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An efficient synthesis of new *N*-pyrazolyl benzodiazaphosphole-2-sulfides conjugates

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Abstract: A series of novel *N*-pyrazolyl benzodiazaphosphole-2-sulfides (**4a-h**) were prepared *via* cyclocondensation reactions between different 5-(2-aminophenylamino)-3-pyrazole derivatives (**3a-h**) and the Lawesson's reagent. Structural elucidations of all compounds were established by mean of 1D-NMR spectroscopy: ^{1}H, ^{13}C, ^{31}P, 2D-NMR techniques and HRMS analysis.

Keywords: 1,5-benzodiazepines, pyrazoles, Lawesson's reagent, diazaphosphole-2-sulfides.

Résumé: Une série de nouveaux *N*-pyrazolyl benzodiazaphosphole-2-sulfides **(4a-h)** ont été synthétisés par condensation entre des dérivés de type 5-(2-aminophénylamino)-3-pyrazoles **(3a-h)** et le réactif de Lawesson. Tous les produits ont été caractérisés par spectroscopie de RMN 1D : ^{1}H, ^{13}C, ^{31}P, RMN 2D et par spectrométrie de masse à haute résolution (SMHR).

Mots-clés: 1,5-benzodiazépines, pyrazoles, réactif de Lawesson, diazaphosphole-2-sulfides.

INTRODUCTION

Organophosphorus heterocycles are well considered for their use in the field of agriculture, medicine and industry. [1,2] In particular, compounds containing a benzodiazaphosphole ring have acquired much importance because of their insecticide, bactericidal, antiviral and anticarcinogenic properties. [3-5] On another hand, among the nitrogenated heterocycles those possessing the pyrazole core are also well recognized for their broad spectrum of anti-tumoral, [6] cytotoxic, [7] anti inflammatory, [8] antimicrobial, [9] and antihypertensive [10] activities.

As a part of our continuing efforts directed toward the development of novel protocols for the synthesis of biologically relevant heterocyclic compounds associating (fusing or linking) two privileged heterocyclic moieties within a same framework, [11-14] we became interested to explore newer methodologies for the access to novel hybrid conjugates linking the pyrazole ring-system to a benzodiazaphosphole-2-sulfide moiety and we report herein our results.

RESULTS AND DISCUSSION

According to what have been previously published by numerous research groups about the heterophosphole scaffold's synthesis, our methodology centered on the ability of the Lawesson's reagent (LR= 2,4-bis-(*p*-methoxyphenyl)-1,2,3,4-dithiaphosphetane-2,4-sulfide) to promote many heterocyclization reactions. Indeed although the classical application of this reagent is for the thionation of carbonyl

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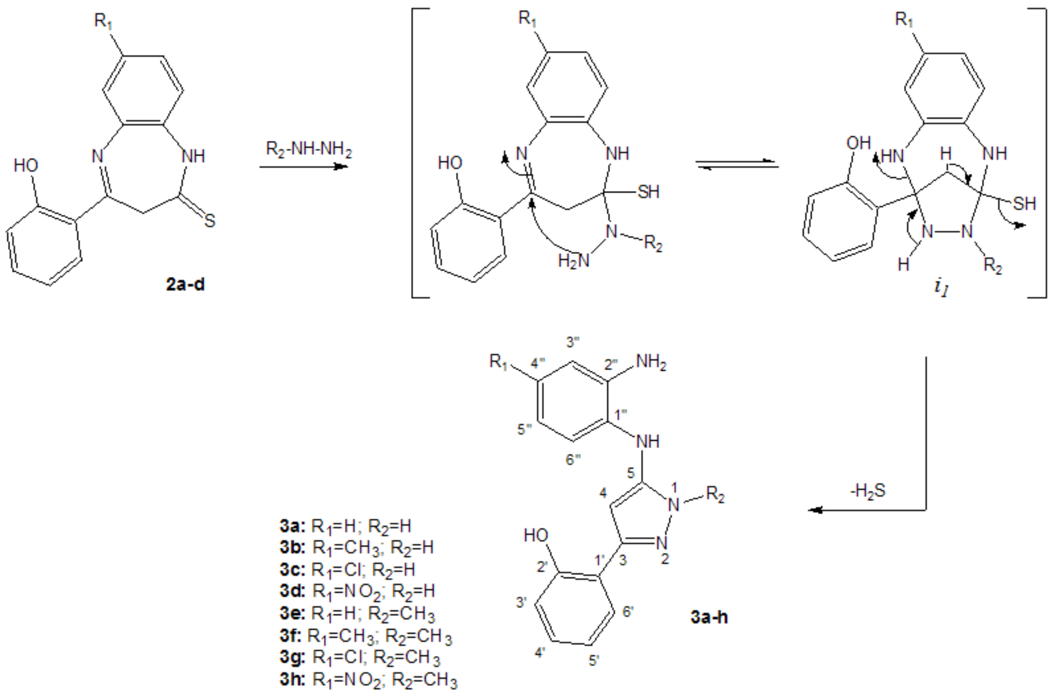
compounds, [15,16] it may act as a dielectrophilic species, capable of reacting with a variety of binucleophiles, which leads to closure of a phosphorus heterocycles. [17-19]

