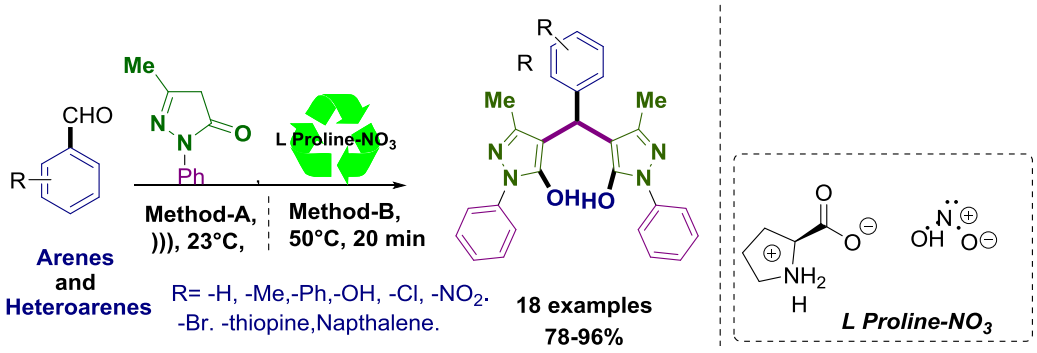
Graphical Abstract

A Green approach for the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) using L Proline-NO_3 as a green and recyclable ionic liquid catalyst under ultrasonic Sonication bearing lower E factors

Dr. Yuvraj Satkar [a], Dr. Lakhan Chaudhari [b], Dr. Sandip Chaudhari [c,] Dr. Paresh G. Patil [d]*



A Green approach for the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) using L Proline-NO_3 as a green and recyclable ionic liquid catalyst under ultrasonic Sonication bearing lower E factors

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Abstract: A Practical, mild and efficient synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) was achieved by simple condensation of aryl aldehyde and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one using L Proline-NO_3 ionic liquid catalyst under ultrasonic sonication or conventional method. The notable features of this protocol are ionic liquid catalyzed, short reaction time, high yielding, mild conditions also this method possess lower E factors. The scope gives excellent yield with electron rich and electron deficient aryl aldehyde as well as heterocycles. Also, the Gram-scale reaction shows reproducibility of our protocol. Reusability catalyst was conformed over number reaction there is no significant loss in reactivity of catalyst and yield of product was observed. Reusability of inexpensive ionic liquid, and environmentally friendly L Proline-NO_3 ionic liquid catalyst allows us to developed broad substrate scope of bis pyrazol derivatives.

1. Introduction

In recent years, ionic liquids (ILs) attract more attention to organic chemist [1] due to their valuable property's formation of cations and anions in reaction media at room temperature or <100°C. Also, ionic liquid resulted in industrial and laboratory application because of their supreme values such as chemical and thermal stability, nonflammability, reusability, miscible in various solvents, low vapour pressure, utility as solvent, reagent, or catalyst in organic reactions [2-4]. Amino acid based ionic liquid are non-toxic, bio-compatible and inexpensive they are synthesized from commercially available material [5]. All those remarkable properties of ionic liquid (ILs) inspired synthetic organic chemist to contribute valuable chemical research in biologically active molecules in organic synthesis.

Nitrogen-containing heterocyclic compounds occur widely in nature and because of their medicinal values they are essential to life. The pyrazolones and bis-pyrazolones are biologically active compounds present in much natural product core (fig. 1). Pyrazole and their derivatives have several pharmacological properties such as antipyretic, analgesic and anti-inflammatory [6-7], antiviral [8], antidepressant [9], anticancer [10], antiproliferativen [11], Antioxidant [12-13], antifungal and antibacterial [14]. Moreover bis-pyrazolones have been employed as fungicides and pesticides dyestuffs [15]. All those broad ranges of biological and chemical importance synthesis of pyrazole has received the sustainable attraction of many organic chemists.

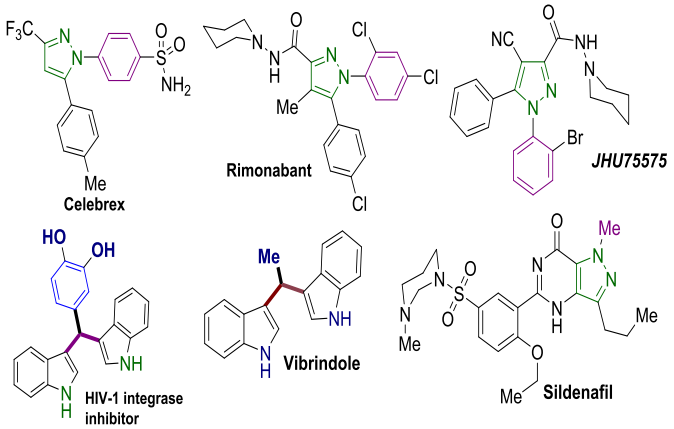


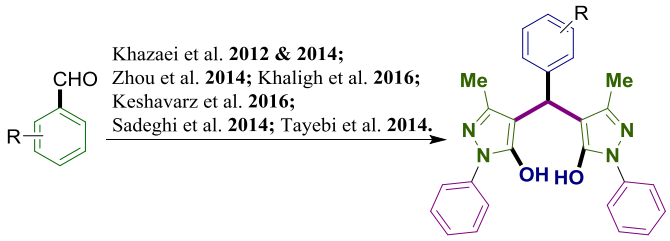
Fig.1. Naturally active Pyrazole and bis-methane core.

The synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) involves condensation of aromatic aldehyde and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one. To date, several procedures have been reported for the synthesis of bis-pyrazolones such 2-hydroxyethylammonium acetate (HEAA) [16], pyridinium salt (1-carboxymethyl) pyridinium chloride {[cmpy]Cl}ac) [17], 3-aminopropylated silica gel [18], silica-bonded S-sulfonic acid [19], Xanthan sulphuric acid [20], Phosphomolybdic acid [21], lithium hydroxide monohydrate [22], PEG-SO_3H [23], 1-sulfopyridinium chloride [2] THBS [24], SASPSPE [25], Recently, [26] devloped synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) using Chitosan-SO_3 catalyst.

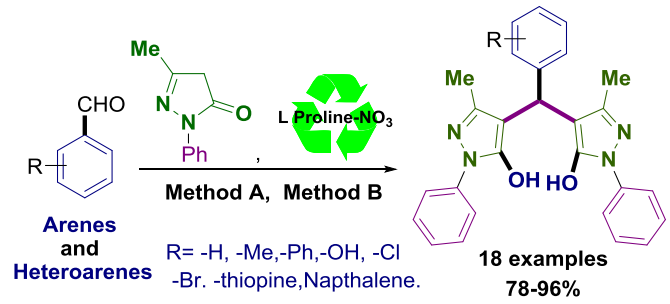
However, most of these methods go through one or more drawbacks such as longer reaction time, unsatisfactory yield, toxic and economically expensive reagents, strongly acidic or basic conditions, all that a limitation which limits their use in practical applications, Therefore, this encourages us to develop efficient clean, high-yielding, and environmentally friendly methodology for synthesis of bipyrazole after deep literature analysis. We were analyzing that there are no reports on the facile one-pot synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives using ionic liquid L Proline-NO_3 in EtOH as a solvent. In this manuscript we report a novel protocol for the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives using L Proline-NO_3 as an ionic liquid catalyst in ethanol as

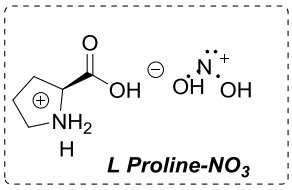
solvent under ultrasonic radiation condition or conventional method. This is a synthesis of those derivatives using an inexpensive and robust catalyst which accomplishes the reactions in short reaction times.

Previous Work



This work



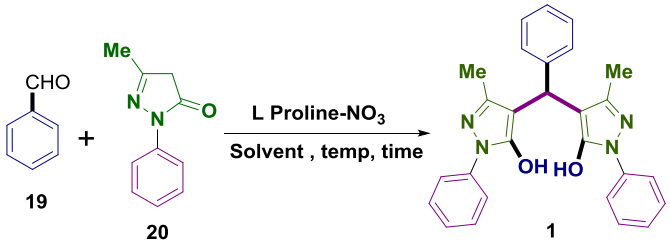


Results and discussion

After analysis of literature we hypothesis new protocol for the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) and its derivatives using L Proline-NO_3 ionic liquid. At this point, we focused our attention to search optimal reaction condition for synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) using benzaldehyde (1mmol) with 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol) was selected as a model reaction. The optimization assay including the amount of catalyst, solvent and temperature were examined are summarized in (Table **1**).

Initially, we started the optimization of reaction in absence and presence of L Proline-NO_3 (20 Mole%) in water under ultrasound irradiation condition (Method-A) obtained expected product 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) in yields of <20% and 42%, respectively (**Entries 1 and 2**). These experiments show that our hypothesis work and in principle and shows the necessity of L Proline-NO_3 catalyst in the procedure. These results motivate us for further optimization. In next optimization assay we used different polar and non-polar solvent n-Hexane, CH_2Cl_2, CH_3CN, THF, EtOH: H_2O and EtOH at room temperature in 20 Mole% of L Proline-NO_3 product **1** yield in 68, 80, 72, 38, 78% respectively (**Entries 3-7**). Surprisingly, under EtOH at room temperature under ultrasonication in 10 min, we observed the formation of product 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol)in excellent yield 90%(**Entry 8**). Subsequently, the optimization proceeded by progressively decreasing the catalyst loading (10% mole) to (5% mole) (**Entries 9-10**). Thereby, the full consumption of the starting material was observed in (10% mole) of catalyst reaction gives product **1** in yield 94% (**Entry 9**) this best yield observes in given optimization assay under ultra-sonication in 10 min. This result remark several features of this new protocol, such as fast and high yield reaction as well as inexpensive L proline-NO_3 ionic liquid catalyst.

Table no 1. Optimization of reaction condition for synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) catalyzed by L Proline-NO_3.



Method	Entry	Catalyst (Mole %)	Solvent	Temp.°C	Time (Min)	Yield (%)[b]
	1	-	H_2O	RT	30	<20
	2	20	H_2O	RT	30	42
	3	20	*n*-Hexane	RT	40	68
	4	20	CH_2Cl_2	RT	25	80
	5	20	CH_3CN	RT	32	72
A	**6**	20	THF	RT	48	38
	7	20	EtOH:H_2O	RT	16	78
	8	20	EtOH	RT	10	90
	9	***10***	***EtOH***	***RT***	***10***	***94***
	10	5	EtOH	RT	20	82
	11	20	H_2O	Reflux	2 h	62
	12	15	EtOH/H_2O	Reflux	1 h	68
	13	20	EtOH	Reflux	40	88
	14	20	EtOH	60	30	86
B	***15***	***20***	***EtOH***	***50***	***20***	***90***
	16	10	EtOH	40	30	80
	17	5	EtOH	30	30	60
	18	-	EtOH	30	1h	<20
	19	20	CH_2Cl_2	*30*	1h	*48*
	20	20	CH_3CN	*30*	1h	*55*
	21	20	*n*-Hexane	30	1h	38

[a]Reaction conditions: benzaldehyde (1mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), solvent (0.15 *M*), open flask, Method **A**= Ultrasonication, Method, **B** = Conventional method, n .r.= No reaction observed. [b] Isolated yield.

