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Guanidine hydrochloride catalyzed efficient one-pot pseudo five-component synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) in water

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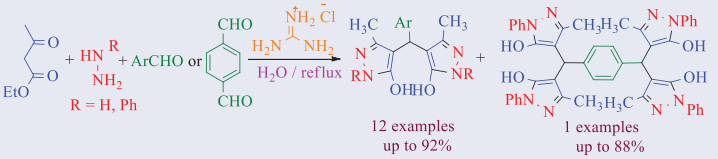
ABSTRACT

The present methodology describes an efficient, environmentally friendly and simple protocol for the synthesis of some 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives through a one-pot pseudo-five-component reaction of hydrazine hydrate/phenyl hydrazine, ethyl acetoacetate, and various aromatic aldehydes catalyzed by guanidine hydrochloride. This condensation reaction was performed by tandem Knoevenagel–Michael reaction in water under refluxing conditions giving the title compounds in 82–92% yields. Atom economy, simple operation, easy work-up, using inexpensive organocatalyst, high yields in short times, clean transformation, and environmentally benign are some of the important features of this new protocol.

GRAPHICAL ABSTRACT



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4,4′-(Arylmethylene)bis(1*H*-pyrazol-5-ols); guanidine hydrochloride; Knoevenagel–Michael; water

Introduction

Heterocycles containing nitrogen atom are of interest because of their biological activities and medicinal importance including ontological research. Pyrazoles are one of these heterocyclic compounds. They have been extensively attracted due to their importance as a class of bioactive drug targets in the pharmaceutical industry and the core structure of numerous biologically active compounds.[1] Pyrazoles, especially 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) is a very important class of compounds with various biological activities such as anti-inflammatory,[2] antipyretic,[3] gastric secretion

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stimulatory,[4] antidepressant,[5] antifilarial agents,[6] antibacterial,[7] fungicides,[8] pesticides,[9] anticancer,[10] antiviral,[11] antiproliferative,[12] hypoglycemic,[13] and antioxidant.[14]

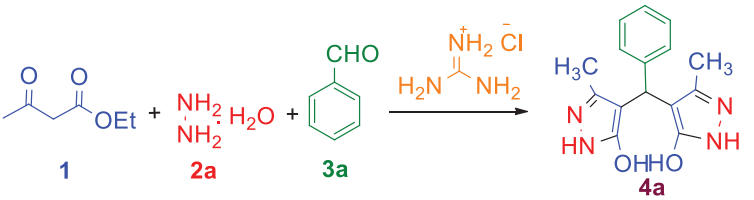
One-pot tandem Knoevenagel–Michael reaction is one of the most broadly used methods for the synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) via three-component condensation of aldehydes with 2 equiv. of 3-methyl-1*H*-pyrazol-5(4*H*)-one or 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and pseudo five-component reaction of hydrazine hydrate/phenyl hydrazine, ethyl acetoacetate and various aromatic aldehydes. In recent years, synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) has been reported using MCR in the presence of some catalyst such as $Ce(SO_4)_2$ $4H_2O$,[15a] ceric ammonium nitrate (CAN),[11] PEG-SO_3H,[15b] ammonium acetate,[15c] *N*-methylimidazolium perchlorate ([MIm]ClO_4),[15d] pyridine trifluoroacetate or acetic acid,[15e] Cu-isatin Schiff base supported on γ-Fe_2O_3[15f], Silica-bonded S-sulfonic acid,[15g] Sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester,[15h] L-proline,[15i] Ph_3CCl,[15j] sulfonated rice husk ash (RHA-SO_3H),[15k] 3-aminopropylated silica gel (AP-SiO_2),[15l] 2-hydroxy ethylammonium propionate,[15m] Ag/TiO_2 nano-thin films,[15n] Mohr's salt,[15o] HAP@AEPH_2-SO_3H,[15p] morpholinium glycolate,[15q] nano-$NiZr_4(PO_4)_6$,[15r] solid state,[15s] and ammonium chloride. However, some of these methods suffer from moderate yields, long reaction times, harsh reaction conditions, use of toxic organic solvents, expensive catalysts, many tedious steps or catalyst preparation.

Organocatalysts have been used widely in many reactions as mono and bifunctional catalysts because of economic and environmental considerations. Among them, guanidines and their corresponding guanidinium salts are becoming powerful tools for activation of the carbonyl functionality in organic transformations.[16] Moreover, guanidinium salts, on the other hand, display weak Brønsted acidity and are bidentate, cationic hydrogen-bond donors, and the possibility of the delocalized guanidinium cation acting as a metal-free "π-Lewis acid" has even been discussed.[17] In this article, we wish to introduce guanidine hydrochloride as a highly efficient organocatalyst for the facile and green synthesis of 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in aqueous media. Using this catalyst, the electrophilic substitution reactions of 3-methyl-1*H*-pyrazol-5(4*H*)-one and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one with carbonyl compounds proceeded smoothly to afford the desired products in high yields and relatively short reaction times.

