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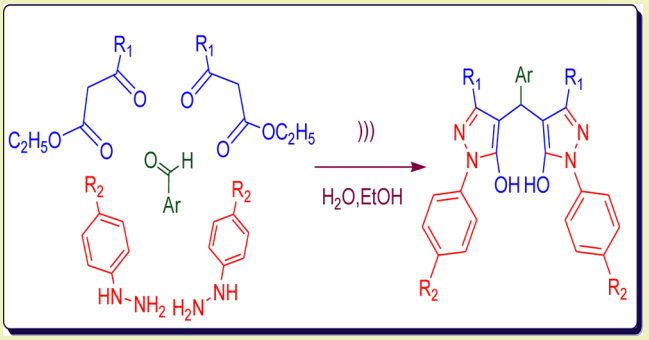
Room-Temperature, Catalyst-Free, One-Pot Pseudo-Five-Component Synthesis of 4,4-(Arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)s under Ultrasonic Irradiation

Alireza Hasaninejed,*[,†] Maryam Rasekhi Kazerooni,[†] and Abdolkarim Zare[‡]

[†]Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran

[‡]Department of Chemistry, Payame Noor University, P.O. Box 19395-3697 Tehran, Iran

ABSTRACT: A green and convenient approach for the synthesis of 4,4-(arylmethylene)bis (3-methyl-1-phenyl-1H-pyrazol-5-ols) by the reaction of aromatic aldehydes, phenylhydrazine derivatives, and ethyl acetoacetate in water/ethanol (1/1) under ultrasound irradiation is described. This method provides several advantages such as environmental friendliness, shorter reaction time, excellent yields, and simple workup procedure.



KEYWORDS: *Bis-pyrazolylmethane, Multi-component reaction, Catalyst-free, Ultrasound irradiation*

INTRODUCTION

In recent years, focus on green chemistry by using environmentally benign reagents and reaction conditions is one of the most fascinating developments in synthesis of widely used organic compounds.[1,2] The use of water as a promising solvent for organic reactions has received considerable attention in the area of organic synthesis owing to its green credentials[3−7] and organic synthesis in aqueous media offering key advantages such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration.

Ultrasound has increasingly been used in organic synthesis. A large number of ultrasonic reactions can be carried out in higher yield, shorter reaction time, or milder conditions.[8−11] As we know, the temperature of hot spots caused by the collapse of acoustic caves is generally as high as more than several hundred degrees, and at this temperature, energy can be transferred to the organic molecules and absorbed by them to dramatically raise their intrinsic energy. Because of the thermal effect of ultrasound waves, a much larger amount of molecules can meet the demand for the active energy in a given reaction, leading to the apparent improvement of the reaction efficiency with increased rates and reduced reaction time. It is also observed that reactions under ultrasound irradiation are commonly easier to work up than those in conventional stirring methods.[8−11]

Pyrazoles and their derivatives are an important class of bioactive drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds.[12−14] For example, they exhibit antianxiety, antipyretic, analgesic, and anti-inflammatory properties.[12−14] Moreover, 2,4-dihydro-3*H*-pyrazol-3-one derivatives including 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s have a broad spectrum of approved biological activity, being used as anti-inflammatory,[15] antipyretic,[16] gastric secretion stimulatory,[17] antidepressant,[18] antibacterial,[19] and antifilarial agents.[20] 4,4′-(Arylmethylene)bis(1*H*-pyrazol-5-ol)s are applied as fungicides,[21] pesticides,[22] insecticides,[23] and dyestuffs[24] and as chelating and extracting reagents for different metal ions.[25]

The most common method for the synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s is the one-pot pseudo-three-component condensation of aldehydes with 3-methyl-1-phenyl-5-pyrazolone. Some catalysts have been used for this transformation including acetic acid or piperidine,[26] sodium dodecyl sulfate,[27] ETBA,[28] silica-bonded S-sulfonic acid,[29] PEG-SO_3H,[30] PEG-400 at 110 °C,[31] CAN,[32] and an electrocatalysis procedure.[33] However, most of these synthetic methods suffer from drawbacks such as employing toxic reagents, strongly acidic or basic conditions, expensive and complex catalysts or reagents, harsh reaction conditions, many tedious steps, and in most cases, low yields of the products and long reaction times that restrict their usage in practical applications. In particular, the title compounds have been synthesized by a pseudo-three-component reaction, and there is no report on the synthesis of these molecules via a pseudo-five-component reaction.