In particular, the reaction of the LR with catechols, *o*-aminophenols and *o*-phenylenediamines has proven to be an efficient route to anisyl derivatives of benzodiazaphosphole-2-sulfides with hetero-atoms in positions 1 and 3.[19] Based on these bibliographic data, we have become interested in the behavior of the Lawesson's reagent towards the 5-(2-aminophenylamino)-3-1*H*-pyrazole (**3a-h**). In the first step of the work we have revisited our previously described synthesis of the key-intermediates of type **3**. Thus the treatment of a series of 1,5-benzodiazepine-2-thiones (**2a-d**) with a slight excess of hydrazine (or methylhydrazine) in refluxing ethanol led to a series of 5-(2-aminophenylamino)-3-1*H*-pyrazole derivatives (**3a -h**) as a result of the heptatomic ring contraction (Scheme 1).[12,13]

As described below our spectroscopic study have confirmed the structure of pyrazoles **3** and was consistent with the mechanism we have suggested. As depicted in scheme 1 and by referring to what have been previously reported, [20,21] it is plausible to conceive that for the derivatives (**3e-h**) the more reactive nitrogen of the methylhydrazine firstly reacts at the thiocarbonyl, this was followed by an internal cyclization *via* an addition of the free amino group on the imine functionality of the benzodiazepine ring. The so formed bicyclic intermediates *i*$_1$ undergoes a ring contraction involving a C-N bond scission and an aromatization of the pyrazole ring with a concomitant elimination of a H_2S molecule.

Total structural assignments for the pyrazoles derivatives which are not so far reported in the literature (**3b-h**), are described in the experimental section. For example, derivative **3f** (R_1=R_2= CH_3) the ^{13}C NMR spectrum, showed characteristic signals related to the pyrazolic moiety namely *N*-CH_3 (δ_C= 34.9 ppm) and the ethylenic C-4 (87.9 ppm). Long-range C-H correlations between H-4 and quaternary C-3 (δ_C = 146.4 ppm), C-5 (δ_C= 148.7 ppm) and C-1" (δC= 140.9 ppm), have been detected from the HMBC map, thereby proving the sequence C-3-C-4-C-5-N-C-1" within the 3,5-disubstituted pyrazole moiety. Moreover the molecular ion-peak at m/z= 295.1561 was detected from the **3f** HRMS (ESI) spectrum and corroborated the formula $C_{17}H_{19}N_4O$ $[M+H]^+$.

The second step of the work was the study of the reaction between the bifunctional compound **3** and the Lawesson's Reagent with the aim to build the heterophosphole-2-sulfide skeleton and thereby



Scheme 1. Synthetic pathway and proposed mechanism for the formation of pyrazoles **3a-h**.

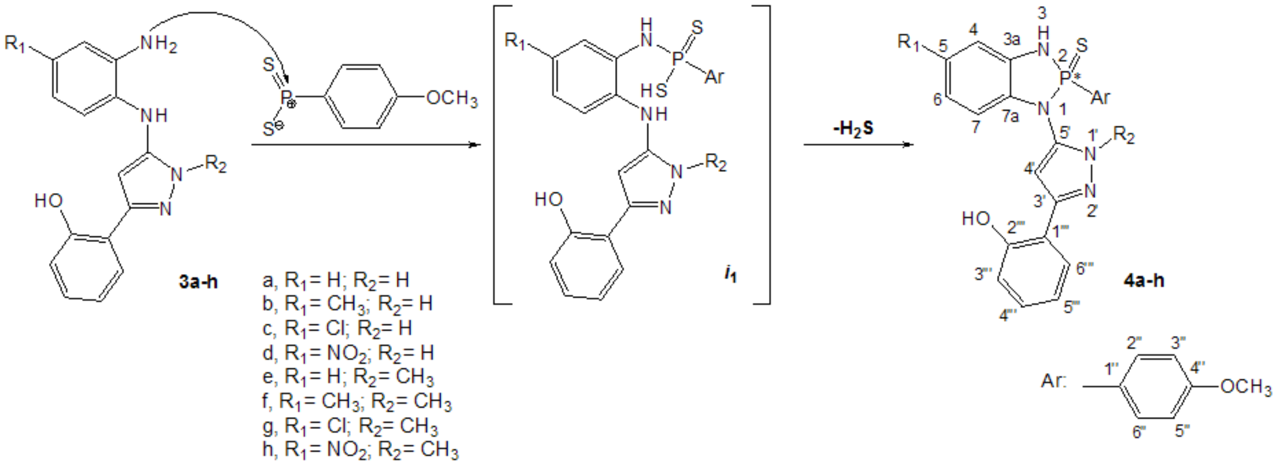
reach the targeted benzodiazaphosphole linked pyrazole conjugates **4**. Thus compounds **3a-h** were allowed to react with L.R. (1.3 equivalents) under refluxing anhydrous toluene. The reaction monitored by TLC led to the formation of a single product which was purified by flash chromatography (petroleum ether/ethyl acetate 3:2) and assigned as *N*-pyrazolyl-benzo[1,3,2]diazaphosphole 2-sulfides (**4a-h**).