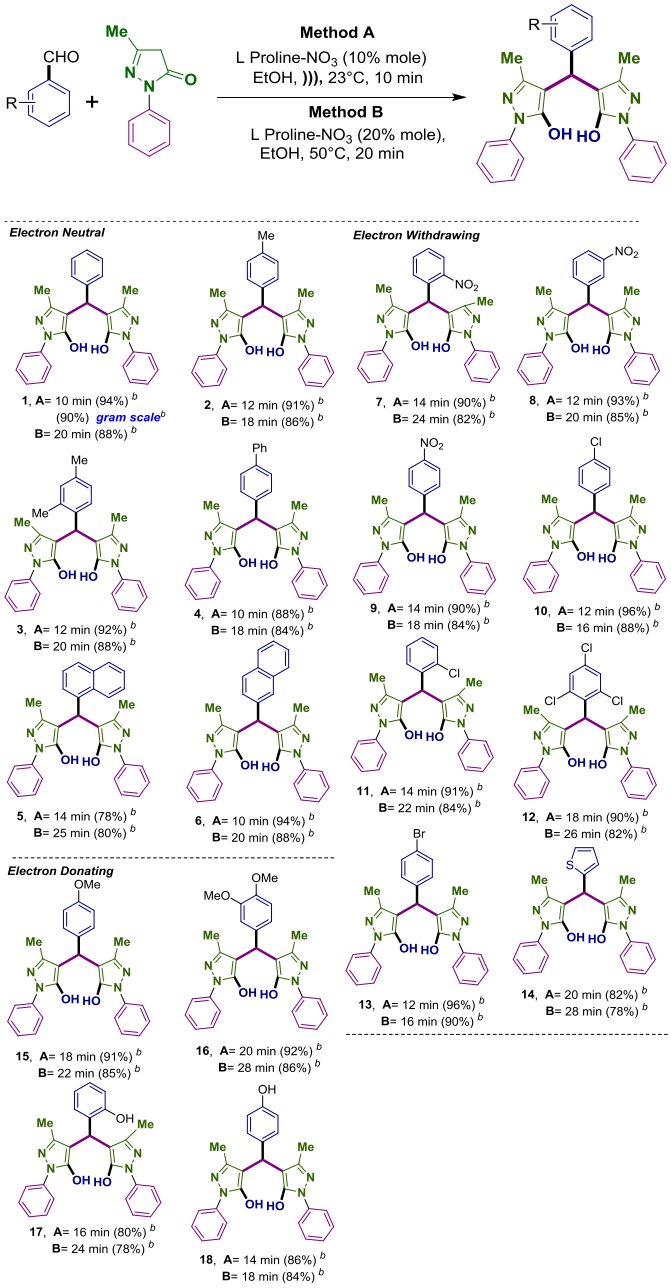
At this point, we were successfully optimized reaction condition for ultra-sonication the condition with excellent yield. Our further interest to optimize this protocol for the conventional method. In further optimization assay Initial attempts to induce the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) under H_2O at reflux condition using 20 mole% of L Proline-NO_3 catalyst. The reaction was water-tolerant, displaying yields of 62% of product **1** (**Entry 11).** These results validated the proposed hypothesis and confirmed that our

protocol work for the conventional method also. In further optimization assay combination of solvent, EtOH/H_2O (1:1) ratio improves the yields (**Entry 12).** After deep analysis and result form, ultrasonication clearly indicates that EtOH works well for this protocol as a solvent we were used EtOH as a solvent in further optimization with decreasing temperature and catalyst loading (**Entries 13-17).** Thereby, the full consumption of the starting material was observed (20% mole), (10% mole), (5% mole) of catalyst at 50°C, 40°C, and 30°C, product **1** yields in 88%, 86%, 90%, 80% and 60% respectively (**Entries 13**, 14, 15,16 and **17**). Surprisingly, under EtOH at 50°C, in 30 min the formation of product 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol)in excellent yield in 90%. This best yield observes by a conventional method (**Entry 15)**. Also, to accomplished control reaction was performed. In absence of L Proline-NO_3 catalyst less than 20 % yield were observed using conventional method (**Entry 18).** Again, thus confirming the necessity of L Proline-NO_3 catalyst in the procedure.

Subsequently, the optimization proceeded by progressively using polar and no-polar solvents did not improve the results. The reaction in CH_2Cl_2, CH_3CN, *n*-Hexane 30°C in 30 min with 20 mole% of L Proline-NO_3 catalyst product **1** yields in 48%, 55%, and 38% respectively (**Entries 19**, **20** and **21**). We were successful, optimized reaction conditions for the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol).by using ultra-sonication and conventional method. This result highlighted several aspects of the process, such as the fast and high-yield reactions as well as its economical L Proline-NO_3 catalyst. With the optimal reaction condition in hand, we proceeded to explore scope (Scheme **2.2**).

