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MICROWAVE ASSISTED ONE POT FIVE COMPONENT SYNTHESIS OF 4,4'-(ARYL METHYLENE)BIS(3-METHYL-1-PHENYL-1*H*-PYRAZOL-5-OLS)

Sachin R. Kolsepatil[1], Devendra Wagare[1], Dinesh L. Lingampalle[1]*

[1]*Department of chemistry, Vivekanand College, Samarth nagar, Aurangabad, Maharashtra*
E-mail: lingampalle@vivekanandcollege.edu.in

Abstract: A new highly efficient and environmentally benign protocol designed for the five component synthesis of 4,4'-(arylmethylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols) from the condensation of substituted aromatic aldehyde, phenyl hydrazine and ethyl acetoacetate. Ionic liquid (NMPYT) is used as an ecofriendly catalyst with high catalytic activity under solvent free condition. Main remarkable features of this new green method are environmentally benign, excellent yield, shorter reaction time and easy workup procedure.

Keywords: Multicomponent reaction, bis-pyrazoles, Ionic liquid, Microwave irradiation, environmentally friendly.

Introduction:

In recent years, Focus on green chemistry by using environmentally benign reagents, easy workup procedures, using minimum amount of catalyst is one of the most important facts development in the synthesis of biologically active organic compounds. In conformity the principle of green and safe chemistry, synthetic method should be design to use substances that show small or no toxicity to human health and effect on environment [i-ii].

Pyrazoles and its derivatives are most important class in pharmaceutical industry due to they found as the core structure of numerous biologically active compounds [iii-iv]. They exhibit antianexiety, anti-inflammatory, analgesic and antipyretic properties [v-vi]. Moreover, 2,4-dihydro-3H-pyrazol-3-one derivatives including 4,4'-(aryl methylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols) have broad spectrum of biological activities such as antipyretic[vii], gastric secretion stimulatory[viii], anti-inflammatory[ix],antidepressant[x], antibacterial agents[xi]. 4,4'-(aryl methylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols) acts as fungicides[xii], insecticides[xiii], dyestuffs[xiv] and pesticides[xv] and also act as a chelating and extracting reagents for different metal ions[xvi]. The observed and studies on bis-pyrazolone based complexes show they have very strong fluorescence properties[xvii-xx] and have antitumor and herbicidal activities. The chemical reaction for the synthesis of 4,4'-(arylmethylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols) involves successful knoevenagel synthesis to corresponding arylidenepyrazolones followed by Michael reaction.[xxi]

Various synthetic methods have been reported for the preparation of 4,4'-(aryl methylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols)such as using sodium dodecyl sulfate[xxii],

silica-bonded s-sulfonicacid[xxiii], acetic acid in ethanolicsolution[xxiv], 3-aminopropylated silica gel(AP-SiO_2)[xxv], silica sulfuric acid[xxvi], PEG-OSO_3H[xxvii], PEG-400 at 100^0C[xxviii], lithium hydroxide monohydrate($LiOH.H_2O$)[xxix], SBPPSA catalyst[xxx], ([sipmim]HSO_4)[xxxi], CAN[xxxii], electro catalytic tandem knoevenagel-Michael reaction[xxxiii], $Ce(SO_4)_2.4H_2O$[xxxiv], ammonium acetate[xxxv]. However, most of synthetic method suffer from various drawbacks such as toxic reagents, strong acidic or basic conditions, expensive catalyst, long duration reaction many tedious steps, low yields of the product and non-recovered catalyst. Thus, there is still a need to develop a new method for the synthesis of 4, 4'-(aryl methylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols). Herein We reported a novel one pot, fivemembered condensation of phenyl hydrazine (2 eq.) and ethyl acetoacetate (2 eq.) with aromaticaldehyde (1eq.) under solvent free and microwave irradiation conditions. (Scheme-1)

Materials and Methods:

All chemicals were purchased from commercial sources. The ^{1}HNMR were run on a Brucker 300Mz and IR was recorded in KBr pellets on Nicolet impact. Melting points were taken in open capillary and are uncorrected. The reaction was carried out in microwave synthesizer, MAS-II, Sineo.

General procedure for the synthesis of 4, 4'-(aryl methylene) bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols): A mixture of ethyl acetoacetate (2 mmol), phenyl hydrazine (2 mmol) and catalyst NMPYT Ionic liquid (10 mol%) was irradiated under microwave for 5 min. and then aromatic aldehyde (1 mmol) was added to the reaction mixture and irradiated under microwave. reaction mixture poured on crushed ice. This solid compound was filtered and was recrystallized from methanol to produce the desired product.