The ^{1}H NMR spectrum of compound **4e**, chosen as an illustration example, exhibited signals which are according to chemical shifts and multiplicities, were consistent with the proposed structure. Thus the two singlets each integrating three protons (3.87 ppm and 3.89 ppm) were assigned as the *N*-methyl and the methoxy groups respectively. On another hand the location of the diazaphosphole moiety was supported by the ^{13}C and 2D-NMR. Thus a HMBC analysis exhibited a long-range correlations between the pyrazolic proton H-4' and the C-5' (133.8 ppm) and C-7a (133.4 ppm) thereby proving the sequence C-4'-C-5'-N-C-7a within the benzodiazaphosphole skeleton. The **4e** HRMS (ESI) spectra gave an additional proof as the peak at 449.1203 supported a molecular composition of $C_{23}H_{22}N_4O_2PS$ $[M+H]^+$. One can, also note that, the heterocyclization process should necessary lead to an asymmetrical phosphorus atom giving rise to a pair of enantiomers of molecule **4**. The presence of the phosphorus atom in benzodiazaphosphole moiety **4a-h**, affects the multiplicity of the NH signals in the ^{1}H NMR spectra. Thus, the signal of the amine NH group, is split into a doublet with $^2J_{P\text{–}H}$ = 18-18.6 Hz (compound **4b-h**) or appears as a broad singlet (compounds **4a**) due to coupling with the phosphorus atom. However, the signals of the anisyl group protons are double doublets with a typical *ortho* constant $^3J_{H\text{–}H}$ = 8.4-8.7 Hz, constants $^3J_{P\text{–}H}$ = 3.3 and $^4J_{P\text{–}H}$ = 13.3-15.3 Hz (see experimental section).

As to the mechanism of compounds **4** formation, it is suggested that under the heating conditions, a nucleophilic attack of the free amino group of the binucleophile **3** should take place at the phosphorus atom of the monomeric species of LR to form intermediates i_1 followed by a ring closure consequent to an elimination of H_2S molecule (Scheme 2). [22-24]

Encouraged by the above mentioned results we were prompted to study the use of a microwave protocol in order to isolate hybrids **4** under neat conditions and shorter times-reaction. Thus, pyrazoles **3** were treated with stoichiometric amounts of LR under solvent-free microwave irradiations. The optimal conditions for the best compound’s **4** yields are summarized in table I.

From the results described in the table, it arouse that the microwave-assisted under solvent-free conditions procedure is in overall competitive with the conventional heating (reflux in toluene) since it leads to better yields and requires shorter reaction times. On another hand it is noticeable that whatever the method we have used lower yields were obtained when the binucleophile was methylated at the position one (derivatives **3e-h**). In this case the reluctance for the heterocyclization may probably be rationalized in terms of a steric hindrance occurring between the methyl and the anisyl groups in the pyrazolo-benzodiazaphosphole



Scheme 2. Proposed mechanism for the formation of compounds **4**.

Table I: Study of the influence of the irradiation-time/microwave power on the yields for compounds **4**

Entry	R^1	R^2	Product	Reflux		MW		
				Yield (%)	Time (hrs)	Yield (%)	Time (minutes)	Power (W)
3a	H	H	**4a**	50	3	80	15	400
3b	CH_3	H	**4b**	48	3	73	20	300
3c	Cl	H	**4c**	58	5	68	25	400
3d	NO_2	H	**4d**	25	7	37	30	300
3e	H	CH_3	**4e**	48	4	50	20	400
3f	CH_3	CH_3	**4f**	40	4	44	20	300
3g	Cl	CH_3	**4g**	45	5	48	30	400
3h	NO_2	CH_3	**4h**	20	7	29	35	300

-2-sulfide structure. As shown in figure 1 the calculations results of the minimized energy structure by (MM2 and AM1) of compound **4** are consistent with the steric considerations we have above proposed.

Minimized energy structure by (MM2 and AM1) of compound **4f**. The optimization was carried out using semi-empirical calculation with MM2 and AM1 force fields. The optimization was carried out for 50,000 steps. Calculations were performed using ChemOffice softwaredeveloped by Cambridge Soft.

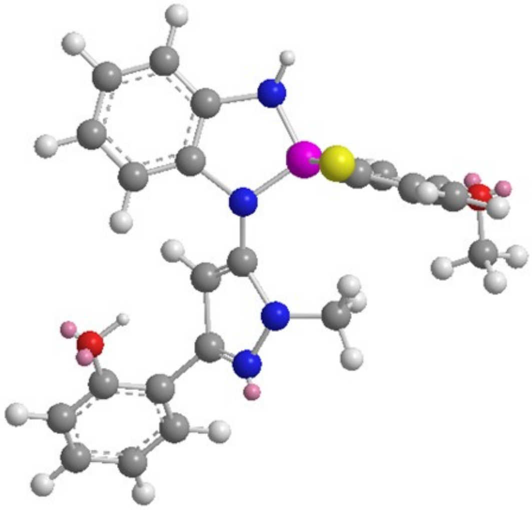


Figure 1.

EXPERIMENTAL SECTION

All air-sensitive reactions were carried out under argon. Melting points were taken on a Buchi-510 capillary apparatus. Flash column chromatography was performed on silica gel chromatography with 32-64 mesh silica and analytical TLC was carried out on pre-coated silica gel plates (Silica gel 60, F254, sds). Organic extracts were dried over anhydrous sodium sulfate. The ^1H-, ^{13}C- and ^{31}P-NMR spectra were taken on AMX 300 MHz spectrometer operating at 300 MHz for ^1H, 75.47 MHz for ^{13}C and 121.4 MHz for ^{31}P, in deuterated acetone, chloroform and dimethylsulfoxyde with all chemical shifts (δ), reported in ppm, refereed to residual non deuterated solvent. High Resolution Mass spectra HRMS (ESI) were recorded with a LCT Premier XE (Waters, ESI technique, positive and negative mode) mass spectrometer. For ESI experiments, leucine-enkephalin peptide was employed as the LockSpray lockmass at L. C-TAC (Paris Descartes, France) and HRMS (GC-MS) were acquired on a Bruker MicrO-Tof-Q spectrometer at INRAP (Tunisia). The annotation brs is used when signals are broad.