Some electron-rich and electron-deficient aryl aldehyde was examined to verify the scope of the reaction. Thus, benzaldehyde was submitted to the synthesis of a corresponding product under standard Method **A** and Method **B,** obtained **1** respectively, in 94 % and 90%. This reaction also gave an excellent 90% on gram-scale the experiment shows the scalability and efficiency of our protocol. 4-methylbenzaldehyde, 2,4-dimethylbenzaldehyde and [1,1'-biphenyl]-4-carbaldehyde submitted to the reaction to the formation of corresponding bis pyrazole product **2**, **3** and **4** yielded in Method **A** (91%, 92% and 88%) and method **B** (86%, 88% and 84%) respectively. Also, bis annular aryl aldehyde moiety show the good result 1-naphthaldehyde and 2-naphthaldehyde obtained corresponding product **5** and **6** with excellent yield in method **A** (78% and 94%) method **B** (80% and 88%) respectively, bis annular naphthaldehyde we do not see any decomposition of a product during a reaction. Our protocol accomplished good results with an electron neutral aryl aldehyde motif. In short reaction time obtained excellent yield. Furthermore, mono or bis substituted aryl aldehyde strongly containing electron-deficient groups such as -NO_2 at position 2-NO_2, 3-NO_2, and 4-NO_2, benzaldehyde give corresponding product **7, 8** and **9** using method **A** and method **B** yielded respectively, (90%, 93% and 90%) and (82%, 85% and 84%). Also, the halogen-containing electron-withdrawing group such as -Cl and -Br substituted on aryl aldehyde did not affect the corresponding product yield. When 4-bromobenzaldehyde, 4-chlorobenzaldehyde, 2-chlorobenzaldehyde and 2,4,6-trichlorobenzaldehyde are submitted to the reaction produced corresponding product **10**, **11**, **12** and **13** under method **A** and **B** yielded in (96%, 91%, 90% and 96%) and (88%, 84%, 82% and 90%) respectively. All electron-deficient aryl aldehyde reaction fully consumed starting material in short reaction time 12 to 26 min. Our protocol shows great tolerance toward the strong electron-withdrawing group. Also, strong sterically hindered 2,4,6-trichlorobenzaldehyde provided product **12** in excellent yield.

Scheme 2. Synthesis of 4,4´-(arylmethylene)bis(1H-pyrazol-5-ol) derivatives under optimized conditions [a]



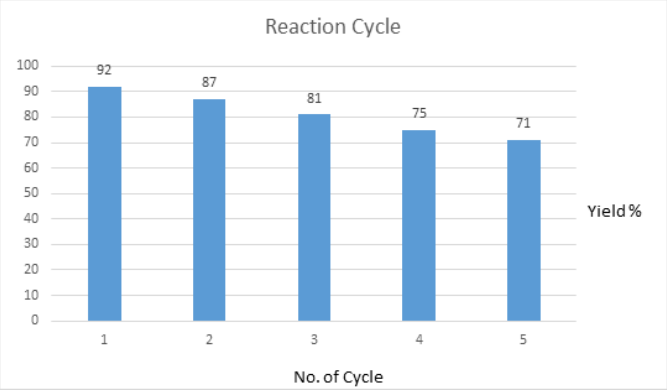
[a] Reaction conditions: aryl benzaldehyde (1mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), solvent (0.15 *M*), open flask, Method **A**= Ultrasonication, Method, **B** = Conventional method, [b] Isolated yield.

This result indicate that our protocol works excellent with electron-deficient and sterically hindered aryl aldehyde in short reaction time. After examining scope our protocol with an electron-deficient substituent. We were moved to explore more scope electron-donating and heterocyclic aryl aldehyde. thiophene-2-carbaldehyde substrate give product **14** yielded in (82% and 78%) respectively, this reaction shows the efficiency of our procedures work toward the heterocyclic aryl aldehyde. 4-methoxybenzaldehyde and 3,4-methoxybenzaldehyde for the reaction give corresponding products **15** and **16** respectively, in methods A and B (91% and 92%) and (85% and 86%) in 18 to 28 min of time. Finally, free -OH group aryl aldehyde motif we

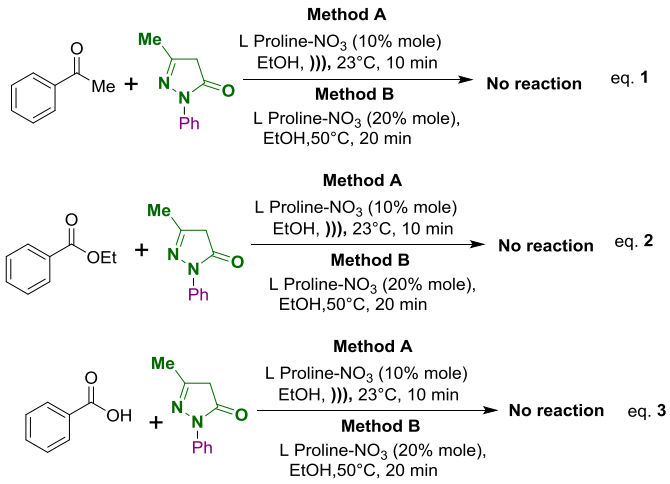
were submitted to the reaction to obtained product **17** and **18** excellent yield. This reaction concludes that -OH group no affect the reaction environment to the obtained corresponding product. After examining all substrate scope for this new protocol, we can claim that our protocol good tolerance toward electron-donating and withdrawing group and heterocyclic substrate. Also, sterically hindered substrate converts corresponding product in excellent yield all those reactions occurred in a short time.

At this point important to highlight some point of this new Protocol; 1) Environmentally friendly procedure, 2) high yielding, 3) short reaction time, 4) Inexpensive ionic liquid catalyst, 5) ultrasonication and conventional method, 6) No need Column purification, 7) reusability of catalyst. After deep literature analysis, we analysed that our protocol overcomes many limitations for this reaction.

Reusability of catalyst it has an important term in organic research "How much amount of catalyst reisolated or recover from the reaction mixture after reaction without losing reactivity" We were also, investigate the regeneration and reusability of the catalyst.



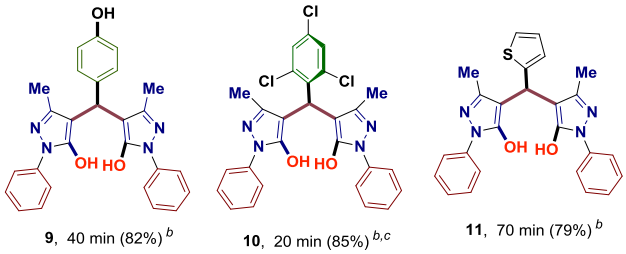
The reaction between benzaldehyde (1 mmol), and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), was studied in standard optimized reaction conditions. After completion of the reaction, the catalyst was recovered from the reaction mixture by filtration and dried under vacuum at 70 °C. The recovered catalyst was washed with diethyl ether and dried under vacuum. The recovered catalyst could be used up to five times without any appreciable loss of activity as shown in (**fig 2**).