Results and discussion

To find the optimum reaction conditions, a mixture of hydrazine hydrate (2.0 mmol), ethyl acetoacetate (2.0 mmol), and benzaldehyde (1.0 mmol) was stirred in the absence of catalyst in water (10 mL) under reflux condition and afforded expected product up to 30% yield within 60 min of reaction time (Table 1). When the reaction was accomplished in the presence of guanidine hydrochloride (5% mol), the desired product was obtained in 78% yield after 60 min (Table 1, entry 2). An increase in the amount of catalyst from 5 to 10% mol not only decreases the reaction time from 60 to 40 min but also increased the product yield from 78 to 90% (Table 1, entry 3). Loading of the

Table 1. Optimization of the synthesis of **4a**.



Entry	Solvent	Catalyst loading (mol%)	Temp. (°C)	Time (min)	Yield (%)
1	H_2O		Reflux	60	30
2	H_2O	5	Reflux	60	78
3	H_2O	10	Reflux	40	90
4	H_2O	15	Reflux	40	91
5	H_2O	20	Reflux	40	91
6	EtOH	10	Reflux	60	65
7	CH_3CN	10	Reflux	60	45
8	THF	10	Reflux	60	41
9		10	70	60	61
10		10	90	60	72

catalyst up to 15 and 20 mol.% did not prove satisfactory in terms of yield or reaction time (Table 1, entries 4 and 5).

Moreover, we examined the effect of different protic and aprotic solvents such as ethanol, acetonitrile, and tetrahydrofuran on the model reaction in the presence of guanidine hydrochloride (10% mol) under reflux conditions within 60 min. As indicated in Table 1, EtOH, CH_3CN, and THF afforded moderate yields of the desired product (Table 1, entries 6–8). Next, we studied the model reaction under the solvent-free condition at 70 and 90 °C and afforded 61 and 72% yields of the corresponding product (Table 1, entries 9–10), respectively. Accordingly, the optimization of reaction conditions was established as indicated in entry 3 of Table 1.

We thus used the reaction condition of entry 3 of Table 1 for further exploration preparing compounds **4a–f**, having a number of electron-withdrawing and electron-donating substituents on aromatic aldehydes. The results are summarized in Figure 1. Under the optimal conditions, products yields (83–92%) were uniformly good and were not particularly substituent dependent.

After the successful application of guanidine hydrochloride as a organocatalyst in the synthesis of compounds **4**, with the optimal conditions in hand, we decided to use it in the condensation of phenyl hydrazine instead of hydrazine hydrate with ethyl acetoacetate and various aromatic aldehydes in aqueous medium leading to 4,4′-(phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives **5a–f** and 4,4′,4″,4‴-(1,4-Phenylenebis(methanetriyl))tetrakis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**5g**) as an important class of bis(pyrazolyl)methanes. For this purpose, one-pot, two-step domino reaction of phenyl hydrazine (**2b**, 2 mmol), ethyl acetoacetate (**1**, 2 mmol) and aromatic aldehydes (**3**, 1 mmol) was investigated. Initially, the reaction of phenyl hydrazine (**2b**, 2 mmol) and ethyl acetoacetate (**1**, 2 mmol) in the presence of guanidine hydrochloride (10 mol.%) in water (10 mL) under reflux condition was studied. The desired 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**6b**) was obtained in high yield (90%) after 90 min. After completion of the reaction, various aromatic aldehydes (**3**, 1 mmol) or terephthaldehyde

