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Synthesis of pyranopyrazoles using isonicotinic acid as a dual and biological organocatalyst†

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In this study, a green, simple and efficient method for the preparation of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles by means of a one-pot four component condensation reaction of aryl aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate is reported. The reaction utilizes isonicotinic acid as a dual and biological organocatalyst at 85 °C under solvent-free conditions.

Pyranopyrazoles are fused heterocyclic compounds, which are important because of their biological properties such as fungicidal,[1] bactericidal,[2] vasodilatory activities[3] and they act as anticancer agents.[4] They also find application as pharmaceutical ingredients and biodegradable agrochemicals.[5] Moreover, pyrano[2,3-*c*]pyrazoles also act as potential insecticidal[6] and molluscicidal agents.[7,8] Consequently, considerable attention has been paid to the development of new procedures for the preparation of these compounds.[8]

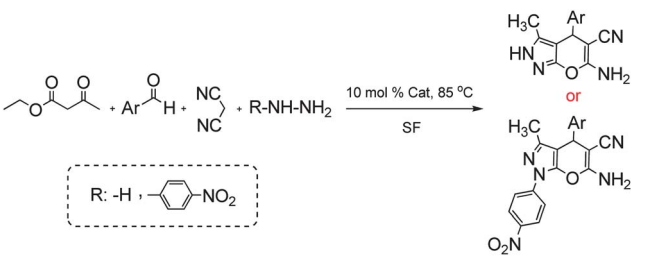
Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of the ability to synthesize target compounds with greater efficiency and atom economy by generating structural complexity in a single step from three or more reactants. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions.[9–11]

Development of organocatalytic processes in which the reactions are catalyzed by organic molecules has become an area of tremendous importance in current organic synthesis particularly from a green chemistry point of view.[12] Unlike conventional catalysis, these organocatalysts are advantageous in many ways such as high stability, availability of the catalyst, metal free nature, reduced toxicity, simple reaction conditions and it can promote a chemical reaction through different activation modes.[13]

Solvent-free reactions were demonstrated to be an efficient technique for various organic transformations instead of using harmful organic solvents. Solvent-free conditions often lead to a remarkable decrease in reaction times, increased yields and easier workup; it also satisfies green chemistry protocols, and may enhance the regioselectivity and stereoselectivity of reactions.[14–18]

Some catalysts have been used to promote this reaction such as imidazole,[8] γ-alumina and KF alumina,[9b] silicotungstic acid,[9c] L-proline,[9d] MgO.[9e] However, some of them suffer from the drawbacks. Therefore, it is highly desirable to develop efficient and cost-effective catalysts and methods for the synthesis of these valuable compounds.

In this research, we report our results on the efficient and solvent-free synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles *via* the one-pot four component condensation of aryl aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate using isonicotinic acid as a dual and biological organocatalyst under solvent-free (SF) condition (Scheme 1).



Scheme 1 The preparation of pyranopyrazoles using isonicotinic acid as catalyst.

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Table 1 Effect of different amounts of the catalyst and temperature on the reaction of hydrazine hydrate (2.2 mmol) ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and benzaldehyde (2 mmol) in the absence of solvent

Entry	Mol% of catalyst	Temp. [°C]	Time [min]	Yield[a] [%]
1	10	60	25	75
2	10	85	10	90
3	10	100	10	90
4	10	120	10	90
5	—	85	90	30
6	1	85	30	25
7	5	85	30	65
8	10	85	10	90
9	15	85	10	90

[a] Isolated yield.

Table 2 The reaction of hydrazine hydrate (2.2 mmol) ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and benzaldehyde (2 mmol) using isonicotinic acid in different solvents

Entry	Solvent	Time (min)	Yield[a] (%)
1	EtOH	30	70
2	CH_3CN	30	50
3	$CHCl_3$	30	45
4	CH_2Cl_2	30	60
5	Acetone	30	60

[a] Isolated yield.