SYNTHESIS

1. General procedure for the synthesis of pyrazoles 3b-h

To a stirred solution of compound **2** (1 g, 2 mmol) in ethanol (50 mL) was added hydrazine monohydrate or methylhydrazine (1.5 equivalents). The reaction mixture was slowly heated for 30 minutes. A stirring at room temperature was continued for 2 hrs until completion of the reaction. The mixture was poured into ice-cold water and was extracted with ethyl acetate (3 × 25 mL), the combined extracts were washed with water and were removed *in vacuo*.

Let's notice that derivative **3a** which has been previously prepared by co-workers of our team is not described in this experimental section. [12]

***5-(2-amino-4-methyl-phenylamino)-3-(2-hydroxyphenyl)-1H-pyrazole* 3b**

White solide (65%); m.p 175-177 °C. ^{1}H NMR (DMSO-d_6): δ 2.14 (s, 3H, H-7''), 4.69 (brs, 2H, NH_2), 6.09 (s, 1H, H-4), 6.34 (d, *J*= 7.8 Hz, 1H, H-6''), 6.52 (s, 1H, H-3''), 6.80-6.90 (m, 2H, H-5''-H-3'), 7.10 (t, *J*= 6.9 Hz, 2H, H-4'-5'), 7.54 (d, *J*= 7.5 Hz, 1H, H-6'), 11.30 (brs, 2 × NH), 11.31 (brs, OH). ^{13}C NMR (DMSO-d_6): δ 20.5 (C-7''), 94.1 (C 4), 115.3 (C-3''), 115.9 (C-3'), 116.2 (C-6''), 116.9 (C-5''), 117.4 (C-1'), 119.0 (C-5'), 126.6 (C 6'), 128.4 (C-4''), 128.9 (C-4'), 135.2 (C-2''), 136.3 (C-1''), 143.1 (C-3), 150.0 (C-5), 154.9 (C-2'). HRMS (ESI) for $C_{16}H_{17}N_4O$ [M+H]$^+$ Anal. calcd. 281.1402; found 281.1406.

***5-(2-amino-4-chlorophenylamino)-3-(2-hydroxyphenyl)-1H-pyrazole* 3c**

Green solide (59%); m.p 220-222°C. ^{1}H NMR (Acetone-d_6): δ 4.76 (brs, 2H, NH_2), 6.12 (s, 1H, H -4), 6.62 (d, *J*= 8.4 Hz, 1H, H-6''), 6.81-6.90 (m, 3H), 7.12 (t, *J*= 6.9 Hz, 2H, H-4'-5'), 7.55 (d, *J*= 7.5 Hz, 1H, H-6'), 11.15 (brs, 2 × NH), 11.46 (brs, OH). ^{13}C NMR (Acetone-d_6): δ 87.4 (C 4), 116.0 (C-3''), 117.3 (C-3'), 118.0 (C-5''), 118.1 (C-6''), 119.7 (C-1'), 123.6 (C-5'), 126.4 (C-4''), 127.4 (C-6'), 129.4 (C-4'), 136.3 (C-2''), 138.0 (C-1''), 142.8 (C-3), 143.4 (C-5), 157.2 (C-2'). HRMS (ESI) for $C_{15}H_{14}ClN_4O$ [M+H]$^+$ Anal. calcd. 301.0856; found 301.0858.

***5-(2-amino-4-nitrophenylamino)-3-(2-hydroxyphenyl)-1H-pyrazole* 3d**

Yellow solide (45%); m.p 200-202 °C. ^{1}H NMR (Acetone-d_6): δ 4.80 (brs, 2H, NH_2), 6.18 (s, 1H, H -4), 6.64 (d, *J*= 8.2 Hz, 1H, H-6''), 6.80-6.90 (m, 2H), 6.91-6.93 (m, 1H), 7.15 (t, *J*= 7.1 Hz, 2H, H-4'-5'), 7.58 (d, *J*= 7.2 Hz, 1H, H-6'), 11.09 (brs, 2 × NH), 11.48 (brs, OH). ^{13}C NMR (Acetone-d_6): δ 87.2 (C 4), 113.1 (C-3''), 113.8 (C-5''), 117.0 (C-3'), 117.9 (C-6''), 119.7 (C-1'), 122.6 (C-5'), 127.8 (C 6'), 129.9 (C-4'), 137.0 (C-2''), 138.9 (C-4''), 139.9 (C-1''), 143.1 (C-3), 143.9 (C-5), 157.5 (C-2'). HRMS (ESI) for $C_{15}H_{14}N_5O_3$ [M+H]$^+$ Anal. calcd. 312.1097; found 312.1002.

