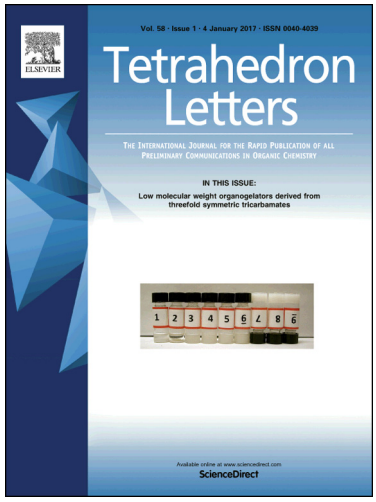

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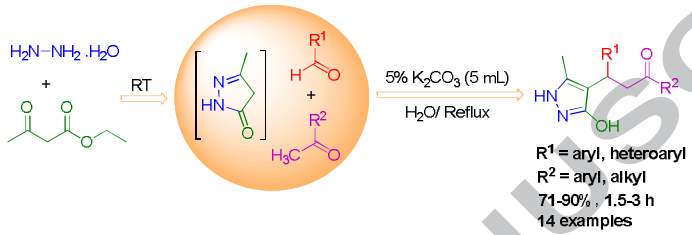

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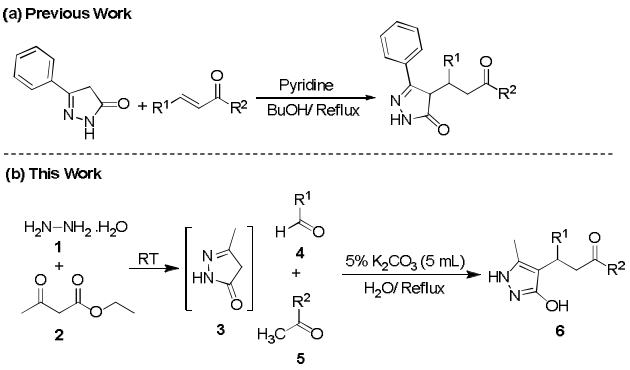
ABSTRACT

A new, simple and efficient synthesis of 4-alkyl-5-methyl-1*H*-pyrazol-3-ols in water by a two-pot four component reaction of ethyl acetoacetate, hydrazine hydrate, aldehyde and ketone in presence K_2CO_3 as the catalyst is described. Use of water as the reaction medium, operational simplicity, mild reaction conditions, application of a cost-effective, nontoxic and easily available catalyst with auto-tandem catalysis, wide substrate scope, easy workup and purification process make the protocol highly attractive.

The syntheses of 4-alkyl-1*H*-pyrazoles have received considerable attention due to their wide range of biological activities like antimicrobial,[1] antioxidant,[2] anticancer,[3] analgesic,[4] anti-inflammatory,[5] antimalarial,[6] antiglaucoma,[7] antiallergic[8] and antidepressant[9] properties. Further, synthetic interest has been increased due to the discovery of these compounds as potential inhibitors of hepatitis C virus (HCV) replication,[10] cannabinoid type-1 receptor antagonists,[11] selective inhibitory activity against COX-2 enzyme,[12] partial agonists for the nicotinic acid receptor,[13] anti-HIV agents,[14] and p38 kinase inhibitors.[15] Some of the 4-alkyl-1*H*-pyrazole drug molecules available in the market are phenylbutazone, metamizole and rimonabant to name a few.[16] In addition, these molecules have also found tremendous applications as bifunctional ligands for metal catalysis.[17] Thus, these heterocycles have attracted the attention of synthetic organic chemists and a number of developed procedures have been reported.