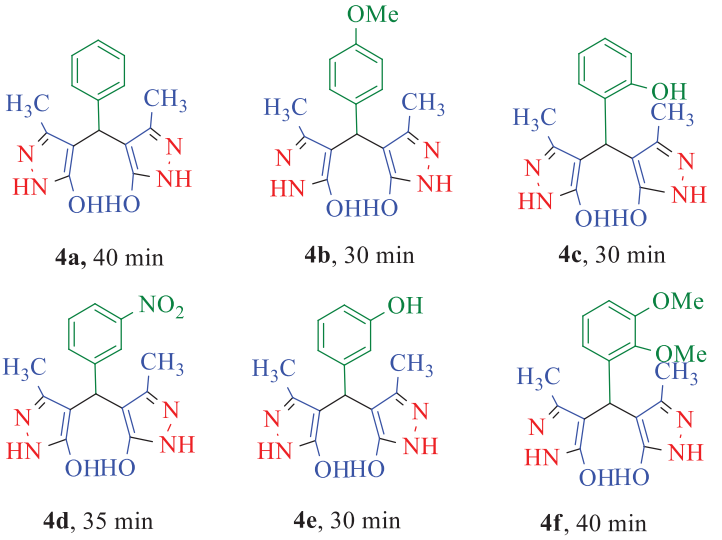
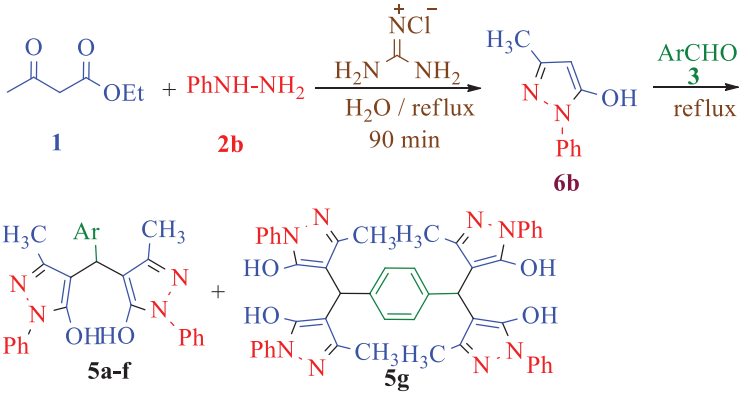


Figure 1. Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) derivatives **4a–f**.



Scheme 1. One-pot synthesis of 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**6**) and bis(pyrazol-5-ol)s **5a–g**

(0.5 mmol) was added to the reaction mixture for the synthesis of a series of compounds **5** (Scheme 1). The reactions proceeded successfully to give bis(pyrazol-5-ol)s **5a–g** in 85–92% yields within 30–60 min.

As shown in Figure 2, the aryl aldehydes that possess electron-donating and electron-withdrawing substituents provided the corresponding products in good to high yields. It should be noted that the purification of the title compounds **4** and **5** is very easy. After cooling the reaction mixture to room temperature, the solid resulting from the reaction was easily separated by simple filtering. Then, the crude product was recrystallized from ethanol to produce the desired pure product.

In another study, the one-pot pseudo-three-component reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**6b**, 2 equiv.) and benzaldehyde (1 equiv.) in the presence of organocatalyst in the water at reflux were examined (Scheme 2). In this process, the same

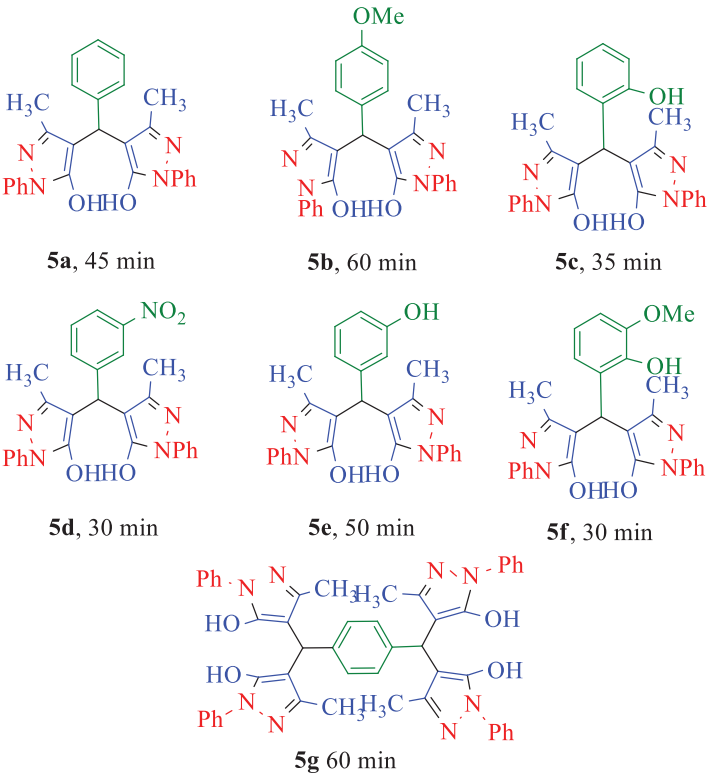
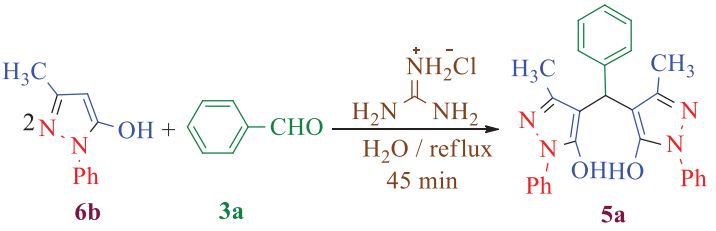


Figure 2. Synthesis of 4,4′-(phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives **5a–g**.