Here we examine the reactivity of different functions with our protocol to determine the chemo the selectivity of our protocol. We were decided to carry out some reactions with different substrate form carbonyl functional groups. Such as acetophenone, methyl benzoate and benzoic acid submitted for reaction with standard reaction condition with 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), in (eq **1** eq **2** and eq **3**) not observed any reaction. With those experimental we conclude that our protocol has excellent chemoselectivity with aldehyde functional group only.

Table No.2 Comparison of previous literature results with our new protocol for synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol).

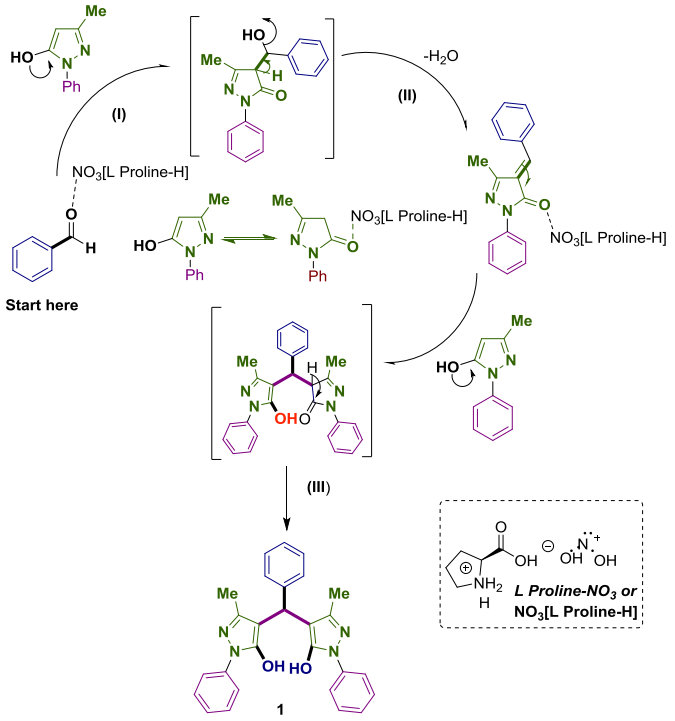
Product	Catalyst	Time (Min)	Yield (%)
1	LProline-NO_3(10% mole)	10	94 This work
	SASPSPE (0.1 g)	18	90 [25]
	([HMIM]HSO_4)	45	90 [27]
	[Sipmim]HSO_4)	60	90 [28]
	SBNPTT	30	90 [29]
	SBPPSA	60	88 [30]



9, 40 min (82%) [b] **10**, 20 min (85%) [b,c] **11**, 70 min (79%) [b]

[a] Reaction conditions: aromatic aldehyde (1 mmol), 3-methyl-l-phenyl-2-pyrazolin-5-one (2 mmol), solvent-free conditions. [b] Isolated yield. [c] Novel Compound.

Finally, we were correlated with our protocol with previous literature represented in (Table **2**). There is some limitation we were observed in previous reports such as 1) Long reaction time, 2) Low yields, 3) Hard reaction conditions, 4) long steps catalyst preparation, 5) expensive catalyst and reagents, 6) hazards catalyst, and reagents. Here we overcome many limitations from previous reports. Our new protocol is, 1) practice and mild reaction condition, 2) high yielding, 3) short reaction time, 4) simple catalyst preparation, 5) inexpensive catalyst and reagents, 6) our protocol has good tolerance toward electron-withdrawing, donating, and heteroaromatic aldehyde for synthesis corresponding product derivatives product **1** and **18.** 7) recyclable and environment friendly. With all those experimental and literature studies we can claim that our new protocol form synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol). And its derivatives using ionic liquid catalyst L Proline-NO_3 is good and environment friendly.



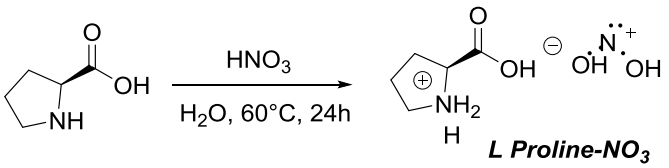
Scheme 2. Plausible mechanistic pathway for synthesis of 4,4´-(arylmethylene)bis(1H-pyrazol-5-ol).

There are some reports available in the literature for plausible the reaction mechanism for types of reactions [26, 31]. All those reports assumed that reaction started with the activation of carbonyl of aldehyde using catalyst followed by nucleophilic attack of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one over the nucleophilic center on aldehyde groups. The condensation of the second a molecule of with the alkene intermediates and then elimination of proton from bis-heterocyclic intermediates to form the desired bis-heterocycles product. Similar way we represented the possible reaction mechanism for our protocol is represented in (**Scheme 2**). The L Proline-NO_3 catalyst activate carbonyl carbon of aldehyde group and nucleophilic attack of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one produced [**I**]. followed aldol type condensation reaction gives benzylidene intermediate [**II**]. The addition of second equivalent 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one by Micheal type addition followed by elimination to form desired product 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) [**III**].