The synthetic strategy employed for the synthesis of 4-alkyl-1*H*-pyrazoles includes condensation of hydrazines with 1,3-dicarbonyl compounds[18] and β-oxodithioesters;[19] [2+3] cycloaddition of 1,3-dipolar diazo compounds with alkenes[20] and alkynes;[21] reactions of hydrazones with nitroolefins.[22] In recent years several Michael addition strategies have been proposed.[23] In 1994, Etman *et al.* reported the first Michael addition of 3-phenyl-2-pyrazolin-5-one with chalcones for the synthesis of 4-alkyl-1*H*-pyrazoles (Scheme 1a).[24] However, this methodology is associated with limitations like the application of expensive and toxic pyridine as the catalyst, butanol as the solvent system, multistep sequence, longer reaction time and limited substrate scope, which reduce its applicability. Thus, it is necessary to develop an environmentally friendly method to construct these types of heterocycles. Therefore, in continuation of our efforts on developing environment-friendly synthetic procedures,[25] we wish to report herein a new, simple, efficient and cost-effective synthesis of 4-alkyl-5-methyl-1*H*-pyrazol-3-ols *via* K_2CO_3 catalyzed two-pot multicomponent reaction under mild reaction conditions. The synthesis proceeds by



Scheme 1. Synthesis of 4-alkyl-5-methyl-1*H*-pyrazol-3-ols.

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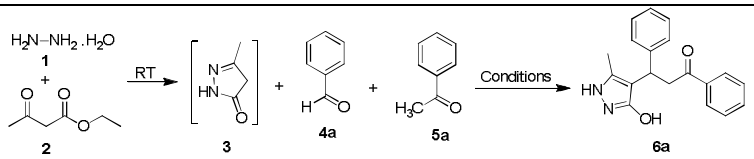
Table 1. Optimization of the reaction[a]



Entry	Catalyst	Solvent[b]	Temp. (°C)	Time (h)	Yield (%)[c]
1	2% K_2CO_3	H_2O	Reflux	3	70
2	5% K_2CO_3	H_2O	Reflux	2	85
3	7% K_2CO_3	H_2O	Reflux	2	85
4	20 mol% L-proline	H_2O	Reflux	2	10
5	20 mol % glycine	H_2O	Reflux	2	12
6	20 mol % $FeCl_3.6H_2O$	H_2O	Reflux	2	10
7	20 mol% $InCl_3$	H_2O	Reflux	2	15
8	5% Na_2CO_3	H_2O	Reflux	2	80
9	5% LiOH	H_2O	Reflux	2	70
10	5% K_2CO_3	EtOH	Reflux	2	25
11	5% K_2CO_3	MeOH	Reflux	2	30
12	5% K_2CO_3	Toluene	Reflux	2	10
13	5% K_2CO_3	H_2O	RT[d]	24	15
14	None	H_2O	Reflux	12	10

[a] Reaction Scale: **1**, **2**, **4a** and **5a** (1 mmol) each. [b] 5 mL. [c] Isolated Yield. [d] RT ≈ 30 °C. Procedure: In a flask, a mixture of **1** and **2** is stirred at RT for 2 min under solvent free condition. The solid product formed is washed with ice cold water to afford **3** in pure state. In an another flask **4a** and **5a** are made to react under the appropriate reaction conditions until the formation of α,β-unsaturated ketone reaches the equilibrium as indicated by TLC, followed by the addition of the whole amount **3** leads to the final product **6a**.

initial Knorr condensation between ethyl acetoacetate and hydrazine hydrate under solvent free condition at room temperature to generate 3-methyl-1*H*-pyrazol-5(4*H*)-one, which subsequently undergoes K_2CO_3 catalyzed Michael addition to the *in situ* generated α,β-unsaturated ketone, formed by the K_2CO_3 catalyzed aldol condensation between an aldehyde and a ketone in water (Scheme 1b).

This protocol proves to be operationally simple and affords high yields under mild reaction conditions. The use of K_2CO_3 as catalyst and water as the solvent system provides cost effectiveness and environmental benignity. Because water is not only most abundant and nontoxic but also with its unique physicochemical properties like polarity, hydrogen bonding, hydrophobic effect and trans-phase interactions greatly influence the reaction course,[26] while K_2CO_3 is cheap, nontoxic, easily available and easy to handle. Moreover, the auto-tandem catalysis[27] of K_2CO_3 gives the maximum utilization of the catalyst and the application of multi-component reactions (MCRs) strategy provides flexible, convergent, and pot, atom and step economic synthesis.[28] In addition, high yields, short reaction time and simple purification process with no chromatography technique make the protocol highly applicable for the synthesis of 4-alkyl-1*H*-pyrazoles library.

