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Synthesis for the 4, 4′-(arylmethylene)bis(*1H*-pyrazol-5-ols) in aqueous medium under microwave irradiation in presence of ionic surfactant

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ABSTRACT

A simple, efficient and environment friendly route has been developed for the synthesis of 4, 4′-(arylmethylene)bis(*1H*-pyrazol-5-ols) by the condensation of pyrazole and aryl aldehyde in presence of ionic surfactant under microwave irradiation. © 2014 Trade Science Inc. - INDIA

KEYWORDS

4,4′-(arylmethylene)bis(1H-pyrazol-5-ols);
Surfactant medium;
Microwave irradiation;
Knoevenagel condensation;
Michael addition.

INTRODUCTION

The realization of simple and green synthetic procedure constitutes an important goal in organic synthesis. Water as reaction medium complies the entire current stringent requirement on sustainable chemistry. Therefore, the development of synthetically useful reaction in water is of considerable interest[1]. However, water is rarely used or even considered as a solvent for organic reactions. One of the major issues is undoubtedly the limited solubility of most organic compounds in pure water. Since solubility is important factor for good reactivity and selectivity, so improving the solubility of organic substrates in water that may will expand the scope of water-based organic synthesis. Incorporation of surface active agents (surfactants) in aqueous media has been proved to enhance the solubility as well as the reactivity of water mediated reactions.

Pyrazoles are an important class of heterocyclic compounds with prominent properties. They are an important class of bio-active drug targets in the pharmaceutical industry[2], they are also the core structure of numerous biologically active compounds[3]. For example, they exhibit antipyretic[4], gastric secretion stimulatory[5], antibacterial[6], antifilarial[7], antidepressant[8], and anti-inflammatory properties[9]. Moreover, the corresponding 4, 4′-(arylmethylene)bis(*1H*-pyrazol-5-ols) are used as fungicides[10], pesticides[11], insecticides[12], and dyestuffs[13] and as the chelating and extracting reagents for different metal ions[14].

In the recent years, several new methods have been developed including the use of various catalyst *viz*; CAN[15], Silica sulfuric acid[16], ionic liquid[17], SDS[18], pyridine trifluoroacetate[19], PEG-400[20], piperidine-ethanol[21], eletrolysis[22], silica bonded sulfamic acid[23]. All these methods, exhibit some advantages but also suffer from certain drawbacks such as unsatisfactory yield, prolonged reaction time, elevated temperature, tedious work-up, and the use of anhydrous organic solvents and relatively expensive reagents. So, the development of simple, convenient and environmental friendly procedure are still demanding for the preparation of 4, 4′-(arylmethylene)bis(*1H*-pyrazol-5-ols).

Application of microwave in surfactant-water me-

dium has been reported for the first time for organic synthesis by our group in recent times[24]. To the best of our knowledge, reports related to the synthesis of 4, 4′-(arylmethylene)bis(*1H*-pyrazol-5-ols) in surfactant medium promoted by microwave irradiation has not been published till date. We herein report a green, one-pot, efficient synthesis of 4, 4′-(arylmethylene)bis(*1H*-pyrazol-5-ols) under microwave irradiation in surfactant medium.

RESULTS AND DISCUSSION

In continuation of our research work in the development of highly expedient methodologies for the synthesis of biologically important heterocyclic compounds[25], we have selected 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one and 1 equiv of benzaldehyde in surfactant medium under microwave irradiation as a model reaction. Initially the reaction was carried out at 50 W and 25 °C for 4 min it furnished a solid product **(3a)** in low yield (34 %). Compound 3a was identified by the spectral methods. The presence of a singlet at δ 4.87and broad singlet at δ 13.38 in ^{1}H-NMR and picks at 1600 cm^{-1} and 3450 cm^{-1} in IR spectrum clearly indicate the formation of 3a. In an attempt to improve the yield, we further optimized the reaction condition by altering watt, temperature and time. Significant improvement was achieved by using 160 W, 60 °C and 4 min. In order to optimize the reaction condition we have screened a number of different surfactant on the model reaction. However, when the same reaction was conducted under above mentioned condition using CPC (cetylpyridinium chloride) or SDS (sodium dodecyl sulphate) as a surfactant it gave comparatively lower yield of product (TABLE 1, entry 2 and 3), best yield (94 %) was achieved by using AOT (sodium *bis* -2-ethyl hexyl sulphosuccinate) as surfactant under microwave-irradiation (TABLE 1, entry 4). Among the three, AOT gave the better results, because of its more hydrocarbon content in the core region.