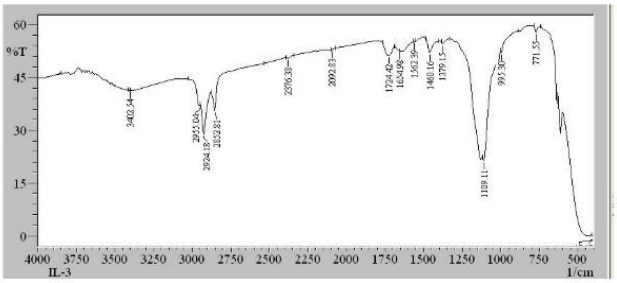
Experimental:

All starting materials such as aromatic aldehydes, 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one L Proline and nitric acid were used of synthetic grade. All melting points were recorded on Buchi melting point apparatus presented in degrees and are uncorrected. The progress of reactions is monitored by thin layer chromatography (TLC) with UV light. The FT-IR spectra recorded on FT-IR Perkin–Elmer550 spectrometer with potassium bromide pellets in the range 400-4000 cm^{-1}. ^1H NMR spectra were scanned on 500 MHz NMR spectrometer using DMSO-d6 as solvent chemical shifts have been expressed in δ (ppm) downfield from TMS as an internal standard.

Synthesis of L Proline-NO_3 ionic liquid: [32]



In 50 ml round bottom flask 11.51 gm (0.1mol) of L Proline was dissolved in 20 ml water. An equal number of nitric acid (0.3 mol) were added to solution. Then reaction mixture heated to 60^0C for 24 hours. After competition of reaction, evaporating in vacuo 17.81 gm of light yellow transparent ionic liquid was obtained. Which is as a catalyst for this research. For characterization of synthesis catalyst, we were analysed by using FTIR stretching frequency of FT-IR corelate with previous report.



General Procedure for Synthesis of 4,4´(arylmethylene)bis(1*H*-pyrazol-5-ol) and its derivatives.

Method A): A 25 mL round-bottom flask a mixture of an aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), and L Proline-Nitrate (10 mol%, 0.1 mmol) in 10 ml EtOH as solvent. The resulting mixture was irradiated at room temperature by ultrasonication until fully consumption of starting material. The appropriate time as mentioned in (scheme **2**). The progress of reaction was monitored by TLC using n-hexane: ethyl acetate/*n*-hexane 6:4. After completion of reaction mixture, the product was filtered, dried and recrystallized from ethanol.

Method B): A 25 mL round-bottom flask a mixture of an aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), and L Proline-Nitrate (20 mol%, 0.2 mmol) in 10 ml EtOH as solvent. The reaction mixture heated at 30^0C, oil bath until fully consumption of starting material. The appropriate time as mentioned in (scheme **2**). The progress of reaction was monitored by TLC using ethyl acetate/*n*-hexane (6:4). After completion of reaction mixture, the product was filtered, dried and recrystallized from ethanol.

4,4'-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (1).

(**Method A**= 408 mg, 94%) & (**Method B**= 382 mg, 88%); as a White solid. The spectroscopic data for this compound match with lit [33]. m.p. =167-169°C, Reported 171-172°C. R_f= 0.28 (50% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3399, 3067, 1575, 1288, 1026. ^1H NMR (DMSO, 500 MHz) δ ppm: 2.32 (s, 6H, $2CH_3$), 4.95 (s, 1H), 7.15-7.29 (m, 7H), 7.43 (t, 4H, *J* = 7.55 Hz,), 7.69 (d, 4H, *J* = 7.55 Hz), 12.48 (1H, brs, OH), 13.97 (1H, brs, OH).

4,4'-(p-tolylmethylene)bis(3-methyl-1-phenyl-1H pyrazol-5-ol) (2).

(**Method A**= 408 mg, 91%) & (**Method B**= 386 mg, 86%); as a White solid. The spectroscopic data for this compound match with lit [34]. m.p. =202-204°C, Reported 203-204°C. R_f= 0.15 (48% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3440, 3045, 1596, 1401, 1371, 1295,748. ^1H NMR (DMSO, 500 MHz) δ ppm: 2.24 (s, 6H), 2.30 (s, 3H), 4.89 (s, 1H), 7.07 (d, 2H), 7.11 (d, 2H), 7.24-7.43 (m, 6H), 7.68 (d, 4H, *J* = 8.25Hz), 12.46 (1H,brs,OH), 13.92 (1H,brs ,OH).

4,4'-((2,4-dimethylphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3).

(**Method A**= 426 mg, 92%) & (**Method B**= 408 mg, 88%); as a White solid. The spectroscopic data for this compound match with lit [26]. m.p. =216-218°C, Reported 216-218°C. R_f= 0.29 (54% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3440, 3071, 1609, 1540, 1495, 1307. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.20 (s, 6H), 2.24 (s, 6H), 4.87 (s, 1H), 6.92 (d, 2H, *J* = 7.6Hz), 7.22-7.35 (m, 3H), 7.42 (t, 4H, *J*=7.55Hz), 7.68 (d, 4H, *J* = 8.25Hz), 12.30 (1H, brs, OH), 13.40 (1H, brs, OH).

4,4'-([1,1'-biphenyl]-4-ylmethylene)bis(3-methyl-1phenyl-1H-pyrazol-5-ol) (4).
(**Method A**= 450 mg, 88%) & (**Method B**= 430 mg, 84%); as a White solid. The spectroscopic data for this compound match with lit [35]. m.p. =202-204°C, Reported 202-204°C. R_f= 0.15 (48 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3438, 3050, 1596, 295, 1196, 883. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.34 (s, 6H), 5.00 (s, 1H), 7.25-7.45 (m, 11H), 7.56 (d, 2H, *J* = 8.25Hz), 7.60 (d, 2H, *J* = 7.55Hz), 7.72 (d, 4H, *J* = 8.25Hz), 12.54 (1H, brs, OH), 14.02 (1H, brs, OH).