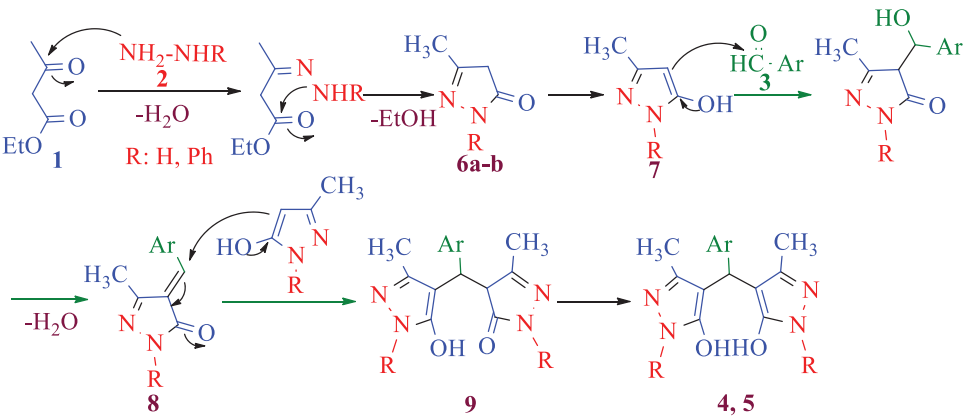


Scheme 2. One-pot synthesis of bis(pyrazol-5-ol) **5a.**

product **5a** was obtained after 45 min in 86% yield. However, the other title compounds **5b–g** can be obtained by this procedure.

The products **4a–e**, **5a–e**, and **5g** were known compounds, their authenticity was established by ^{1}H NMR and their melting points compared with that reported in literature. The products **4f** and **5f** were unknown and established by their ^{1}H NMR, ^{13}C NMR, FTIR, CHN, and MS.

A plausible reaction mechanism for the formation of **4** and **5** is proposed in Scheme 3. On the basis of this mechanism, first, a condensation of phenylhydrazine derivative (**2**) with ethyl acetoacetate (**1**) catalyzed by guanidinium chloride is proposed to give the adducts **6a–b**. Subsequently, the intermediate **8** is likely formed by the condensation of aromatic aldehyde **3** with **7**, which is the tautomer of **6**. The next step, Michael addition



Scheme 3. Proposed mechanism for the one-pot pseudo-five-component synthesis of bis(pyrazol-5-ol)s **4** and **5.**

of another intermediate of **7** to **8** gives adduct **9** which undergoes tautomerization to afford the desired products **4** and **5**.

Experimental

General procedure for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives 4a–f

Hydrazine hydrate (1.0 mmol), ethylacetoacetate (1.0 mmol), aromatic aldehyde (0.5 mmol), guanidine hydrochloride (10% mol) and 5 mL of H_2O were placed in a 50 mL round bottom flask over a magnetic stirrer and the contents were refluxed for appropriate times (30–50 min). After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool at room temperature and the resulting solid (crude product) filtered and dried. The crude products were recrystallized from ethanol to afford the pure products.

General procedure for the synthesis of 4,4′-(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives 5a–g

Phenyl hydrazine (1.0 mmol), ethylacetoacetate (1.0 mmol), guanidine hydrochloride (10% mol), and 5 mL of H_2O were placed in a 50 mL round bottom flask over a magnetic stirrer and the contents were refluxed for 90 min (the progress of the reaction was monitored by TLC). Then, aromatic aldehyde (0.5 mmol) or terephthaldehyde (0.25 mmol) was added to the reaction mixture and the contents were refluxed for appropriate times (30–60 min). After completion of the reaction (monitored by TLC), the reaction mixture was cooled at room temperature and the resulting solid (crude product) filtered and dried. The crude products were recrystallized from ethanol to afford the pure products.

Conclusion

In summary, the present research is an operationally simple, cleaner and highly efficient method for the green synthesis of one-pot pseudo-five-component synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) in the water at reflux using a catalytic quantity of guanidine hydrochloride. Compared to the classical methods, a library of pyrazole derivatives was obtained in excellent yields. The current protocol has the advantages of short reaction time, generality, the use of small amount of the low-cost catalyst, the use of water instead of toxic solvents, simple environmentally friendly, isolation products, and being environmentally benign.

Full experimental detail for unknown compounds, ^{1}H, and ^{13}C NMR spectra can be found through the "Supplementary Content" section of this article's webpage.

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