtration, washed with water and recrystallized from ethanol, yield 78% (cf. Table 1).

Synthesis of Compound **10**

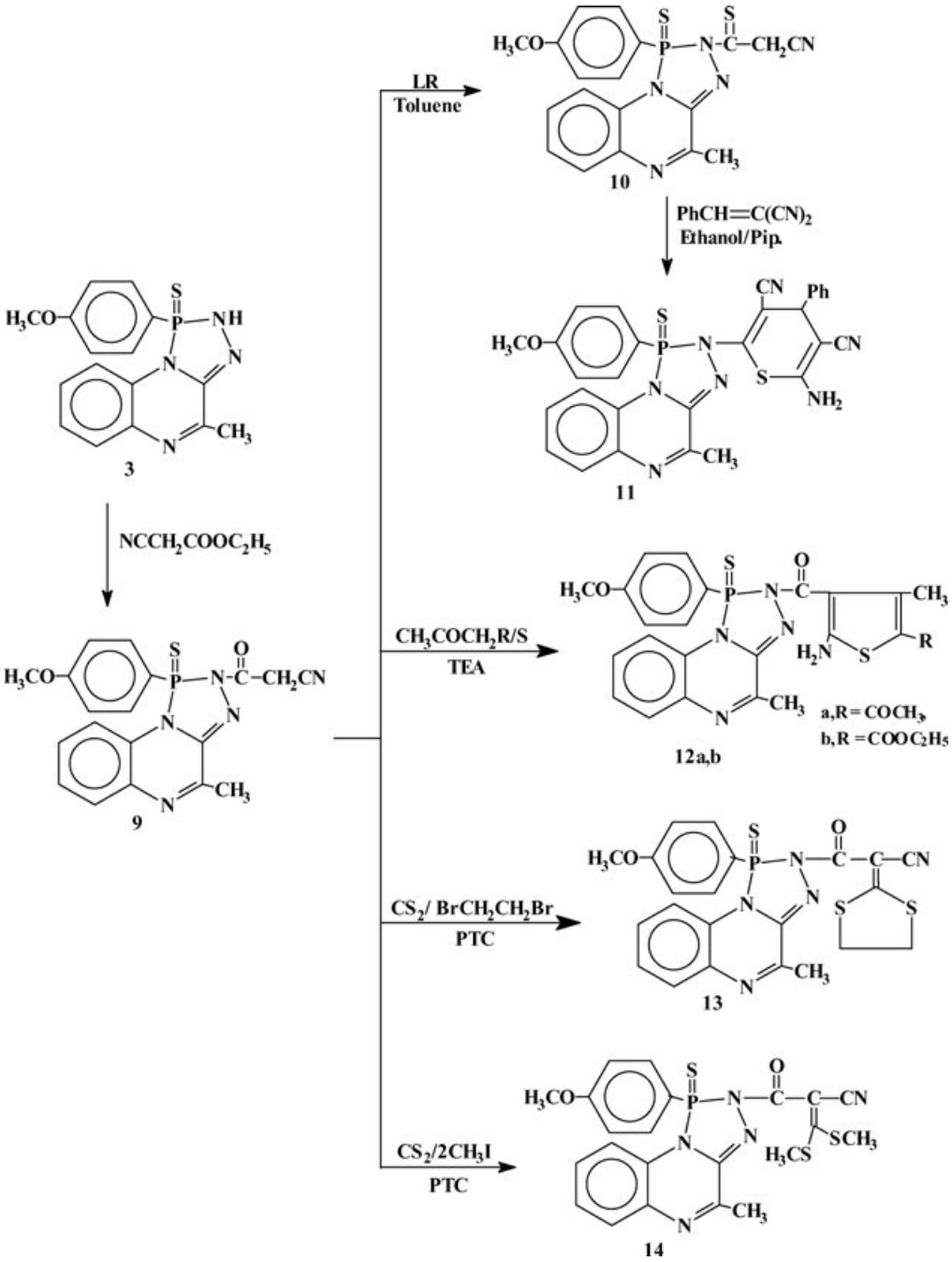
A mixture of compound **9** (0.005 mol) and LR **1** (0.005 mol) in dry toluene (50 mL) was refluxed for 8 h. The reaction mixture was concentrated. The formed precipitate was collected by filtration and recrystallized from ethanol to give compound **10**, yield 69% (cf. Table 1).

Synthesis of Compound **11**

Benzylidenemalononitrile (0.01 mol) was added to a stirred mixture of compound **9** (0.1 mol) and a catalytic amount of piperidine in 50 mL of ethanol. The reaction mixture was refluxed for 5 h, then concentrated, and left to cool. The formed precipitate was filtered off and recrystallized from ethanol, yield 72% (cf. Table 1).