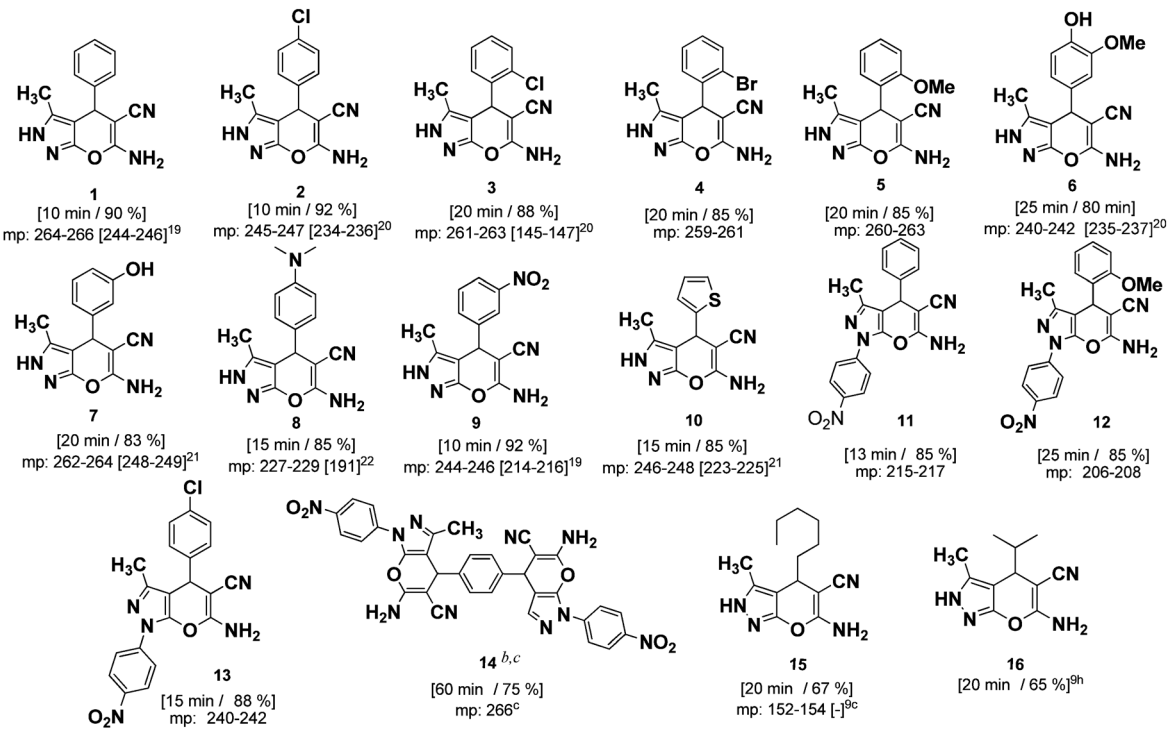
In order to optimize the reaction conditions, we chose the model reaction of hydrazine hydrate (2.2 mmol) ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and benzaldehyde (2 mmol). This reaction was studied in the presence of different amounts of isonicotinic acid at temperatures ranging between 60 and 120 °C under solvent-free conditions (Table 1). The reaction was most efficient with 10 mol% of the catalyst at 85 °C, and it gave the desired product in high yield within a short reaction time (Table 1, entry 2). The reaction was also examined at 85 °C without catalyst under solvent-free conditions in which the reaction did not proceed significantly even after long reaction times (Table 1, entry 5).

Also the model reaction was tested in the presence of 10 mol% of picolinic acid in comparison with isonicotinic acid. The corresponded product was obtained with 90% of yield in 20 minutes at 85 °C. Although, after 10 minutes of the reaction time; the yield was 81%. This observation indicated that isonicotinic acid was more successful than picolinic acid as catalyst in this reaction. It should be noted that the products of this reaction are isolated as a racemic mixture.