Considering the above points, and also in continuation of our interest on catalyst-free and or multi-component organic

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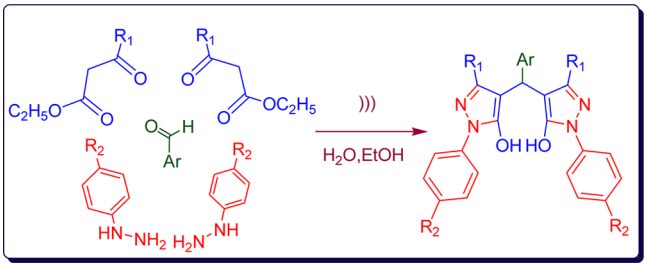
reactions,[34−42] we report here a novel method for preparation of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s via one-pot pseudo-five-component condensation of phenyl hydrazine derivatives (2 equiv) and *β*-ketoesters (2 equiv) with aromatic aldehydes (1 equiv) under catalyst-free and ultrasound irradiation conditions (Scheme 1).

Scheme 1. One-Pot Pseudo-Five-Component Synthesis of Bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) under Ultrasonic Irradiation



RESULTS AND DISCUSSION

To find an appropriate reaction medium for the catalyst-free synthesis of 4,4′-(aryllmethylene)-bis-(3methyl-1-phenyl-pyrazol-5-ol), a one-pot pseudo-five-component reaction between 4-Cl-benzaldehyde (1 mmol), phenylhydrazine (2 mmol), and ethyl acetoacetate (2 mmol) was selected as a model reaction and was examined in different solvents. Reaction times were monitored in the presence of ultrasonic irradiation at room temperature. We examined the effect of different solvents such as water, $CHCl_3$, $ClCH_2CH_2Cl$, THF, CH_3CN, 1,4-dioxane, and EtOH on the model reaction under ultrasound irradiation. The results were listed in Table 1. Water and ethanol afforded

Table 1. Synthesis of 4,4′-((4-Chlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (4b) in Different Solvents under Ultrasound Irradiation

entry	solvent	time (min)	yield[a] (%)
1	H_2O	40	80
2	CH_3CN	70	63
3	$ClCH_2CH_2Cl_2$	35	72
4	1,4-dioxane	65	56
5	EtOAc	60	70
6	THF	45	58
7	EtOH	30	90
8	H_2O/EtOH (3/1)	20	90
9	H_2O/EtOH (1/3)	20	92
10	H_2O/EtOH (1/1)	15	98
11	H_2O/SDS (10 mol %)	30	70

[a]Isolated yield.

good yields of the desired product (Table 1, entries 1 and 7). Poor results were observed when the reactions were carried out in $CHCl_3$, $ClCH_2CH_2Cl$, THF, CH_3CN, and 1,4-dioxane. The reactions took a long time, and the yields were low (Table 1, entries 2−6). Nevertheless, the most dramatic improvement was observed when the solvent was switched from H_2O to H_2O/EtOH. Therefore, the volume ratio of H_2O and EtOH was examined, and the best results were obtained by carrying out the reaction in H_2O/EtOH with a ratio of 1:1 (v/v) (Table 1, entry 10).

In the next step the scope and efficiency of the process was explored under the optimized conditions. For this purpose, *β*-ketoester (2 mmol), phenyl hydrazine (2 mmol), and a broad range of structurally diverse aromatic aldehydes were condensed in the presence of ultrasonic irradiation at room temperature to achieve the desired product, and the results are displayed in Table 2.

As it is shown in Table 2, aromatic aldehydes bearing electron-donating or -withdrawing substituents gave the desired 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s in high yields and in short reaction times. The method tolerates key functional groups such as halides, nitro, ethoxy, and naphtyl (Table 2, entries **4b**, **4g**, **4i**, **4m**,...), and besides the *para* and *meta* positions on the aromatic ring of aldehyde, different functional groups were also introduced to *ortho* positions, indicating the method is not sensitive to steric or electronic *ortho* variation of substituents. In the same way, the reaction was examined using ethyl benzoylacetate in which the desired 4,4′-(phenylmethylene)bis(1,3-diphenyl-1*H*-pyrazol-5-ol)s were obtained in high yields and in short reaction times (Table2, entries **4s**, **4t**). Moreover, different substitutions on the phenyl ring of phenylhydrazine were used for the synthesis of the corresponding product in excellent yields (Table 2, entries **4n**−**4r**). To investigate the role of ultrasonic irradiation in this method, the reactions were carried out in water/ethanol (1/1) under a stirring condition. The results are summarized in Table 2. When the reaction was carried out using the stirring method, it gave low yield of product (20% or trace) even after 3 h (Table 2), while the same reaction carried out under the influence of ultrasonic irradiation gave excellent yields of 3methyl-1-phenyl-pyrazol-5-ol derivatives.