After optimizing the reaction condition, the generality of the method was examined by the several substituted aryl aldehydes, it is evident from TABLE 2 that the reaction can tolerate a wide range of aryl aldehydes containing electron donating to electron withdrawing groups. All the products were analytically pure and structures were determined by comparing the physical (mp)[15-22] and the spectral data.

TABLE 1 : Optimization of the reaction condition under microwave-irradiation and conventional methods in presence of different surfactants[a].

	Microwave			Conventional		
Entry	Surfactant water	Time (min)	Yields (%)[b]	Surfactant water	Time (h)	Yields (%)[b]
1	H_2O	8	55	H_2O	8	76
2	SDS	4	80	SDS	1	86[18]
3	CPC	4	83	CPC	1.3	76 [present work]
4	AOT	4	94	AOT	1.3	80 [present work]

[a] **5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one (2 mmol) , benzaldehyde (1 mmol), 60 °C and 160 watt.; [b]Isolated yields**

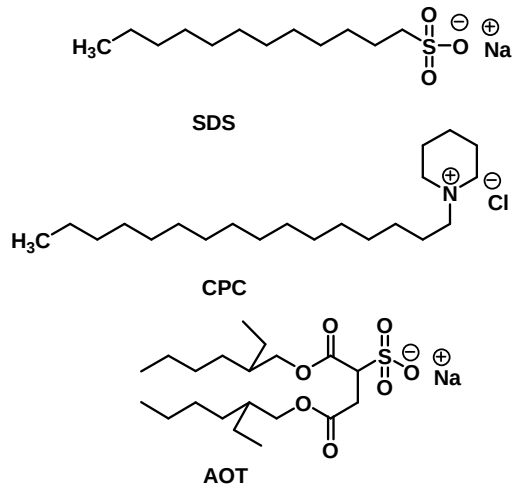
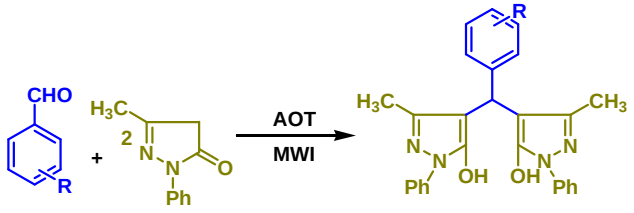


Figure 1 : Structure of different surfactants

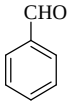
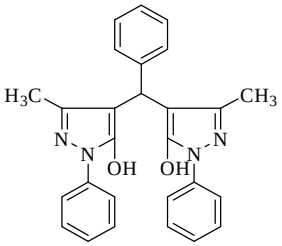
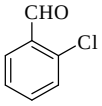
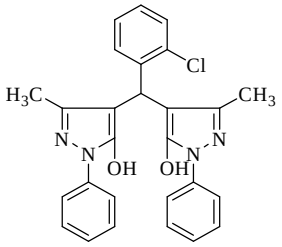
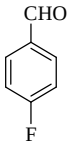
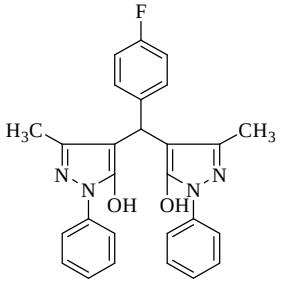
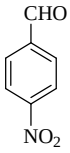
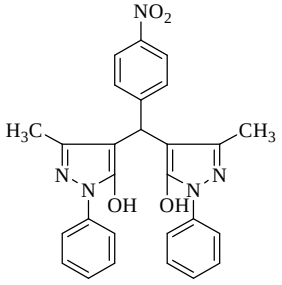
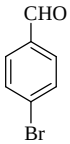
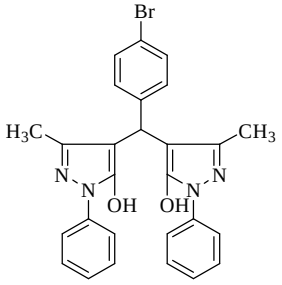
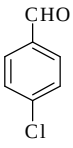
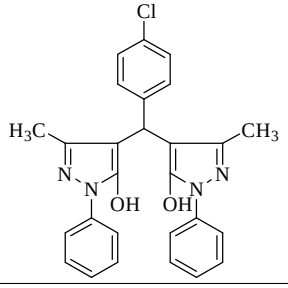