4,4'-(naphthalen-1-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)(5).
(**Method A**= 379 mg, 78%) & (**Method B**= 388 mg, 80%); as a White solid. The spectroscopic data for this compound match with lit [36] m.p. =202-204°C, Reported 208-210°C. R_f= 0.45 (36 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3440, 3058, 1496, 295, 1396, 880.

4,4'-(naphthalen-2-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)(6).
(**Method A**= 456 mg, 94%) & (**Method B**= 427 mg, 88%); as a White solid. The spectroscopic data for this compound match with lit [33] m.p. =206-208°C, Reported 206-207°C. R_f= 0.28 (34 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3440, 3058, 1496, 295, 1396, 880.

4,4'-((2-nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (7).
(**Method A**= 432 mg, 90%) & (**Method B**= 394 mg, 82%); as a White solid. The spectroscopic data for this compound match with lit [23]. m.p. =222-224°C, Reported 221-223°C. R_f= 0.29 (30 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3450, 3075, 1598, 1480, 1372, 832, 744.

4,4'-((3-nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)(8).
(**Method A**= 447 mg, 93%) & (**Method B**= 408 mg, 85%); as a White solid. The spectroscopic data for this compound match with lit [38]. m.p. =152-154°C, Reported 151-153°C. R_f= 0.15 (42% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3470, 3050, 1595, 1403, 1240, 809, 687.

4,4'-((4-nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (9).
(**Method A**= 432 mg, 90%) & (**Method B**= 404 mg, 84%); as a White solid. The spectroscopic data for this compound match with lit [23]. m.p. =230-232°C, Reported 229-231°C. R_f= 0.29 (40% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3480, 3040, 155o, 1430, 1240, 809, 687.

4,4'-((4-chlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)(10).
(**Method A**= 451 mg, 96%) & (**Method B**= 413 mg, 88%); as a White solid. The spectroscopic data for this compound match with lit [34]. m.p. =208-210°C, Reported 210°C. R_f= 0.29 (40% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3430, 3050, 2900, 1595, 1294, 745, ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.31 (s, 6H, 2CH$_3$), 4.96 (s, 1H), 7.24 (d, 4H, *J* = 8.25 Hz), 7.32-7.43 (m, 6H), 7.68 (d, 4H, *J* = 7.55 Hz), 12.54 (1H, brs, OH), 13.87 (1H, brs, OH).

4,4'-((2-chlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (11).
(**Method A**= 427 mg, 91%) & (**Method B**= 394 mg, 84%); as a White solid. The spectroscopic data for this compound match with lit [34]. m.p. =232-234°C, Reported 235-237°C. R_f= 0.45 (38% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3452, 3060, 2790, 1610, 1555, 1497, 1436, 1399, 1350, 1295, 836, 744, 687. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.28 (s, 3H), 3.36 (s, 3H) 5.13 (s, 1H), 7.21-7.31 (m, 4H), 7.39-7.42 (m, 6H), 7.68 (d, J=7.55, 4H), 12.65 (1H, brs, OH), 13.92 (1H, brs, OH).

4,4'-((2,4,6-trichlorophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (12).
(**Method A**= 485 mg, 90%) & (**Method B**= 441 mg, 82%); as a White solid. The spectroscopic data for this compound match with lit [26]. m.p. =230-232°C, Reported 230-232°C. R_f= 0.5 (40 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3460, 3077, 1595, 1424, 1382, 1290, 819. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.27 (s, 6H), 5.13 (s, 1H), 7.26 (m, 2H), 7.44 (t, 4H, *J* = 7.6 Hz), 7.69 (d, 5H, *J* = 8.25 Hz), 7.75 (d, 1H), 12.83 (1H, brs, OH), 13.89 (1H, brs, OH).

4,4'-((4-bromophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (13).
(**Method A**= 494 mg, 96%) & (**Method B**= 463 mg, 90%); as a White solid. The spectroscopic data for this compound match with lit [35]. m.p. =208-210°C, Reported 208-210°C. R_f= 0.15 (34 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3454, 3065, 1598, 1401, 1372, 744, 688. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.31 (s, 3H), 3.34 (s, 3H), 4.94 (s, 1H), 7.18-7.24 (4H, m), 7.43-7.47 (m, 6H) ,7.70 (d, 4H, *J* = 8.25Hz), 12.55 (1H, brs, OH), 13.87 (1H, brs, OH).

4,4'-(thiophen-2-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (14).
(**Method A**= 362 mg, 82%) & (**Method B**= 344 mg, 78%); as a White solid. The spectroscopic data for this compound match with lit [26]. m.p. =181-182°C, Reported 181-183°C. R_f= 0.15 (30 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3416, 3066, 1595, 1405, 1368, 1221, 1192, 757. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.31 (s, 6H), 5.12 (s, 1H), 6.74 (d, 1H, J=3.5Hz), 6.90 (t, 1H, J=5Hz), 7.25-7.29 (m, 3H), 7.44 (t, 4H, *J* = 8.25 Hz), 7.70 (d, 4H, *J* = 8.25Hz), 12.56 (1H, brs, OH), 13.98 (1H, brs, OH).

4,4'-((4-methoxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (15).
(**Method A**= 424 mg, 91%) & (**Method B**= 396 mg, 85%); as a White solid. The spectroscopic data for this compound match with lit [34]. m.p. =173-175°C, Reported 171-172°C. R_f= 0.15 (42% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3502, 3066, 2971, 1603, 1402, 1364, 1165. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.30 (s, 6H), 3.69 (s, 3H, -OMe), 4.89 (s, 1H), 6.8426 (d, 2H, *J* = 8.25 Hz), 7.16-7.25 (m, 4H), 7.43 (t, 4H, *J* = 7.55 Hz), 7.70 (d, 4H, *J* = 7.55 Hz), 12.43 (1H, brs, OH), 13.93 (1H, brs, OH).