It is presumed that the efficiency using ultrasound irradiation is due to the cavitation phenomena. An ultrasonic wave is a pressure wave with alternate compressions and rarefactions that break the intermolecular forces maintaining the cohesion of the liquid and produce a cavity in the rarefaction section of the wave. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation that includes formation, growth, and collapse of the cavity.[44] Bubble collapse in liquids results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of the contents of the bubble. The high local temperatures and pressures produced by cavitation lead to a diverse set of applications of ultrasound.[45] It is well known that all of these reactions have negative activation volumes owing to the condensation of the molecules into a reactive intermediate. In this regard, it is well known that reactions with negative activation volumes are accelerated with pressure. On the other hand, ultrasound irradiation as well as solvophobic interactions of aqueous media generates a microscopic internal pressure in the solvent cavity.[46] So owing to ultrasonic cavitations, microscopic internal high pressures and high temperatures have been generated in reaction media.[47] Accordingly, it is reasonable to assume that these effects should accelerate this type of pseudo-five-component condensation reaction.

According to the reported procedures for the synthesis of pyrazole derivatives under ultrasonic irradiation,[48,49] the formation of compound **3** could be explained by the reaction sequence in Scheme 2. On the basis of this mechanism, first, a condensation of phenylhydrazine derivative **1** with *β*-keto esters **2** is proposed to give the intermediate **5**. Then, the

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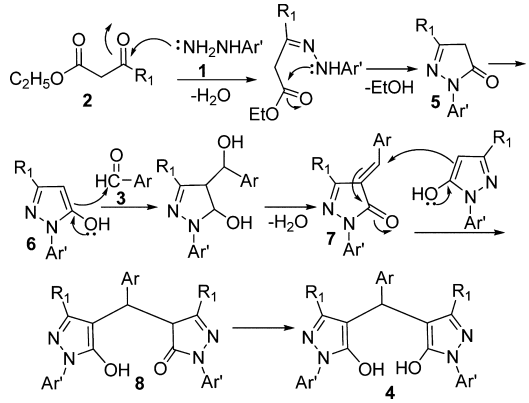
Table 2. Reaction of Aromatic Aldehydes, Phenyl Hydrazine Derivatives, and β-Ketoesters with and without Ultrasound Irradiation

				ultrasound		classical stir		
entry	R^1	R^2	Ar	time (min)	yield[a] (%)	time (min)	yield[a] (%)	mp °C (ref)
4a	Me	H	C_6H_5	15	98	180	15	170–172 (171–172)[30]
4b	Me	H	4-C–C_6H_4	15	92	180	trace	210–212 (207–209)[30]
4c	Me	H	3-Cl–C_6H_4	14	95	180	10	150–151 (153–154)[30]
4d	Me	H	2-Cl–C_6H_4	15	93	180	trace	237–239 (236–237)[30]
4e	Me	H	4-Br–C_6H_4	17	98	180	18	183–184 (183–185)[30]
4f	Me	H	2-Br–C_6H_4	12	97	180	trace	198–200
4g	Me	H	4-NO_2–C_6H_4	12	96	180	20	228–130 (230–232)[30]
4h	Me	H	3-OH–C_6H_4	18	98	180	10	166–168 (165–168)[29]
4i	Me	H	4-OE–C_6H_4	19	98	180	15	187–189 (186–188)[30]
4j	Me	H	2-thienyl	14	98	180	trace	190–192 (190–192)[30]
4k	Me	H	2-furyl	12	97	180	15	188–190 (189–191)[30]
4l	Me	H	2-naphthyl-	15	96	180	10	206–208 (204–206)[43]
4m	Me	H	1-naphthyl-	20	94	180	trace	202–204 (204–206)[43]
4n	Me	Br	3-Cl–C_6H_4	18	83	180	trace	219–220
4o	Me	Br	4-Cl–C_6H_4	20	90	180	Trace	208–209
4p	Me	Br	4-Br–C_6H_4	20	87	180	trace	173–174
4q	Me	Br	4-CF_3–C_6H_4	14	98	180	10	195–194
4r	Me	Me	4-CN–C_6H_4	20	85	180	trace	242–244
4s	ph	H	4-Cl–C_6H_4	12	97	180	10	170–172
4t	Ph	H	3-NO_2–C_6H_4	10	98	180	15	171–172

[a]Isolated yield.