***5-(2-aminophenylamino)-3-(2-hydroxyphenyl)-N-methylpyrazole* 3e**

White solide (69%); m.p 130-132 °C. ^{1}H NMR (DMSO-d_6): δ 3.74 (s, 3H, NCH_3), 4.83 (brs, 2H, NH_2), 6.04 (s, 1H, H-4), 6.54 (t, *J*= 7.2 Hz, 1H, H-6''), 6.75-6.89 (m, 5H), 6.98-7.16 (m, 1H), 7.53 (d, *J*= 7.5 Hz, 1H, H-6'), 10.12 (brs, NH), 10.86 (brs, OH). ^{13}C NMR (DMSO-d_6): δ 34.9 (NCH_3), 89.2 (C 4), 115.4 (C-3''), 116.2 (C-6''), 116.8 (C-3'), 117.1 (C-5''), 118.9 (C-4''), 120.5 (C-1'), 123.5 (C-5'), 126.3 (C 6'), 128.4 (C-4'), 128.5 (C-2''), 140.2 (C-1''), 145.6 (C-3), 148.7 (C-5), 155.4 (C-2'). HRMS (ESI) for $C_{16}H_{17}N_4O$ [M+H]$^+$ Anal. calcd. 281.1402; found 281.1068.

***5-(2-amino-4-methyl-phenylamino)-3-(2-hydroxyphenyl)-N-methylpyrazole* 3f**

White solide (64%); m.p 136-138 °C. ^{1}H NMR (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 3.70 (s, 3H, NCH_3), 4.76 (brs, 2H, NH_2), 5.85 (s, 1H, H-4), 6.34 (d, *J*= 7.2 Hz, 1H, H-6''), 6.55 (s, 1H, H-3''), 6.74-6.78 (m, 1H, HH-5''), 6.81-6.85 (m, 1H, H-3'), 7.04-7.07 (m, 1H, H-5'), 7.10 (t, 1H, H-4'), 7.47 (d, *J*= 7.5 Hz, 1H, H-6'), 10.10 (brs, NH), 10.91 (brs, OH). ^{13}C NMR (DMSO-d_6): δ 20.6 (CH_3), 34.9 (NCH_3), 87.9 (C 4), 116.0 (C-3''), 116.2 (C-6''), 117.0 (C-3'), 117.4 (C-5''), 118.9 (C-1'), 122.0 (C-5'), 125.5 (C-4''), 126.2 (C 6'), 128.3 (C-4'), 133.0 (C-2''), 140.9 (C-1''), 146.4 (C-3), 148.7 (C-5), 155.4 (C-2'). HRMS (ESI) for $C_{17}H_{19}N_4O$ [M+H]$^+$ Anal. calcd. 295.1559; found 295.1561.

***5-(2-amino-4-chlorophenylamino)-3-(2-hydroxyphenyl)-N-methylpyrazole* 3g**

White solide (49%); m.p 153-155 °C. ^{1}H NMR (Acetone-d_6): δ 3.78 (s, 3H, NCH_3), 4.80 (brs, 2H, NH_2), 5.82 (s, 1H, H-4), 6.63-6.79 (m, 2H), 6.81-6.88 (m, 3H), 7.00 (t, *J*=7.2 Hz, 1H, H-4'), 7.47 (d, *J*= 6.3 Hz, 1H, H-6'), 9.84 (brs, NH), 10.91 (brs, OH). ^{13}C NMR (Acetone-d_6): δ 35.2 (NCH_3), 90.2 (C 4), 115.8 (C-3''), 116.9 (C-6''), 117.8 (C-3'), 118.0 (C-5''), 120.5 (C-1'), 123.8 (C-5'), 126.0 (C-4''), 128.6 (C 6'), 130.9 (C-4'), 132.3 (C-2''), 140.2 (C-1''), 146.3 (C-3), 150.8 (C-5), 155.7 (C-2'). HRMS (ESI) for $C_{16}H_{16}ClN_4O$ [M+H]$^+$ Anal. calcd. 315.1013; found 315.1020.

***5-(2-amino-4-nitrophenylamino)-3-(2-hydroxyphenyl)-N-methylpyrazole* 3h**

Yellow solide (35%); m.p 125-127 °C. ^{1}H NMR (Acetone-d_6): δ 3.30 (s, 3H, NCH_3), 4.81 (brs, 2H, NH_2), 5.84 (s, 1H, H-4), 6.67-6.83 (m, 2H), 6.90-

7.33 (m, 4H), 7.70 (d, J= 6.3 Hz, 1H, H-6'), 9.98 (brs, NH), 10.90 (brs, OH). ^{13}C NMR (Acetone-d_6): δ 35.0 (NCH$_3$), 90.1 (C 4), 115.6 (C-3"), 116.3 (C-6"), 117.9 (C-3'), 118.2 (C-5"), 120.3 (C-1'), 123.5 (C-5'), 128.4 (C 6'), 130.5 (C-4'), 133.6 (C-2"), 137.0 (C-4"), 141.3 (C-1"), 146.8 (C-3), 150.3 (C-5), 155.5 (C-2'). HRMS (ESI) for $C_{16}H_{16}N_5O_3$ [M+H]$^+$ Anal. calcd. 326.1253; found 326.1260.