4,4'-((3,4-dimethoxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (16).
(**Method A**= 456 mg, 92%) & (**Method B**= 426 mg, 86%); as a White solid. The spectroscopic data for this compound match with lit [37]. m.p. =192-194°C, Reported 194-196°C. R_f= 0.15 (42

% EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3504, 3060, 2970, 1630, 1482, 1368, 1168.

4,4'-((2-hydroxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (17).
(**Method A**= 360 mg, 80%) & (**Method B**= 351 mg, 78%); as a White solid. The spectroscopic data for this compound match with lit [38]. m.p. =228-2230°C, Reported 228-231°C. R_f= 0.45 (42% EtOAc /Hexane).

4,4'-((4-hydroxyphenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (18).
(**Method A**= 387 mg, 86%) & (**Method B**= 378 mg, 84%); as a White solid. The spectroscopic data for this compound match with lit [34]. m.p. =154-156°C, Reported 155-157°C. R_f= 0.29 (30 % EtOAc /Hexane). IR (neat) ν/cm^{-1} = 3472, 3139, 1574, 1487, 1438, 1369, 1274, 875. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.29 (s, 6H), 4.84 (s, 1H), 6.66 (d, 2H, *J* = 8.25 Hz), 7.04 (d, 2H, *J* = 8.25 Hz), 7.24-7.43 (m, 6H), 7.70 (d, 4H, *J* = 7.55 Hz), 9.17 (s, 1H, OH), 12.40 (1H, brs, OH), 13.93 (1H, brs, OH).

E- Factor Calculations:
For Compound
1: E = [0.106 (Benzaldehyde) + 0.156(24)-0.213 g (product × yield) /0.213 g = 0.230
2: E = [0.120 (4-MethylBenzaldehyde) + 0.156(24)-0.215 g (product × yield) /0.215 g = 0.283
3: E = [0.136 (4-MethoxylBenzaldehyde) + 0.156(24)-0.241 g (product × yield) /0.241 g = 0.211
4: E = [0.182 (4-phenylBenzaldehyde) + 0.156(24)-0.271 g (product × yield) /0.271 g = 0.247
5: E = [0.140 (4-chloroBenzaldehyde) + 0.156(24)-0.260 g (product × yield) /0.260 g = 0.138
6: E = [0.185 (4-bromoBenzaldehyde) + 0.156(24)-0.282 g (product × yield) /0.282 g = 0.209
7: E = [0.151 (3-nitroBenzaldehyde) + 0.156(24)-0.262 g (product × yield) /0.262 g = 0.171
8: E = [0.122 (2-hydroxyBenzaldehyde) + 0.156(24)-0.212 g (product × yield) /0.212 g = 0.311
9: E = [0.122 (4-hydroxyBenzaldehyde) + 0.156(24)-0.223 g (product × yield) /0.223 g = 0.246
10: E = [0.112 (2-thiophenealdehyde) + 0.156(24)-0.204 g (product × yield) /0.204 g = 0.313
11: E = [0.156 (1-napthaldehyde) + 0.156(24)-0.234 g (product × yield) /0.234 g = 0.333
12: E = [0.106 (Benzaldehyde) + 0.156(24) + 0.066 (25) -0.271 g (product × yield) /0.271 g = 0.210
13: E = [0.140 (2-chloro Benzaldehyde) + 0.156(24) + 0.066 (25) -0.288 g (product × yield) /0.288 g = 0.256
14: E = [0.140 (4-chloro Benzaldehyde) + 0.156(24) + 0.066 (25) -0.316 g (product × yield) /0.316 g = 0.145
15: E = [0.185 (4-bromo Benzaldehyde) + 0.156(24) + 0.066 (25) -0.348 g (product × yield) /0.348 g = 0.169
16: E = [0.151 (2-nitro Benzaldehyde) + 0.156(24) + 0.066 (25) -0.311 g (product × yield) /0.311 g = 0.199
17: E = [0.151 (3-nitro Benzaldehyde) + 0.156(24) + 0.066 (25) -0.318 g (product × yield) /0.318 g = 0.172
18: E = [0.120 (4-methyl Benzaldehyde) + 0.156(24) + 0.066 (25) -0.291 g (product × yield) /0.291 g = 0.175
19: E = [0.136 (4-methoxy Benzaldehyde) + 0.156(24) + 0.066 (25) -0.311 g (product × yield) /0.311 g = 0.151
20: E = [0.122 (3-hydroxy Benzaldehyde) + 0.156(24) + 0.066 (25) -0.266 g (product × yield) /0.266 g = 0.293
21: E = [0.120 (4-hydroxy Benzaldehyde) + 0.156(24) + 0.066 (25) -0.279 g (product × yield) /0.279 g = 0.225
22: E = [0.156 (1-napthaldehyde) + 0.156(24) + 0.066 (25) -0.315 g (product × yield)/0.315 g = 0.200

Conclusions

In conclusion, we have developed practice, a mild and efficient protocol for the synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) and its derivatives using L Proline-NO_3 under ultrasonication or conational method. This reaction takes place at room temperature in a short time. To best our knowledge this method overcomes limitations form previous literature. Our new method tolerates electron-withdrawing, electron-donating and heterocyclic aryl aldehyde. We are providing two methods of ultrasonication and conventional method our catalyst works very well in those conditions. L Proline NO_3 are cheap and easily prepared also, reusability of L Proline NO_3 shows the good result without losing reactivity by recyclization. Also, an experimental study with different carbonyl groups shows excellent chemo-selectivity toward the aldehyde group. In addition we developed greener approach bearing lower Environmental impact factor or E factors. With all those experimental study's and literature analysis here we are providing the best protocol for synthesis of 4,4´-(arylmethylene)bis(1*H*-pyrazol-5-ol) and its derivatives using L Proline-NO_3.

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The authors declare no competing financial interest.

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