Scheme 2. Proposed Mechanism for the One-Pot Pseudo-Five-Component Synthesis of Bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) under Ultrasonic Irradiation



intermediate **7** is likely formed via condensation of aromatic aldehyde **3** with **6**, which is the tautomer of **5**. The next step is a Michael addition of another intermediate of **6** to **8** to yield adduct **8**. Finally, after the tautomeric proton shift, the desired product **4** is formed.

In conclusion, we have found an efficient and practical procedure for the synthesis of 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-pyrazol-5-ol)s via the condensation of aromatic aldehyde, phenylhydrazine, and ethyl acetoacetate under ultrasound irradiation and catalyst-free conditions at room temperature. Compared to the classical method, the advantages of the present procedure are milder conditions, shorter reaction time, and higher yield.

EXPERIMENTAL SECTION

All chemicals were purchased from Merck or Fluka Chemical Companies. The ^{1}H NMR (500 MHz, 400 MHz) and ^{13}C NMR (125 MHz, 100 MHz) were run on a Bruker Avance DPX-250 FT-NMR spectrometer (δ in ppm). Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Sonication was performed by Hielscher sonicator (UP200H) with a frequency of 24 kHz and a nominal power of 200 W.

General Procedure for the Synthesis of 4,4-(Arylmethylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ol). A mixture of β-ketoester (2 mmol) and phenyl hydrazine (2 mmol) in water/ethanol (5 mL/5 mL) was irradiated by ultrasound at room temperature for 5 min, and then aromatic aldehyde (1 mmol) was added to the reaction mixture and continued for the required time (Table 2). Progress of the reaction was monitored by TLC. After the completion of the reaction, the residue was filtered and was recrystallized from hot ethanol to produce the desired pure product. The structures of the products were confirmed from physical and spectroscopic data such as melting points, ^{1}H NMR, and ^{13}C NMR spectra. Some new compounds were also established by mass spectra and the data of elemental analysis.

*4,4′-(Phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4a**).* Mp = 170–172 °C (ref 30, 171–172 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.33 (s, 6H, CH3), 4.88 (s, 1H), 7.07 (m, 1H), 7.18 (m, 6H), 7.44 (t, J = 7.5 Hz, 4H), 7.58 (d, J = 7.8 Hz, 4H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 12.0, 33.5, 121.4, 126.2, 126.8, 127.6, 128.2, 129.1, 137.3, 142.9, 146.1.

*4,4′-((4-Chlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4b**).* Mp = 210–212 °C (ref 30, 207–209 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.32 (s, 6H, CH_3), 4.97 (s, 1H), 7.26 (d, J = 8.2 Hz, 4H), 7.34 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.1 Hz, 4H), 7.71 (d, J = 7.6 Hz, 4H).

*4,4′-((2-Chlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4d**).* Mp = 237–239 °C (ref 30, 236–237 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.26 (s, 6H, CH_3), 5.08 (s, 1H), 7.27–7.29 (m, 2H), 7.41–7.43 (m, 8H), 7.75–7.77 (m, 4H).

*4,4′-((4-Nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4g**).* Mp = 228–230 °C (ref 30, 230–232 °C). ^{1}H NMR (DMSO-d_6.500 MHz): δ (ppm) 2.35 (s, 6H), 5.13 (s, 1H, CH), 7.25–7.27 (m, 2H), 7.43–7.46 (t, J = 7 Hz, 4H), 7.51–7.53 (d, J = 8 Hz, 2H), 7.70–7.72 (d, J = 8 Hz, 4H), 8.16–8.18 (d, J = 8 Hz, 2H), 12.64 (s, 1H, OH), 13.86 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ (ppm) 12.5, 19.4, 34.0, 56.9, 121.5, 124.2, 126.6, 129.5, 129.8, 146.8, 147.1, 151.2.

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*4,4′-((3-Hydroxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4h**).* Mp = 166−168 °C (ref 29, 165−168 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.42 (s, 6H), 4.98 (s, 1H), 6.67 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1H), 6.76−6.80 (m, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 4H), 7.83 (d, *J* = 7.8 Hz, 4H), 9.34 (s, 1H), 14.08 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 32.5, 114.2, 119.5, 120.5, 128.9, 129.0, 132.7, 137.5, 143.7, 147.0, 157.2.