Synthesis of Compound **12a,b***: General Procedure*

To a solution of compound **9** (0.005 mol) in ethanol (50 mL), 0.005 mol of acetylacetone and/or ethyl acetoacetate and sulfur (0.005 mol) were added. The reaction mixture was treated with a catalytic amount of triethylamine (0.5 mL), refluxed for 5 h, evaporated in vacuo and the residual solid was collected

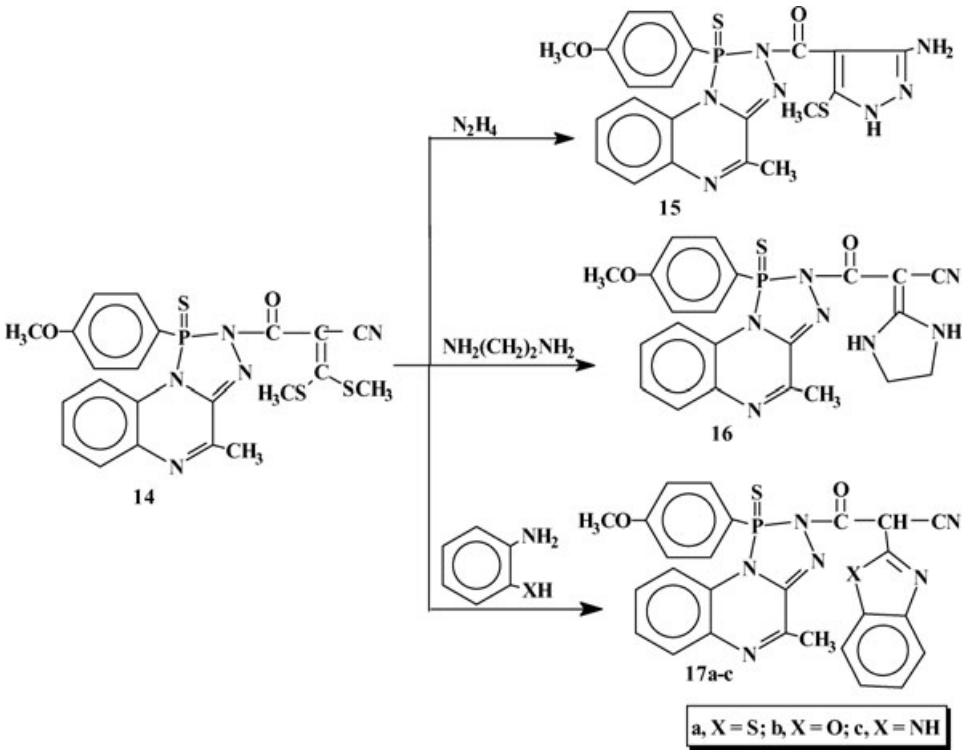


SCHEME 3

by filtration, washed with water and recrystallized from the suitable solvent, yield 59.81% (cf. Table 1).

Synthesis of Compounds **13** *and* **14***: General Procedure*

A mixture of compound **9** (0.01 mol), carbon disulfide (0.012 mol), anhydrous potassium carbonate (3 g), and a catalytic amount of tetrabutylammonium bromide (TBAB) in 50 mL of dry dioxan was stirred for 15 min at 60°C. To the formed dianionic ambident, 1,2-dibromoethane (0.01 mol) and/or methyl iodide (0.02 mol) was added. The reaction mixture was stirred for 3 h at 60°C and then filtered, and the solvent was evaporated under reduced pressure. The residue was triturated with petroleum



SCHEME 4

ether (60–80°C) and recrystallized from appropriate solvent to give compounds **13** and**14**, yield 79% and 85% respectively (cf. Table 1).

Synthesis of Compounds **15,16** *and* **17a–c***: General Procedure*

An equimolar mixture (0.005 mol) of compound **15** and the proper amine in dimethylformamide (25 mL) was refluxed until the evolution of MeSH ceased (~38 h). The reaction mixture was concentrated, and the precipitate solid was collected by filtration, washed with pet. ether 40/60°C, and recrystallized from the suitable solvent to afford compounds **15,16** and **17a–c**, yield 74%–89%, respectively (cf. Table 1).

CONCLUSION

This article introduced a convenient and an efficient method for the synthesis of some new P-heterocycles. The pharmacological activity of the obtained compounds will be tested, expecting that it will be biologically active.

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