We began our study by simply refluxing benzaldehyde (**4a**, 1 mmol) and acetophenone (**5a**, 1 mmol) in the presence of 5 mL of 2% K_2CO_3 in water until the generation of α,β-unsaturated ketone, followed by the addition of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3**) synthesized from ethyl acetoacetate (**2**, 1 mmol) and hydrazine hydrate (**1**, 1 mmol) under room temperature stirring, and further refluxing generated 3-(3-hydroxy-5-methyl-1*H*-pyrazol-4-yl)-1,3-diphenylpropan-1-one (**6a**) in 70% yield in 3 h (Table 1, entry 1). The progress of the reaction was monitored by TLC. Inspired by this result the reaction was set for optimization and was found that 5 mL of 5% K_2CO_3 in H_2O afforded the high yield of 85% in 2 h; further increasing the catalyst load up to 5 mL of 7% K_2CO_3 did not show any significant difference in reaction time and yield (Table 1, entries 2-3). Other potential bases like Na_2CO_3 and LiOH also yielded the desired product but with relatively lower yields. Organocatalysts like L-proline and glycine and Lewis acid catalysts like $FeCl_3.6H_2O$ and $InCl_3$ were also tested but failed to catalyze the reaction effectively (Table 1, entries 4-7). To find the best effect of solvent, several organic solvents like

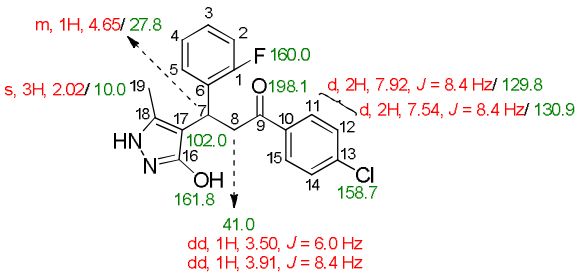


Fig 1. Selected ^1H and ^{13}C NMR shift of **6b**

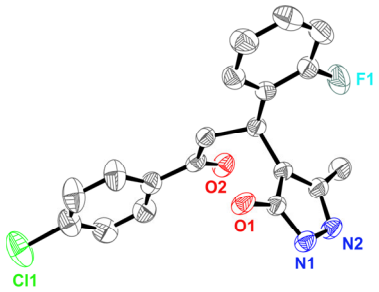
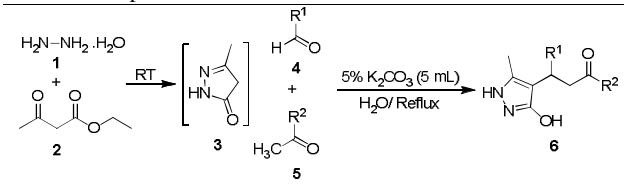
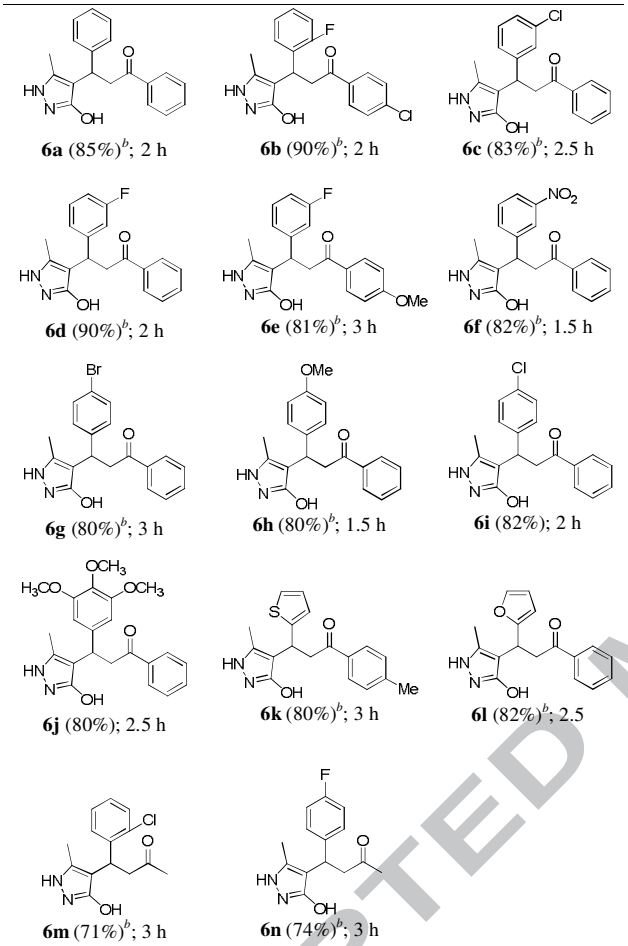