*4,4′-((4-Ethoxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4i**).* Mp = 187−189 °C (ref 30, 185−188 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm)1.07 (t, 3H, *J* = 7.0 Hz, CH_3), 2.34 (s, 6H, CH_3), 3.46 (q, *J* = 7.0 Hz, 2H), 5.01 (s, 1H) 7.25−7.29 (m, 4H), 7.38−7.46 (m, 6H), 7.71−7.73 (d, *J* = 8.0 Hz, 4H), 13.94 (s, 2H, OH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 12.4, 19.4, 33.7, 56.9, 121.4, 122.4, 126.5, 127.3, 129.8, 130.7, 131.1, 146.0, 147.1.

*4,4′-(Thiophen-2-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4j**).* Mp= 190−192 °C (ref 30, 190−192 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.21 (s, 6H, CH_3), 4.87 (s, 1H), 6.14 (s, 1H), 6.48 (s, 1H), 7.37 (t, 2H), 7.44 (t, 4H), 7.53 (s, 1H), 7.78 (d, 4H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 12.2, 28.6, 106.4, 110.2, 121.6, 126.4, 129.9, 142.4, 146.9, 154.4.

*4,4′-(Furan-2-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4k**).* Mp = 188−190 °C (ref 30, 189−191 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.21 (s, 6H, CH_3), 4.87 (s, 1H, CH), 6.14 (s, 1H), 6.48 (s, 1H), 7.37 (t, 2H), 7.44 (t, 4H), 7.53 (s, 1H), 7.78 (d, 4H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 12.2, 28.6, 106.4, 110.2, 121.6, 126.4, 129.9, 142.4, 146.9, 154.4.

*4,4′-(Naphthalen-2-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4l**).* Mp = 206−208 °C (ref 43, 204−206 °C). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.36 (s, 6H), 5.14 (s, 1H), 7.24 (t, *J* = 6.9 Hz, 2H), 7.41−7.45 (m, 7H), 7.72 (d, *J* = 8.7 Hz, 5H), 7.81−7.85 (m, 3H), 13.93 (brs, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 34.2, 121.5, 125.8, 126.3, 126.8, 127.4, 128.2, 128.5, 128.6, 129.8, 132.5, 133.7, 140.5, 147.2.

*4,4′-(Naphthalen-1-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**4m**).* Mp = 202−204 °C (ref 43, 204−206 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.5 (s, 6H, CH_3), 5.5 (s, 1H), 7.47−7.51 (m,7H), 7.65 (d, *J* = 5.2 Hz, 4H), 7.7−7.8 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H).

*4,4′-((3-Chlorophenyl)methylene)bis(1-(4-bromophenyl)-3-methyl-1H-pyrazol-5-ol) (**4n**).* Mp = 219−220 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.32 (s, 6H, CH_3), 4.8 (s, 1H), 7.15−7.22 (m, 4H), 7.47−7.65 (m, 4H), 13.2 (brs, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 10.7, 29.5, 106.1, 122.8, 124.9, 125.0, 127.5, 130.0, 132.0, 138.3, 144.5, 145.0, 159.0. *m*/*z* (%) = 440 (5), 314 (35), 296 (68), 254(15), 185 (64), 163 (27), 145 (15), 128 (32), 105 (35), 91 (63), 77 (100), 64 (25), 51(52). Anal. Calcd for $C_{27}H_{21}Br_2ClN_4O_2$: C, 51.58; H, 3.37; N, 8.91%. Found: C, 51.52; H, 3.41; N, 8.85%.

*4,4′-((4-Chlorophenyl)methylene)bis(1-(4-bromophenyl)-3-methyl-1H-pyrazol-5-ol) (**4o**).* Mp = 208−209 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm)2.4 (s, 6H, CH_3), 4.85 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.3 (d, *J* = 6.4 Hz, 2H), 7.46−7.47 (d, *J* = 8.2 Hz, 4H), 7.64−7.65 (d, *J* = 8.1 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 11.0, 32.9, 106.4, 121.8, 123.7, 128.7, 132.7, 133.4, 137.9, 145.9, 159.5. *m*/*z* (%) = 296 (96), 261 (10), 185 (100), 163 (21), 145 (10), 128 (57), 105 (39), 91 (78), 77 (96), 64 (21), 51(42). Anal. Calcd for $C_{27}H_{21}Br_2ClN_4O_2$: C, 51.58; H, 3.37; N, 8.91%. Found: C, 51.14; H, 3.40; N, 9,11%.

