Simple and efficient protocol for the synthesis of novel dihydro-1H-pyrano[2,3-c]pyrazol-6-ones via a one-pot four-component reaction

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**Abstract**

Ba(OH)$_2$ catalyzed simple and efficient one-pot four-component reaction of Meldrums acid, ethyl acetoacetate, hydrazine hydrate, and aromatic aldehydes to give 3-methyl-4-aryl-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-ones in refluxing water is reported. The yields are high and the reactions go to completion in 1–2 h.

**Keywords:**
Pyranopyrazole-6-ones  
Aromatic aldehydes  
Meldrums acid  
Ethyl acetoacetate  
Hydrazine hydrate  
Ba(OH)$_2$  
Water

Multicomponent reaction (MCR) is a process in which three or more accessible components are combined together in one-pot to produce a final product which shows the features of all the input reactants and therefore, offers the greatest possibilities for molecular diversity in one step with minimum synthetic time and effort. As MCRs are one-pot reactions, they are easier to carry out than the multistep syntheses. This strategy is an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. In addition, MCRs are environmentally friendly, and often proceed with excellent chemoselectivities. There are three wings (techniques) of green chemistry which, if combined, would result in an excellent green chemistry protocol. These techniques are: the efficient use of solvent-free reactions, reusability of heterogeneous catalysts, and use of multicomponent reactions.

One of the most challenging aspects in the medicinal chemistry is the design and synthesis of biologically active compounds, and dihydro-1H-pyrano[2,3-c]pyrazoles represent an interesting template for medicinal chemistry and play an essential role as biologically active molecules. Many of the pyrazol-2,3-c-pyrazoles are known for their antimicrobial, insecticidal, anti-inflammatory, anticancer, and molluscidal activities.

During the last few years, synthesis of dihydroprano[2,3-c]pyrazoles has received great interest. Pyranopyrazoles are also used as pharmaceutical ingredients and biodegradable agrochemicals. The first reported pyranopyrazole was synthesized by the reaction between 3-methyl-1-phenyl-pyrazolin-5-one and tetracyanoethylene.

Another attractive area in green chemistry is designing organic reactions in aqueous media. Water offers several benefits such as control over exothermic reactions, salting out, and salting in, as well as variation of pH. We have earlier reported the synthesis of 6-amino-3-methyl-4aryl-1,4-dihydropyrano[2,3-c]pyrazol-5-carbonitriles using glycine, iodine, and imidazole as catalysts in water. In continuation of our efforts to develop methods for the synthesis of novel heterocyclic compounds using readily available, inexpensive, and environmentally friendly catalysts, herein, we report a rapid and efficient one-pot four-component synthesis of some novel 3-methyl-4-aryl-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-ones by the reaction of aromatic aldehydes, Meldrums acid, hydrazine hydrate, and ethyl acetoacetate in the presence of readily available, inexpensive, mild, green, and common laboratory chemical Ba(OH)$_2$ as a basic catalyst in water (Scheme 1).

In order to optimize the reaction conditions, we carried out the reaction between 3,4,5-trimethoxybenzaldehyde, ethyl acetoacetate, Meldrums acid, and hydrazine hydrate in the presence of 10 mol % of Ba(OH)$_2$ at reflux in different solvents such as EtOH, MeOH, H$_2$O, and CH$_3$CN; among all these solvents, H$_2$O was found to be the best in terms of the yield of the product and time of completion compared to common organic solvents. The results of this study are presented in Table 1.
To select the best catalyst, we carried out the reaction between 3,4,5-trimethoxybenzaldehyde, ethyl acetoacetate, Meldrums acid, O
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To select the best catalyst, we carried out the reaction between 3,4,5-trimethoxybenzaldehyde, ethyl acetoacetate, Meldrums acid,
and hydrazine hydrate in the presence of 10 mol % of different basic catalysts such as Ba(OH)2, K2CO3, piperidine, and NaOH. We found that, K2CO3 did not afford the product in good yield and reaction time was very long, similar results were obtained with piperidine. The yield of the desired product improved to a very less extent when NaOH was used as a basic catalyst and the product was a mixture and a sticky mass. When the same reaction was carried out in the presence of Ba(OH)2, the product was obtained in very high yield (93%) within 1.5 h (Table 2, entry 4). The results of this study are presented in Table 2.

We have also varied the amount of Ba(OH)2 from 5, 7, and 10 to 12 mol % and the results revealed that, 10 mol % gives excellent yield of the product in a short duration as shown in Table 3.

After optimizing the conditions, the generality of this method was examined by the reaction of different substituted aldehydes with ethyl acetocetate, Meldrum’s acid, and hydrazine hydrate in the presence of 10 mol % Ba(OH)2 in water under reflux. We also examined the use of aliphatic aldehydes to get the corresponding products (Table 4 entries 8–11) but there was no product formation even after 10 h under the optimized reaction conditions, and the results of this study are shown in Table 4.

It is found that, various aromatic aldehydes containing electron-donating or electron-withdrawing functional groups at different positions did show a difference in the reaction time but the yields of products were almost same (Table 4).

The formation of the product in the present reaction is expected to involve the following tandem reaction mechanism:

**Formation of pyrazolone I by the reaction between 1 and 2 and Knoevenagel condensation between 3 and 4 to give II.**

Michael addition of I with II followed by cyclization is expected to give a tricyclic intermediate III which may lose a molecule of acetone and a molecule of CO2 in subsequent steps to give the final product 5 as shown in Scheme 2. In order to establish the mechanism of the reaction, the intermediates-pyrazolone 29 and the Knoevenagel adduct 30 were prepared separately (characterized by the 1H NMR and 13C NMR spectral analysis) and were treated with each other to get the product 5a under the standardized reaction condition, which clearly indicates that the intermediates I and II are formed during the course of the present reaction.

In summary, we have demonstrated a simple, efficient, and a novel one-pot four-component protocol for the synthesis of some new pyrazopyrazol-6-one derivatives in water using Ba(OH)2 as a readily available, inexpensive, and efficient catalyst. The advantages offered by this method are: simple reaction condition, short reaction time, ease of product isolation, and excellent yields. We wish to state that this method involves environmentally friendly procedure, and is the first procedure for the synthesis of novel 3-methyl-4-aryl-4,5-dihydro-1H-pyran-2,3-c-pyrazol-6-one derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.025.

**References and notes**

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30. Synthesis of 2,2-dimethyl-5-(3′,4′,5′-trimethoxybenzylidene)-1,3-dioxane-4,6-dione (II): A mixture of 2,2-dimethyl-5-(3′,4′,5′-trimethoxybenzylidene)-1,3-dioxane-4,6-dione (II) and Ba(OH)₂ (10 mol%) were taken in 5 ml water, stirred at 26°C for 45 min. The crude solid thus separated was filtered, washed with water, and dried to get 2,2-dimethyl-5-(3′,4′,5′-trimethoxybenzylidene)-1,3-dioxane-4,6-dione in quantitative yield whose structure was established by 1HNMR and 13CNMR spectral analysis. White solid, mp: 215–216°C; 1HNMR (400 MHz, CDCl₃): δ 1.55 (s, 3H, CH₃), 3.14 (s, 2H, CH₂), 6.80 (s, 1H, NH); 13CNMR (100 MHz, CDCl₃): δ 168.1 (NH=C=O), 153.9 (C=O), 43.5 (CH_{2}), 20.6 (CH₃).