2. General procedure for the synthesis of *N*-pyrazolyl-benzodiazaphospholes 2-sulfide 4a-h.

A suspension of **3** (1 mmol) and Lawesson's reagent (1.3 mmol) in anhydrous toluene (50 mL) were heated under reflux for 3-7 hrs. The same reaction was also carried out in an open vessel under solvent-free conditions and microwaves in a bis-mode oven (300-400 W). The progress of the reaction was monitored by thin layer chromatography (TLC) in a 3:2 mixture of petroleum ether and ethyl acetate as mobile solvents. The residue obtained after removing the solvent under *vacuo* was chromatographed on silica gel, employing petroleum ether/ethyl acetate; 7:3 as eluent system affording pure compounds **4a-h.**

1-(3-(2-hydroxyphenyl)-1H-pyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-benzo[1,3,2] diazaphosphole 2-sulfide 4a

White solide (80%); m.p 102-104°C. ^{1}H NMR (CDCl$_3$) δ 3.85 (s, 3H, OCH$_3$), 5.91 (brs, NH), 6.24 (s, 1H, H-4'), 6.74-6.81 (m, 2H, H-4,7), 6.96 (dd, $J_{P\text{-}H}$= 3.3 Hz, J= 8.7 Hz, 2H, H-3",5"), 7.01-7.04 (m, 1H, H-5), 7.19-7.24 (m, 3H, H-6,3''',5'''), 7.33 (t, J= 7.2 Hz, 1H, H-4'''), 7.56 (d, J= 7.5 Hz, 1H, H -6'''), 7.83 (dd, $J_{P\text{-}H}$= 15.3 Hz, J= 8.7 Hz, 2H, H-2",6"), 10.65 (brs, 1H, NH). 10.69 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 55.5 (OCH$_3$), 92.1 (C-4'), 114.1 (d, $J_{C\text{-}P}$= 17.3 Hz, C-3"-5"), 116.3 (C-3'''), 119.1 (C-4,7), 119.8 (C-5,6), 123.8 (C-1'''), 124.8 (C-5'''), 125.3 (d, C-1", $J_{C\text{-}P}$= 7.5 Hz), 128.0 (C-6'''), 130.6 (C-4'''), 134.1 (d, $J_{C\text{-}P}$= 15.1 Hz, C-2",6"), 134.4 (C-3a), 136.0 (C-7a), 143.0 (C-3'), 147.8 (C-5'), 159.3 (C-2'''), 164.0 (C-4"). ^{31}P NMR (120 MHz, CDCl$_3$): d 70.79 ppm. HRMS (ESI) for $C_{22}H_{20}N_4O_2PS$ [M+H]$^+$ Anal. calcd. 435.1045; found 435.1049.

1-(3-(2-hydroxyphenyl)-1H-pyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-4-methyl-benzo [1,3,2]diazaphosphole 2-sulfide 4b

White solide (73%); m.p 104-106°C. ^{1}H NMR (CDCl$_3$) δ 2.28 (s, 3H, CH$_3$), 3.85 (s, 3H, OCH$_3$), 5.72 (d, 1H, NH, $J_{P\text{-}H}$ = 18 Hz), 6.17 (s, 1H, H-4'), 6.56-6.62 (m, 2H, H-4,7), 6.99-7.08 (m, 3H, H-3",5",6), 7.18-7.34 (m, 3H, H-3''',5''',4'''), 7.55 (d, J= 7.2 Hz, 1H, H-6'''), 7.82 (dd, $J_{P\text{-}H}$= 15.3 Hz, J= 8.7 Hz, 2H, H-2",6"), 10.64 (brs, 1H, NH), 10.68 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 21.0 (CH$_3$), 55.4 (OCH$_3$), 92.0 (C 4'), 114.1 (d, $J_{C\text{-}P}$= 17.4 Hz, C-3",5"), 116.0 (C-4), 116.8 (C-3'''), 119.7 (C-7), 121.4 (C-6), 123.3 (C-1'''), 124.7 (C-5'''), 124.8 (d, C-1", $J_{C\text{-}P}$= 7.8 Hz), 125.2 (C-6'''), 125.3 (C-5), 130.5 (C-4'''), 134.0 (d, $J_{C\text{-}P}$= 15.2 Hz, C-2",6"), 134.5 (C-3a), 136.1 (C-7a), 143.8 (C-3'), 147.9 (C-5'), 159.9 (C-2'''), 164.0 (C-4"). ^{31}P NMR (120 MHz, CDCl$_3$): d 70.73 ppm. HRMS (ESI) for $C_{23}H_{22}N_4O_2PS$ [M+H]$^+$ Anal. calcd. 449.1201; found 449.1204.

1-(3-(2-hydroxyphenyl)-1H-pyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-4-chlorobenzo[1,3,2] diazaphosphole 2-sulfide 4c

White solide (68%); m.p 152-154 °C. ^{1}H NMR (CDCl$_3$) δ 3.85 (s, 3H, OCH$_3$), 5.34 (d, 1H, NH, $J_{P\text{-}H}$ = 18.3 Hz), 6.73 (s, 1H, H-4'), 6.84-6.88 (m, 2H, H-4,7), 6.95-6.97 (m, 1H, H-6), 7.17 (dd, $J_{P\text{-}H}$= 3.3 Hz, J= 8.7 Hz, 2H, H-3",5"), 7.20-7.25 (m, 2H, H-3''',5'''), 7.33 (t, J= 7.3 Hz, 1H, H-4'''), 7.57 (d, J= 7.2 Hz, 1H, H-6'''), 7.84 (dd, $J_{P\text{-}H}$= 15.3 Hz, J= 8.7 Hz, 2H, H-2",6"), 10.66 (brs, 1H, NH), 10.69 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 55.6 (OCH$_3$), 96.1 (C 4'), 114.0 (d, $J_{C\text{-}P}$= 17.0 Hz, C-3",5"), 115.6 (C-4), 115.7 (C-3'''), 119.8 (C-7), 122.5 (C-6), 124.5 (C-1'''), 124.9 (C-5'''), 125.0 (d, C-1", $J_{C\text{-}P}$= 8 Hz), 125.7 (C-6'''), 126.2 (C-5), 130.8 (C-4'''), 134.0 (d, $J_{C\text{-}P}$= 15.2 Hz, C-2",6"), 134.3 (C-3a), 136.0 (C-7a), 143.5 (C-3'), 147.6 (C-5'), 159.8 (C-2'''), 164.0 (C-4"). ^{31}P NMR (120 MHz, CDCl$_3$): d 70.37 ppm. HRMS (ESI) for $C_{22}H_{19}ClN_4O_2PS$ [M+H]$^+$ Anal. calcd 469.0655; found 469.0657.