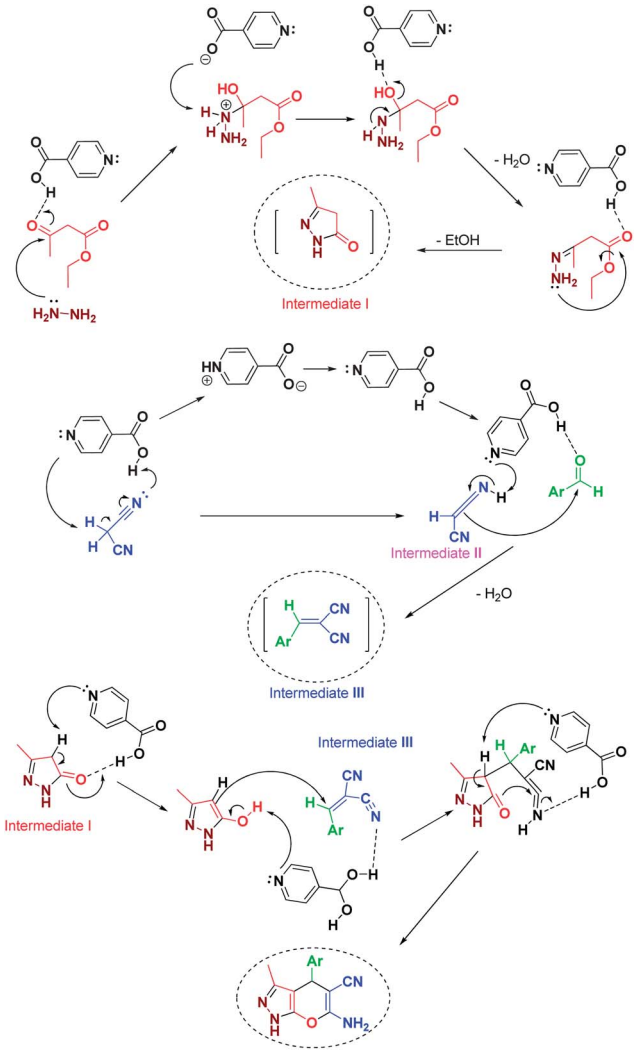
In the next step, the model reaction, was examined in several solvents using 10 mol% of isonicotinic acid under reflux conditions. The results are depicted in Table 2. It is clear that the addition of solvent was not efficient, and afforded the product in low yields. Increasing the reaction times did not improve the yields.

After optimization of the reaction conditions, we wanted to explore the efficacy of isonicotinic acid in the synthesis of a

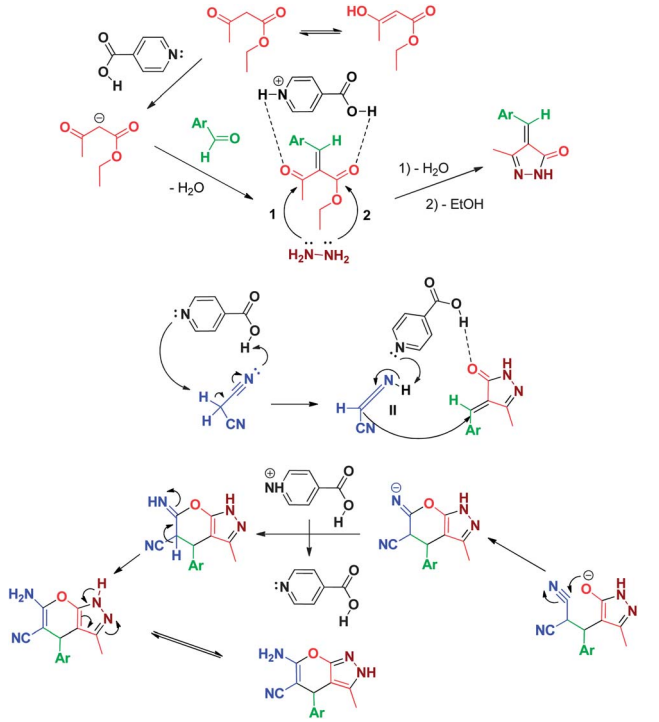
Table 3 Preparation of pyranopyrazoles using isonicotinic acid as catalyst at 85 °C (ref. 23)[a]



[a] Isolated yield was reported for all of compounds. [b] The product was produced by the reaction of hydrazine hydrate (4.4 mmol) ethyl acetoacetate (4 mmol), malononitrile (4 mmol) and terephthaldehyde (2 mmol) in the absence of solvent. [c] In this temperature the product was decomposed.



Scheme 2 Plausiblemechanism for the synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles.