Spectral Data:

4,4'-(phenyl methylene) bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ol): (Table 2, entry 1) ^{1}H NMR (DMSO-d_6, 300MHz) 2.31(s, 6H, $2CH_3$), 4.95 (s, 1H, CH), 7.16-7.28 (m, 7H, ArH), 7.43 (t, *J*=7.5 Hz, 4H, ArH), 7.70 (d, *J*=8. Hz, 4H, ArH). IR (KBr) v: 3357, 3062, 2964, 2581, 1595, 1496, 1415, 1273, 1075, 793, 735, 690 cm^{-1}

4,4'-[(4-methylphenyl) methylene] bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ol): (Table 2, entry 5) ^{1}H NMR (DMSO-d_6, 300MHz) 2.25 (s, 3H, CH_3), 2.31 (s, 6H, $2CH_3$), 4.90 (s, 1H, CH), 7.08 (d, j=8.4 Hz, 2H, ArH), 7.12 (d, *J*=8.0 Hz, 2H, ArH), 7.25 (t, *J*=7.1Hz, 2H, ArH), 7.45 (t, *J*=7.6 Hz, 4H, ArH), 7.71 (d, *J*=7.5Hz, 4H, ArH). IR (KBr) v: 3412, 3052, 2928, 1605, 1582, 1508, 1414, 1298, 807, 753, 694 cm^{-1}

Results and Discussion:

In initial study synthesis of 4,4'-(aryl methylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols) was carried out from the reaction of benzaldehyde, phenyl hydrazine and ethyl acetoacetate in presence of different catalyst under microwave irradiation and result obtained were summarised in table.1.

Table-1: Comparison of a number of different reported catalysts.

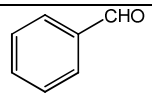
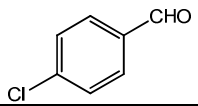
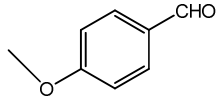
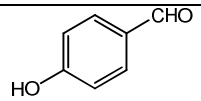
Entry	Catalyst	Solvent free	Temperature	Time/min.	Yields[a]
1	SBPPSA	Solvent free	80	45	90
2	Sodium dodecyl sulfate	H_2O	Reflux	60	86
3	SASPSPE	EtOH	Reflux	180	90

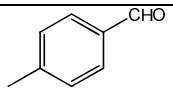
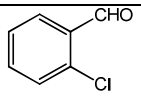
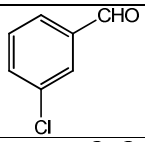
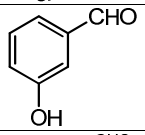
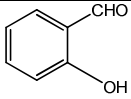
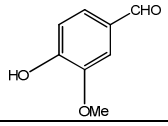
4	Silica sulfuric acid	EtOH-H_2O	70	60	90
5	Silica bonded s-sulfonic acid	EtOH	Reflux	120	80
6	Silica bonded ionic liquid[spipim]HSO_4	EtOH	Reflux	120	89
7	{[Dsim]$AlCl_4$}	Solvent free	50	60	86
8	[Et_3NH][HSO_4]	Solvent free	90	35	85
9	Na_2CO_3	Solvent free	Room temperature	60	65
10	**NMPYT Ionic liquid**	**Solvent free**	**100**	**10**	**96**

[a]Isolated yield.

From the results of Table 1 it it clear that NMPYT ionic liquid is an effective catalyst for this one pot five component synthesis of 4,4'-(aryl methylene) bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols). To study the generality of this method, differently substituted aromatic aldehyde condensed with phenyl hydrazine in the presence of same reaction condition and results were depicted in table 2. it was observed that NMPYT ionic liquid revealed that good catalytic role, which gave 96% yield.(Table 1, entry 10). When we use of SBPPSA and sodium dodecyl sulfate as a catalyst,it was observed that corresponding yield was+90% and 86% (Table 1, entry 1-2). The reaction was carried out in same condition using other catalyst such as SASPSPE, silica sulfuric acid, silica bonded s-sulfonic and silica bonded ionic liquid [spipim] the product was obtained with 90%, 91%, 80% and 89% respectively (Table 1, entry 3-6). The use of catalyst {[Dsim]$AlCl_4$}, [Et_3NH][HSO_4] and Na_2CO_3 these catalyst give low yield of products respectively, 86%, 85% and 65% (Table 1, entry 7-9). 10 mol% NMPYT acts as a efficient catalyst for the synthesis of bis-pyrazolone derivatives with excellent yield. (Table 1, **entry 10**).

Table 2: Reaction of aromatic aldehydes, phenyl hydrazine and ethyl acetoacetate and Microwave irradiation.

Entry	Aldehyde	Time (min.)	Yields[a]%
1		10	95
2		12	92
3		15	93
4		8	91

5		11	89
6		13	90
7		10	85
8		15	94
9		14	93
10		12	91

[a]Isolated yield.

It was observed that excellent yield of the products were obtained when aromatic aldehyde containing electron donating substituents. Furthermore, the reaction is compatible in the presence of different functional group such as –Cl, -OCH_3, and –OH. The reaction gave corresponding compounds in good yields.

Conclusion:

In conclusion, we have described green one pot five component condensation reaction between phenyl hydrazine, ethyl acetoacetate and aromatic aldehyde to give 4,4'-(aryl methylene)bis(3-Methyl-1-phenyl-1*H*-Pyrazol-5-ols) in very good to excellent yield using NMPYT ionic liquid used as an efficient and inexpensive, non-toxic catalyst. We believe that this protocol will be good in addition to most recent environmentally benign methods for the synthesis.

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