Fig 2. ORTEP diagram of **6b** [CCDC 1511960]

Table 2. Scope of the reaction[a]





6a (85%)[b]; 2 h **6b** (90%)[b]; 2 h **6c** (83%)[b]; 2.5 h

6d (90%)[b]; 2 h **6e** (81%)[b]; 3 h **6f** (82%)[b]; 1.5 h

6g (80%)[b]; 3 h **6h** (80%)[b]; 1.5 h **6i** (82%); 2 h

6j (80%); 2.5 h **6k** (80%)[b]; 3 h **6l** (82%)[b]; 2.5

6m (71%)[b]; 3 h **6n** (74%)[b]; 3 h

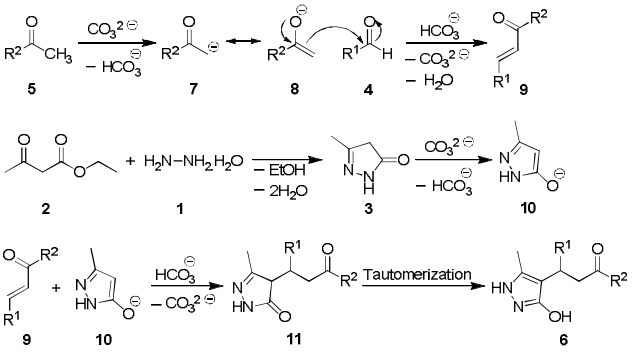
[a] Reaction scale: **1**, **2**, **4** and **5** (1 mmol each). [b] Isolated yield

EtOH, MeOH and toluene were tested; all of them afforded the desired product in low yields which may be due to the low solubility of K_2CO_3 in these organic solvents (Table 1, entries 10-12). The attempt to obtain the synthesis at room temperature and under catalyst-free condition also failed (Table 1, entries 13-14). Thus the study confirms that 5 mL of 5% K_2CO_3 in water under reflux condition are the optimum reaction conditions to achieve the synthesis efficiently.

Next, with these optimized reaction conditions, we further studied the scope of the reaction by reacting 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3**), synthesized from ethyl acetoacetate (**2**) and hydrazine hydrate (**1**) with various aldehydes and ketones. As shown in Table 2, various aromatic aldehydes participated well in the reaction to give the desired product in moderate to high yields. The presence of electron donating or withdrawing group in *ortho*-, *meta*- and *para*- positions of the benzene ring of the benzaldehydes had no significant effect on the reaction and all the corresponding products were obtained satisfactorily (Table 2, **6a-6j** and **6m-6n**). Heteroaromatic aldehydes like thiophene-2-carbaldehyde and furan-2-carbaldehyde also reacted efficiently, affording the corresponding products **6k** and **6l** in 80% and 82% yields respectively (Table 2). Various substituted acetophenones also participated well in the reaction (Table 2). When acetone was used instead of acetophenones similar results were observed and the corresponding products were obtained in good yields (Table 2, **6m**-**6n**).

