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GLYCINE-CATALYZED EFFICIENT SYNTHESIS OF PYRANOPYRAZOLES VIA ONE-POT MULTICOMPONENT REACTION

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A facile and convenient protocol is developed for the fast (5–20 min) and high-yielding (85–95%) synthesis of fused pyranopyrazoles from ethyl acetoacetate, hydrazine hydrate, an aldehyde, and malononitrile in the presence of nontoxic, simple, and readily available organocatalyst glycine in aqueous medium at 25°C.

Keywords: Aldehydes; ethylacetoacetate; glycine; hydrazine hydrate; malononitrile; pyranopyrazoles; water

INTRODUCTION

In recent years, pyranopyrazoles have interested synthetic organic chemists and biochemists because of their biological and pharmacological activities.[1] Pyranopyrazoles exhibit analgesic, anti-inflammatory activity and act as vasodilators as well as hypotensive and hypoglycemic agents.[2] Substituted 6-aminopyrano[2,3-*c*]pyrazoles were first synthesized by a reaction between 3-methyl-5-pyrazolone with tetracyanoethylene.[3] After that, numerous methods were developed for the synthesis of these compounds from arylidenemalononitriles and 3-methyl-5-pyrazolone,[4] 4-arylidene-3-methyl-5-pyrazolones and malononitrile, and the condensation of aromatic aldehydes, malononitrile, and 3-methyl-5-pyrazolone.[5] Shestopalov et al. reported a chemical[6] as well as electrochemical method[7] for their synthesis. Peng et al. developed a two-component reaction involving pyran derivatives and hydrazine hydrate under combined microwave and ultrasound irradiation,[8] and recently Vasuki and coworkers reported a four-component synthesis of pyranopyrazoles from ethylacetoacetate, hydrazine hydrate, aldehyde, and malononitrile.[9]

Multicomponent reactions (MCRs) are processes "in which more than two educts directly get converted into their products by one-pot reaction."[10] MCRs play an important role in modern organic chemistry, because they generally exhibit higher atom economy and selectivity as well as produce fewer by-products compared to classical multistep synthesis.[11] Further, in many cases, MCRs are easy to perform,

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inexpensive, and quick, consume less energy, and involve simple experimental procedures.[12] The first MCR was described in 1850 by Strecker,[13] and thereafter many such reactions have been reported in the literature.[14]

Aqueous reactions have also received considerable attention in organic synthesis because of environmental safety reasons. Water as a reaction medium has been utilized for a large number of organic reactions.[15]

In addition, molecules such as cinchona alkaloids and amino acids have been used as organocatalysts in various organic synthesis[16] and proved to be highly efficient catalysts in MCRs.[17]

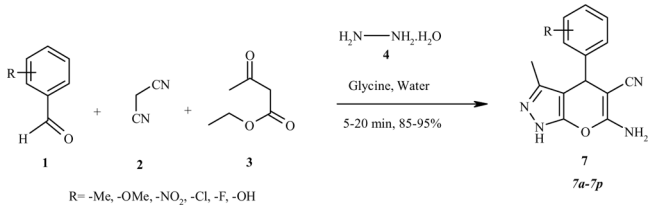
In continuation of our work on the synthesis of biologically important compounds using simple, efficient, nontoxic, and readily available catalysts,[18] we have used the organocatalyst glycine, an amino acid, for the synthesis of pyranopyrazoles from araldehydes (**1**), malononitrile (**2**), hydrazine hydrate (**3**), and ethylacetoacetate (**4**) at 25 °C in water with good to excellent yield within 5–20 min.

EXPERIMENTAL

Araldehydes (**1**), malononitrile (**2**), ethyl acetoacetate (**3**), hydrazine hydrate (**4**), and glycine, all commercial compounds, were used without further purification. All reactions were performed at 25 °C in water as solvent. Yields refer to isolated yields of the products. Melting points were measured on a Büchi B-540 apparatus; infrared (IR) and ^{1}H NMR spectra were recorded on a Nicolet 400D Fourier transform (FT)–IR and Bruker AMX (200-MHz) spectrophotometers respectively. The IR spectra were taken as KBr pellets. Liquid chromatography–mass spectra (LC-MS) were recorded on an Agilent Technologies 1200 series spectrometer.