Reagent and condition: AOT-water, MWI, 160 W, 60°C, 4-6 min

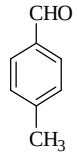
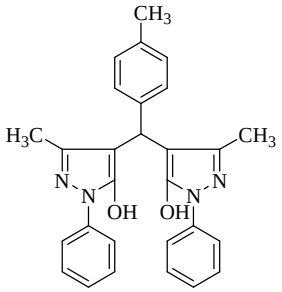
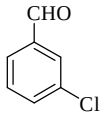
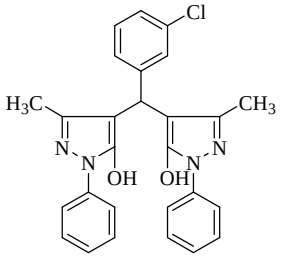
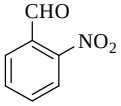
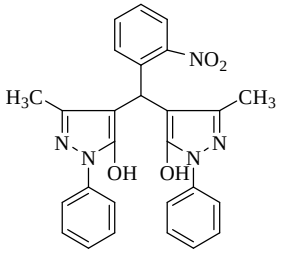
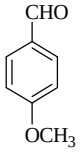
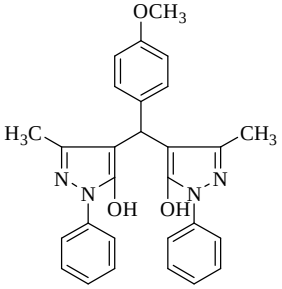
SCHEME 1

The plausible reaction mechanism is depicted in Scheme 2, Initially, 5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one **(2)** undergo Knoevenagel condensation with aryl aldehyde **(1)**, affords intermediate **(4)**. Intermediate **(4)** acts as a Michael acceptor and it react with another molecule of 5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one 2, under Michael fashion

TABLE 2 : The reaction of with 5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one with aryl aldehydes under microwave irradiation in presence of AOT-water

Entry	Aryl aldehyde	Product	Time (min)	Yield (%)[b]	M. p (°C)
1			4	94	171-173[16]
2			5	91	233-234[16]
3			4	90	228-229
4			4	95	226-228[19]
5			5	92	241-143
6			6	90	214-216[16]

Full Paper

Entry	Aryl aldehyde	Product	Time (min)	Yield (%)[b]	M. p (°C)
7			6	88	200-201[19]
8			4	89	150-152[16]
9			3	91	210-211
10			6	90	243-244

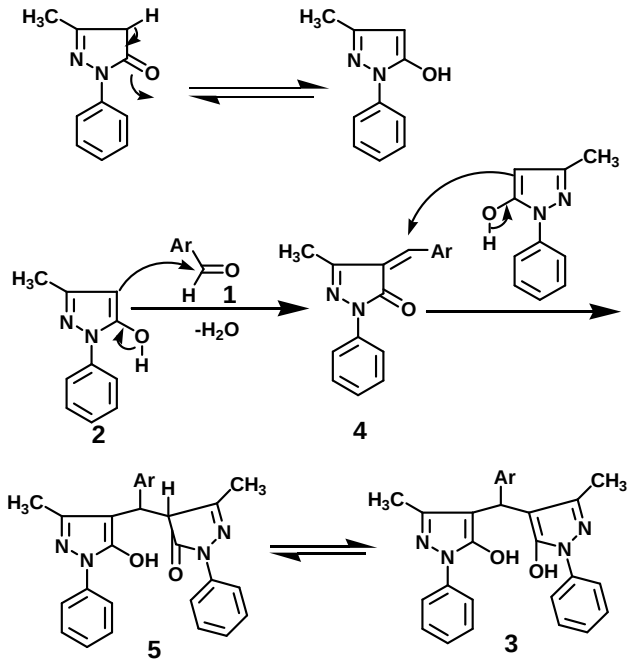
furnished a new intermediate **(5)**. Final product 3 is obtained after tatomerisation of **(5)**.