1-(3-(2-hydroxyphenyl)-1H-pyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-4-nitrobenzo[1,3,2] diazaphosphole 2-sulfide 4d

Yellow solide (37%); m.p 123-125 °C. ^{1}H NMR (CDCl$_3$) δ 3.86 (s, 3H, OCH$_3$), 5.17 (d, 1H, NH, $J_{P\text{-}H}$ = 18.6 Hz), 6.73 (s, 1H, H-4'), 6.82-6.83 (m, 1H, H-7), 6.92-6.99 (m, 3H), 7.17 (dd, $J_{P\text{-}H}$= 2.7 Hz, J= 8.7 Hz, 2H, H-3",5"), 7.32 (d, J= 7.8 Hz, 1H, H-4), 7.75 (m, 2H, H-6, 6'''), 7.87 (dd, 2H, H-2",6", $J_{P\text{-}H}$= 15 Hz, J= 8.7 Hz), 10.52 (brs, 1H, NH), 10.57 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 55.5 (OCH$_3$), 96.0 (C 4'), 110.9 (C-4), 111.0 (C-6), 114.0 (d, $J_{C\text{-}P}$= 17.3 Hz, C-3",5"), 115.6 (C-3'''), 119.8 (C-7), 124.5 (C-1'''), 124.9 (C-5'''), 125.6 (d, C-1", $J_{C\text{-}P}$= 7.6 Hz), 126.1 (C-6'''), 130.7 (C-4'''), 134.1 (d, $J_{C\text{-}P}$= 15.2 Hz, C-2",6"), 134.4 (C-3a), 136.3 (C-5), 140.0

(C-7a), 142.7 (C-3'), 146.5 (C-5'), 158.7 (C-2'''), 163.9 (C-4''). ^{31}P NMR (120 MHz, CDCl$_3$): d 70.35 ppm. HRMS (ESI) for $C_{22}H_{19}N_5O_4PS$ [M+H]$^+$ Anal. calcd 480.0895; found 480.0897.

***1-(3-(2-hydroxyphenyl)-N-methylpyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-benzo[1,3,2] diazaphosphole 2-sulfide* 4e**

White solide (50%); m.p 111-113 °C. ^{1}H NMR (CDCl$_3$) δ 3.88 (s, 3H, NCH$_3$), 3.89 (s, 3H, OCH$_3$), 5.42 (d, 1H, NH, J_{P-H} = 18 Hz), 5.89 (s, 1H, H-4'), 6.32 (d, J= 7.5 Hz, 1H, H-7), 6.81-6.86 (m, 2H), 6.90-7.00 (m, 5H), 7.17-7.26 (m, 2H), 7.81 (dd, J_{P-H}= 13.5 Hz, J= 8.7 Hz, 2H, H-2'',6''), 10.70 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 36.3 (NCH$_3$), 55.0 (OCH$_3$), 101.1 (C 4'), 113.3 (d, J_{C-P}= 16.6 Hz, C-3'',5''), 115.7 (C-3'''), 116.7 (C-4,7), 118.6 (C-5,6), 120.5 (C-1'''), 121.1 (C-5'''), 125.5 (d, C-1'', J_{C-P}= 8 Hz), 128.7 (C-6'''), 132.0 (C-4'''), 132.3 (d, J_{C-P}= 15.0 Hz, C-2'',6''), 132.5 (C-3a), 133.4 (C-7a), 133.6 (C-3'), 133.8 (C-5'), 155.3 (C-2'''), 163.0 (C-4''). ^{31}P NMR (120 MHz, CDCl$_3$): d 73.70 ppm. HRMS (ESI) for $C_{23}H_{22}N_4O_2PS$ [M+H]$^+$ Anal. calcd. 449.1201; found 449.1203.

***1-(3-(2-hydroxyphenyl)-N-methylpyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-4-methyl-benzo [1,3,2]diazaphosphole 2-sulfide* 4f**