*4,4′-((4-Bromophenyl)methylene)bis(1-(4-bromophenyl)-3-methyl-1H-pyrazol-5-ol) (**4p**).* Mp = 173−174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.1 (s, 6H, CH_3), 4.6 (s, 1H), 6.9 (d, 2H), 7.17 (d, 2H), 7.29−7.3 (m, 4H), 7.43−7.49 (m, 4H). *m*/*z* (%) = 340 (27), 314 (14), 163 (26), 128 (42), 105 (35), 91 (56), 77 (100), 64 (11), 51 (31), 105 (16), 91 (79), 64 (2). Anal. Calcd for $C_{27}H_{21}Br_3N_4O_2$: C, 48.17; H, 3.14; N, 8.32%. Found: C, 47.97; H, 3.20; N, 8.45%.

*4,4′-((4-(Trifluoromethyl)phenyl)methylene)bis(1-(4-bromophenyl)-3-methyl-1H-pyrazol-5-ol) (**4q**).* Mp = 195−196 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.3 (s, 6H, CH_3), 4.9 (s, 1H), 7.34−7.56 (m, 12H). *m*/*z* (%) = 408 (95), 263 (100), 183(25),163 (59), 155 (95), 128 (59), 105 (11), 91 (55), 77 (59), 51 (37). Anal. Calcd for $C_{28}H_{21}Br_2F_3N_4O_2$: C, 50.78; H, 3.20; N, 8.46%. Found: C, 50.59; H, 3.27; N, 8,39%.

*4-(Bis(5-hydroxy-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)methyl) benzonitrile (**4r**).* Mp = 242−244 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.3 (s, 6H, CH_3), 2.4 (s, 6H, CH_3), 4.9 (s, 1H), 7.15 (d, 4H, *J* = 8.2 Hz), 7.35 (d, *J* = 8.1 Hz, 2H), 7.59−7.62 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 10.8, 21.4, 105.6, 122.2, 128.3, 130.2, 131.8, 133.0, 138.6, 144.7, 159.0. *m*/*z* (%) = 470 (11), 400 (17), 374 (18), 341 (13), 301 (100), 199 (89), 153 (11), 127 (21), 105 (16), 91 (79), 64 (26). Anal. Calcd for $C_{30}H_{27}N_5O_2$: C, 73.60; H, 5.56; N, 14.31%. Found: C, 73.81; H, 5.29; N, 14.11%.

*4,4′-((4-Chlorophenyl)methylene)bis(1,3-diphenyl-1H-pyrazol-5-ol) (**4s**).* Mp = 170−172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): 5.26 (s, 1H), 7.22−7.34 (m, 12H), 7.38−7.40 (m, 4H), 7.51 (t, *J* = 7.8 Hz, 4H), 7.84 (d, *J* = 7.6 Hz, 4H), 14.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.5, 121.4, 121.8, 126.1, 126.6, 126.7, 128.6, 128.9, 129.2, 129.4, 129.9, 131.4, 137.6, 141.1, 149.3. *m*/*z* (%) = 358 (40), 274 (51), 225 (25), 189 (37), 163 (11), 125 (14), 105 (27), 91 (37), 77 (100), 64 (18), 51 (40). Anal. Calcd for $C_{37}H_{27}ClN_4O_2$: C, 74.68; H, 4.57; N, 9.41%. Found: C, 74.32; H, 4.51; N, 9.93%.

*4,4′-((3-Nitrophenyl)methylene)bis(1,3-diphenyl-1H-pyrazol-5-ol) (**4t**).* Mp = 171−173 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.36 (s, 1H), 7.23−7.34 (m, 10H), 7.49−7.53, (t, *J* = 8.0 Hz, 6H), 7.63−7.70 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 4H), 8.0 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 14.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.9, 121.4, 121.6, 121.9, 122.0, 126.1, 126.6, 126.9, 128.6, 129.3, 129.5, 130.6, 134.4, 144.5, 148.5, 149.3. *m*/*z* (%) = 446 (3), 369 (100), 313 (4), 236 (97), 189 (78), 163 (13), 131 (4), 103 (53), 77 (94), 51 (36). Anal. Calcd for $C_{37}H_{27}N_5O_4$: C, 73.38; H, 4.49; N, 11.56%. Found: C, 73.49; H, 4.37; N, 11.70%.

AUTHOR INFORMATION

Corresponding Author

*Fax: +98(771)4541494. E-mail: a_hasaninejad@yahoo.com.

Notes

The authors declare no competing financial interest.

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