Furthermore, knowing that surfactant is non-biodegradable, in order to minimize the waste of the reaction, we have studied the reusability of AOT in the optimized reaction condition. After completion of the reaction as monitored by TLC, the organic compound was extracted with ethyl acetate and AOT-containing water was reused for another five runs and no significant drops in product yield was observed.

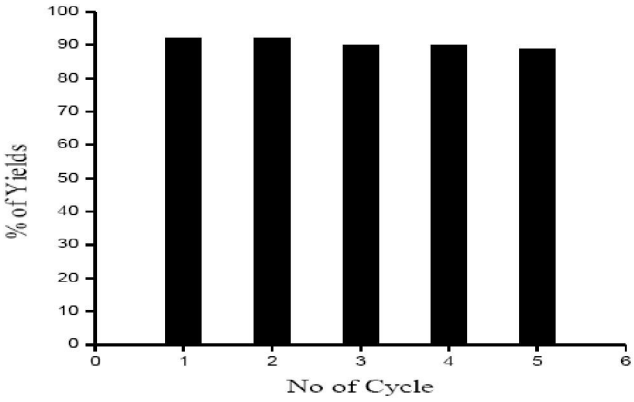
EXPERIMENTAL

General

All the experiments were carried out in MATTHEWS, NC- MADE IN USA. MODEL-DISCOVER-S. MODEL NO-NP-1009, Microwaves Digester in sealed vessel. Melting points were deter-



Scheme 2 : Plausable reaction mechanism



mined in open capillaries and are uncorrected. IR spectra were recorded on Spectrum BX FT-IR, Perkin Elmer (υ_{max} in cm^{-1}) on KBr disks. ^1H NMR NMR (400 MHz) spectra were recorded on Bruker Avance II-400 spectrometer. Mass spectra were recorded on Waters ZQ-2695. CHN were recorded on CHN-OS analyzer (Perkin Elmer 2400, Series II). Silica gel G (E-mark, India) was used for TLC. Hexane refers to the fraction boiling between 60 and 80 °C.

General procedure for the synthesis of 4, 4/-(arylmethylene)bis(1H-pyrazol-5-ols) derivatives (3a-j)

A mixture of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) and aryl aldehydes (1 mmol) was added to an aqueous solution of AOT (15 mmol, 5ml) and irradiated at 60 °C and 160 watt for the time mention in the table 2. After completion, (TLC) the reaction mixture was cooled to room temperature, extracted with ethyl acetate (3 × 10 ml) and washed with water (3 × 10 ml) followed by brine solution and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the crude product was purified by column chromatography.

SPECTRAL DATA

2.2a 4,4'-(Phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3450, 2925, 1600 cm^{-1}. ^1H NMR ($CDCl_3$+ DMSO-d_6, 400 MHz): δ = 2.26 (s, H), 4.84 (s, 1H), 7.09-7.39 (m, 11H), 7.66 (d, *J* = 8.0 Hz, 4H), 13.38 (brs, 2H). ESI-MS *m/z* 437 $[M + H]^+$. Anal calcd for $C_{27}H_{24}N_4O_2$: C, 74.29; H, 5.54; N, 12.84. Found: C, 74.18; H, 5.42; N, 12.67.

2.2b 4,4'-[(2-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3489, 2925, 1593 cm^{-1}. ^1H NMR ($CDCl_3$+ DMSO-d_6, 400 MHz): δ = 2.30 (s, 6H), 5.16 (s, 1H), 7.03-7.17 (m, 7H), 7.66 (d, *J* = 8.0 Hz, 5H), 7.89 (d, *J* = 7.6 Hz, 2H), 13.56 (brs, 2H). ESI-MS *m/z* 471, 473 $[M + H]^+$. Anal calcd for $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.92; N, 11.90. Found: C, 69.09; H, 4.82; N, 11.72.

2.2c 4,4'-[(4-Fluorolphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3476, 2919, 1600 cm^{-1}. ^1H NMR ($CDCl_3$+ DMSO-d_6, 400 MHz): δ = 2.29 (s, 6H), 4.82 (s, 1H), 6.87 (t, *J* = 8.6 Hz, 2H), 7.11-7.40 (m, 12H), 13.45 (brs, 2H). ESI-MS *m/z* 455$[M + H]^+$. Anal calcd for $C_{27}H_{23}FN_4O_2$: C, 71.35; H, 5.10; N, 12.33. Found: C, 71.14; H, 5.27; N, 12.39.