RESULTS AND DISCUSSION

Initially, attempts were made to carry out the model reaction of benzaldehyde (**1**, Scheme 1), malononitrile (**2**), ethyl acetoacetate (**3**), and hydrazine hydrate (**4**) at room temperature without any catalyst in dicholormethane (DCM), but very little formation of solid product (**7a**, 20%) was observed after 1 h. Thin-layer chromatography (TLC) of the reaction mixture indicated the presence of starting materials, and when the reaction was performed with glycine as the catalyst, increase in the yield was noticed. At this stage, we thought of varying the nature of solvent to increase the product yield; and we carried out reactions in DCM, dichloroethane (DCE), dimethylformamide (DMF), ethyl acetate, MeOH, ethanol (EtOH), and



Scheme 1. Synthesis of pyranopyrazoles from araldehydes, malononitrile, ethylacetoacetate, and hydrazine hydrate.

Table 1. Synthesis of pyranopyrazoles from various aromatic aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate

Entry	Aromatic aldehydes (**1**)	Product[a] (**7**)	Yield (%)[b]
a	C_6H_5CHO	**7a**	90
b	4-NO_2-C_6H_4CHO	**7b**	87
c	3-NO_2-C_6H_4CHO	**7c**	95
d	4-Me-C_6H_4CHO	**7d**	91
e	4-OMe-C_6H_4CHO	**7e**	90
f	3-OMe-C_6H_4CHO	**7f**	88
g	2-OMe-C_6H_4CHO	**7g**	90
h	3,4-$(OMe)_2$-C_6H_3CHO	**7h**	89
i	3,5-$(OMe)_2$-C_6H_3CHO	**7i**	85
j	3,4,5-$(OMe)_3$-C_6H_2CHO	**7j**	93
k	4-OH-C_6H_4CHO	**7k**	91
l	4-F-C_6H_4CHO	**7l**	88
m	4-Cl-C_6H_4CHO	**7m**	89
n	2,3-Cl_2-C_6H_3CHO	**7n**	87
o	2,4-Cl_2-C_6H_3CHO	**7o**	90
p	2-Furfural	**7p**	94

[a]All the products were known and characterized by comparison with the authentic samples.

[b]Yield refers to isolated product.

distilled water. When the reaction mixture was stirred for 5 min at room temperature in distilled water using a catalytic amount of glycine, the yield of **7a** improved significantly (90%). This clearly demonstrates that the solvent has an effect on the reaction: with the increase in the polarity of the solvent, the yield of the product increased. Thus, we optimized the reaction conditions to examine the generality of this reaction. The reaction was performed using various aromatic and heterocyclic aldehydes. It was found that the reaction proceeded smoothly with all the aldehydes at 25 °C in water to give the products in excellent yield (85–95%) within 5–20 min. To summarize the effect of electron-donating or electron-withdrawing substituents on an aromatic ring of araldehyde, the results are presented in Table 1.

General Procedure for the Synthesis of Pyranopyrazoles in Water

A mixture of ethyl acetoacetate (0.260 g, 2 mmol), hydrazine hydrate (0.107 g, 2 mmol), malononitrile (0.132 g, 2 mmol), corresponding aromatic or heterocyclic aldehyde (2 mmol), and glycine (2 mol%) in water (5 mL) was vigorously stirred at 25 °C for 5–20 min. The soild was filtered and washed with ethyl acetate/light petroleum (2:8, 2 × 10 mL) to get nearly pure products. The product of desired purity was obtained by silica-gel column chromatography with ethyl acetate/light petroleum or by recrystallization from ethanol.

CONCLUSIONS

In conclusion, we have developed an efficient protocol for the synthesis of pyranopyrazoles by a one-pot MCR of hydrazine hydrate, ethylacetoacetate,

araldehydes, malononitrile, and a catalytic amount of an organocatalyst, glycine, in water at 25 °C. The catalyst is simple, inexpensive, readily available, nontoxic, and environmentally friendly, and the reaction procedure is very mild and involves simple workup to obtain the desired products in good to excellent yields.

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