The structure of **6b** was deduced from one and two dimensional NMR spectroscopic data, mass spectrum, IR, elemental analysis and X-ray crystallographic studies. The ^{1}H NMR spectrum shows a singlet at 2.03 ppm due to 3H at C-19, and a multiplet at 4.65 ppm due to the 1H at C-7, which was further evident by H,C-COSY. The diastereotopic –CH_2 appears as a pair of dd at 3.50 ppm (J = 6.0 Hz) and 3.91 ppm (J = 8.4 Hz), with geminal coupling constant J = 17.4 Hz which was correlated from H,C-COSY and H,H-COSY. There are two doublets, one of which appears at 7.54 ppm (J = 8.4 Hz) due to 2H at C-14 and C-12 and the other at 7.92 ppm (J = 8.4 Hz) due to 2H at C-15 and C-11. From H,C-COSY and DEPT experiment it was confirmed that the methine carbon C-7, methylene carbon C-8 and methyl carbon C-19 appear at 27.8, 41.0 and 10.0 ppm respectively. From DEPT experiment it was also concluded that C-1, C-9, C-16, C-17 appear at 160.0, 198.1, 161.8, 102.0 ppm respectively. Further, C-11,15 and C-12,14 appear at 129.8 and 130.9 ppm respectively (Fig. 1). In addition, the structure of **6b** has been unambiguously confirmed by X-ray crystallography as shown in Fig. 2.

Mechanistically, it is believed that the reaction proceeds by an initial K_2CO_3 catalyzed aldol condensation of an aldehyde (**4**) and a ketone (**5**) to generate α,β-unsaturated ketone (**9**). In an another reaction, ethyl acetoacetate (**2**) and hydrazine hydrate (**1**) undergo Knorr condensation to yield 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3**) which subsequently undergoes K_2CO_3 promoted Michael addition to α,β-unsaturated ketone (**9**), followed by protonation and tautomerization to yield the final product (**6**). The bicarbonate ion generated during the reaction involves in protonation to regenerate the carbonate ion.



Scheme 2. Plausible reaction mechanism.

In summary, we have demonstrated a new and highly efficient procedure for the synthesis of 4-alkyl-5-methyl-1*H*-pyrazol-3-ols by two-pot four component reaction of ethyl acetoacetate, hydrazine hydrate, aldehyde and ketone in the presence of K_2CO_3 as the catalyst in water under mild reaction conditions. The notable advantages of the protocol are the use of K_2CO_3 as mild and easily available base catalyst and water as the reaction medium, which make it cost-effective and environmentally benign. The synthesis also expands the scope of less explored aqueous media organic synthesis. On the whole, the versatility of the catalyst, wider substrate scope, high yields, operational simplicity and simple purification process make the protocol highly applicable in the synthesis of a huge library of biologically active 4-alkyl-5-methyl-1*H*-pyrazol-3-ols.

Acknowledgments

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29. *Experimental details*: All reagents were obtained from commercial sources and were used without further purification.
*General procedure for the synthesis of 4-alkyl-5-methyl-1H-pyrazol-3-ols (**6a-6n**)*: In a round bottom flask, a mixture of ethyl acetoacetate (**2**, 1 mmol) and hydrazine hydrate (**1**, 1 mmol) is stirred at room temperature for 2 min under solvent free condition. The white solid formed is washed with ice cold water (5 mL x 2) to obtain 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3**) in quantitative yield. In an another round bottom flask, a mixture of aldehyde (**4**, 1 mmol) and ketone (**5**, 1 mmol) in 5 mL of 5% aqueous K_2CO_3 solution is refluxed until the formation of α,β-unsaturated ketone reaches equilibrium as indicated by TLC. To this mixture the whole amount of **3** is added and the refluxing continued for appropriate time (Table 2). On completion of the reaction, as indicated by TLC, the reaction mixture is cooled and extracted with ethyl acetate (10 mL x 3). After drying the combined extract with anhydrous Na_2SO_4 and evaporation under reduced pressure, the crude product is purified by recrystallization from EtOH : DCM (1 : 1) solvent mixture.

Supplementary Material

Supplementary data [characterization data *viz* ^{1}H, ^{13}C NMR, IR and Mass spectral data and elemental analysis data of all the compounds and copies of ^{1}H and ^{13}C NMR spectra of all compounds can be found in the electronic supplementary information (ESI)].

Highlights:

- Simple multicomponent strategy for 4-alkyl-5-methyl-1*H*-pyrazol-3-ols.
- Water has been used as the reaction medium.
- K_2CO_3 is used as the cost effective and non-toxic catalyst.
- *In situ* generation of α,β-unsaturated ketone reduces the number of purification steps.
- The products are purified by simple recrystallization technique.