White solide (44%); m.p 128-130 °C. ^{1}H NMR (CDCl$_3$) δ 2.31 (s, 3H,CH$_3$), 3.87 (s, 3H, NCH$_3$), 3.90 (s, 3H, OCH$_3$), 5.39 (d, 1H, NH, J_{P-H} = 18.6 Hz), 5.88 (s, 1H, H-4'), 6.21 (d, J= 7.8 Hz, 1H, H-7), 6.62 (d, J= 8.1 Hz, 1H, H-4), 6.72-6.86 (m, 2H), 6.93-7.00 (m, 3H), 7.14-7.26 (m, 2H), 7.82 (dd, J_{P-H}= 14.4 Hz, J= 8.4 Hz, 2H, H-2'',6''), 10.69 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 20.6 (CH$_3$), 36.3 (NCH$_3$), 55.0 (OCH$_3$), 100.4 (C 4'), 113.2 (d, J_{C-P}= 16.6 Hz, C-3'',5''), 115.7 (C-3'''), 116.6 (C-4), 118.6 (C-7) 119.0 (C-6), 120.6 (C-1'''), 121.2 (C-5'''), 125.5 (d, C-1'', J_{C-P}= 7.7 Hz), 128.7 (C-6'''), 130.9 (C-5), 131.4 (C-4'''), 131.4 (d, J_{C-P}= 14.8 Hz, C-2'',6''), 132.5 (C-3a), 133.3 (C-7a), 133.5 (C-3'), 133.8 (C-5'), 155.3 (C-2'''), 162.9 (C-4''). ^{31}P NMR (120 MHz, CDCl$_3$): d 73.97 ppm. HRMS (ESI) for $C_{24}H_{24}N_4O_2PS$ [M+H]$^+$ Anal. calcd. 463.1358; found 463.1361.

***1-(3-(2-hydroxyphenyl)-N-methylpyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-4-chlorobenzo[1,3,2] diazaphosphole 2-sulfide* 4g**

White solide (48%); m.p 135-137 °C ^{1}H NMR (CDCl$_3$) δ 3.84 (s, 3H, NCH$_3$), 3.88 (s, 3H, OCH$_3$), 5.36 (d, 1H, NH, J_{P-H} = 18 Hz), 5.89 (s, 1H, H-4'), 6.24 (d, J= 8.1 Hz, 1H, H-7), 6.82 (dd, J= 1.8, 8.1 Hz, 2H, H-4''',5'''), 6.83 (s, 1H, H-4), 6.93-7.00 (d, J= 7.8 Hz, 3H), 7.16-7.20 (m, 2H, H-3'',5''), 7.81 (dd, J_{P-H}= 14.7 Hz, ^3J= 8.4 Hz, 2H, H-2'',6''), 10.51 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 36.8 (NCH$_3$), 55.6 (OCH$_3$), 100.0 (C 4'), 113.9 (d, J_{C-P}= 16.7 Hz, C-3'',5''), 115.7 (C-3'''), 116.6 (C-4), 117.2 (C-7), 119.1 (C-6), 120.6 (C-1'''), 121.6 (C-5'''), 126.0 (d, C-1'', J_{C-P}= 8 Hz), 126.5 (C-5), 129.3 (C-6'''), 131.2 (C-4'''), 132.8 (d, J_{C-P}= 15.2 Hz, C-2'',6''), 132.9 (C -3a), 133.7 (C-7a), 133.9 (C-3'), 134.1 (C-5'), 155.8 (C-2'''), 163.7 (C-4''). ^{31}P NMR (120 MHz, CDCl$_3$): d 74.79 ppm. HRMS (ESI) for $C_{23}H_{21}ClN_4O_2PS$ [M+H]$^+$ Anal. calcd. 483.0811; found 483.0815.

***1-(3-(2-hydroxyphenyl)-N-methylpyrazolyl)-2-(4-methoxyphenyl)-1,3-dihydro-4-nitrobenzo[1,3,2] diazaphosphole 2-sulfide* 4h**

Yellow solide (29%); m.p 115-117 °C ^{1}H NMR (CDCl$_3$) δ 3.83 (s, 3H, NCH$_3$), 3.87 (s, 3H, OCH$_3$), 5.35 (d, 1H, NH, J_{P-H} = 18.3 Hz), 5.88 (s, 1H, H-4'), 6.26 (d, J= 8.3 Hz, 1H, H-7), 6.34-6.37 (m, 2H), 6.53 (s, 1H, H-4), 6.83-6.95 (m, 3H), 7.14-7.19 (m, 2H, H-3'',5''), 7.82 (dd, J_{P-H}= 14.4 Hz, J= 8.4 Hz, 2H, H-2'',6''), 10.50 (brs, 1H, OH). ^{13}C NMR (CDCl$_3$) δ 36.7 (NCH$_3$), 55.5 (OCH$_3$), 100.1 (C 4'), 111.0 (C-4), 111.3 (C-6), 113.8 (d, J_{C-P}= 16.6 Hz, C-3'',5''), 115.8 (C-3'''), 118.7 (C-7), 120.6 (C-1'''), 121.2 (C-5'''), 125.8 (d, C-1'', J_{C-P}= 7.8 Hz), 129.0 (C-6'''), 131.1 (C-4'''), 132.6 (d, J_{C-P}= 15.1 Hz, C-2'',6''), 132.8 (C-3a), 133.0 (C-5), 134.9 (C-7a), 135.2 (C-3'), 135.4 (C-5'), 155.7 (C-2'''), 163.8 (C-4''). ^{31}P NMR (120 MHz, CDCl$_3$): d 74.72 ppm. HRMS (ESI) for $C_{23}H_{21}N_5O_4PS$ [M+H]$^+$ Anal. calcd. 494.1052; found 494.1055.

CONCLUSION

In this work, we have successfully designed and developed a synthetic way to a series of novel benzodiazphoshole 2-sulfide linked *N*-pyrazoles. The methodology for which we have opted involved a one-pot microwave-assisted cyclo-condensation between different 5-(2-amino-phenylamino)-3-pyrazole derivatives and the Lawesson's reagent. In addition, obtaining these potentially bioactive conjugates is particularly advantageous in relation to the availability of the reactants and the versatility of the protocols.

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