2.2d 4,4'-[(4-Nitrophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3416, 2925, 1600 cm^{-1}. ^1H NMR ($CDCl_3$+ DMSO-d_6, 400 MHz): δ = 2.29 (s, 6H), 4.88 (s, 1H), 7.12-7.12 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 4H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 4H), 8.05 (d, *J* = 8.4 Hz, 2H), 13.26 (brs, 2H). ESI-MS *m/z* 482 $[M + H]^+$. Anal calcd for $C_{27}H_{23}N_5O_4$: C,

67.35; H, 4.81; N, 14.54. Found: C, 67.07; H, 4.76; N, 14.14.

2.2e 4,4'-[(4-Bromophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3390, 2925, 1600 cm^{-1}. ^1H NMR ($CDCl_3$+ DMSO-d_6, 400 MHz): δ = 2.30 (s, 6H), 4.92 (s, 1H), 7.17-7.25 (m, 4H), 7.40-7.46 (m, 6H), 7.69 (d, *J* = 8.0 Hz, 4H), 13.89 (brs, 2H). ESI-MS *m/z* 515, 517 $[M + H]^+$. Anal calcd for $C_{27}H_{23}BrN_4O_2$: C, 62.92; H, 4.50; N, 10.87. Found: C, 63.10; H, 4.38; N, 11.03.

2.2f 4,4'-[(4-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3400, 2932, 1593 cm^{-1}. ^1H NMR ($CDCl_3$+ DMSO-d_6, 400 MHz): δ = 2.27 (s, 6H), 4.80 (s, 1H), 7.10-7.18 (m, 6H), 7.28-7.32 (m, 4H), 7.66 (d, *J* = 7.6 Hz, 2H), 13.35 (brs, 2H). ESI-MS *m/z* 471, 473 $[M + H]^+$. Anal calcd for $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.92; N, 11.90. Found: C, 68.94; H, 4.95; N, 11.92.

2.2g 4,4'-[(4-Methylphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3g)

IR (KBr): 3396, 2932, 1593 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.95 (s, 6H), 2.17 (s, 3H), 4.61 (s, 1H), 6.93-7.00 (m, 6H), 7.12-7.18 (m, 4H), 7.45 (d, *J* = 7.6 Hz, 2H) . ESI-MS *m/z* 451 $[M + H]^+$. Anal calcd for $C_{28}H_{26}N_4O_2$: C, 74.65; H, 5.82; N, 12.44. Found: C, 74.60; H, 5.93; N, 12.32.

2.2h 4,4'-[(3-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3394, 2935, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.04 (s, 6H), 4.68 (s, 1H), 7.06-7.8.02 (m, 16H). ESI-MS *m/z* 471, 473 $[M + H]^+$. Anal calcd for $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.92; N, 11.90. Found: C, 68.75; H, 4.78; N, 11.93.

2.2i 4,4'-[(2-nitrophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3390, 2935, 1595 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.09 (s, 6H), 4.68 (s, 1H), 7.11-7.92 (m, 16H). ESI-MS *m/z* 482 $[M + H]^+$. Anal calcd for $C_{27}H_{23}N_5O_4$: C, 67.35; H, 4.81; N, 14.54 Found: C, 67.22; H, 4.90; N, 14.29.

2.2j 4,4'-[(4-methoxyphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)

IR (KBr): 3395, 2934, 1606 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.19 (s, 6H), 3.73 (s, 3H) 4.76 (s, 1H), 6.71-8.59 (m, 16H). ESI-MS *m/z* 467 $[M + H]^+$. Anal calcd for $C_{28}H_{26}N_4O_3$: C, 72.09; H, 5.62; N, 12.01 Found: C, 72.07; H, 5.89; N, 12.13.

CONCLUSION

In summary, we have developed a microwave promoted straightforward synthesis of 4, 4/-(arylmethylene)bis(*1H*-pyrazol-5-ols) in surfactant medium (AOT-water). The methodology is high yielding, rapid and relatively inexpensive, and environmental friendly.

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