Scheme 3 Another mechanism for the synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles.

series of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles. This was achieved by using aliphatic aldehydes, various aromatic aldehydes (including aldehydes with electron-releasing substituents, electron withdrawing substituents and halogens on the aromatic ring) as well as hetero aromatic aldehydes in the reaction with hydrazine hydrate or phenyl hydrazine, ethyl acetoacetate and malononitrile to give the corresponding products in high yields and in short reaction times. The results are summarized in Table 3. These results indicate that the corresponding products were produced in high yields and short reaction times.

In another investigation, the condensation of terephthaldehyde, malononitrile, ethyl acetoacetate and (4-nitrophenyl)hydrazine hydrate using isonicotinic acid was studied. Interestingly, the condensation of hydrazine hydrate (4.4 mmol) ethyl acetoacetate (4 mmol), malononitrile (4 mmol) and terephthaldehyde (2 mmol) at 85 °C under solvent-free conditions, afforded 4,4′-(1,4-phenylene)bis(6-amino-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) (15) in 74% yield within 60 min (Table 3, entry 14). Thus, the catalyst was general and highly efficient.

In a plausible mechanism, initially, ethyl acetoacetate is activated by isonicotinic acid and hydrazine attacks to the carbonyl group of the activated ethyl acetoacetate. Then, loss of H_2O, and intramolecular nucleophilic attack by another NH_2 group of hydrazine to the next carbonyl group of ethyl acetoacetate affords 5-methyl-2,4-dihydro-pyrazol-3-one (intermediate I) and removes EtOH. In the next step, the aromatic aldehyde which is activated by isonicotinic acid and malononitrile after rearrangement in II form, attacks to the carbonyl group of the activated aldehyde, removes H_2O and affords intermediate III. Finally, addition of I to III in the presence of isonicotinic acid follows by intramolecular nucleophilic attack, can give the expected pyranopyrazole as shown in Scheme 2.

In this reaction condition, another mechanism can be discussed. Due to use of isonicotinic acid as a dual catalyst, it is plausible that ethyl acetoacetate or malononitrile abstracted one acidic hydrogen in the presence of catalyst and attacks to aryl aldehyde. Then the presented product was reacted to other substrates to give the main products (Scheme 3). For this purpose, we studied the reaction of two different substrates at 85 °C using isonicotinic acid in a separate test in comparison with other substrates. After that the reaction was completed, we investigated the reaction of two other substrates with the first test. The results are summarized in Table 4. Although in all of tests, the main product was produced, but the reaction between hydrazine hydrate and ethyl acetoacetate is faster than others. In other hands, the reaction time of the product is near to entry 1.

Table 4 The study on the reaction between two different substrates to give product

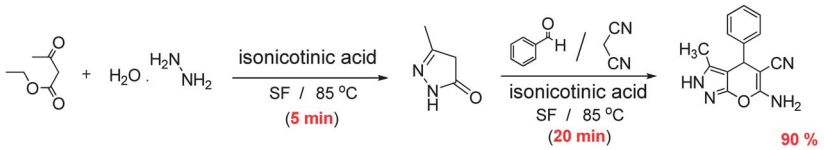
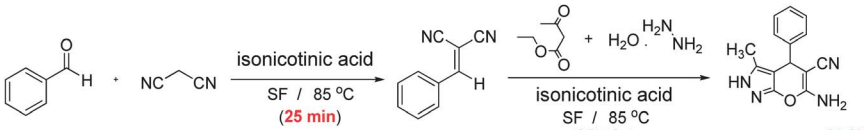
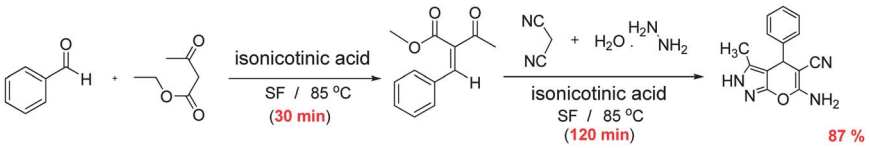
Entry	Paths of reactions
1	
2	
3	

Table 5 The reaction of hydrazine hydrate (2.2 mmol) ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and benzaldehyde (2 mmol) in the presence of reused isonicotinic acid (10 mol%) as catalyst at 85 °C under solvent-free conditions

Entry	Cycle	Time [min]	Yield[a] [%]
1	1st run	10	90
2	2st run	12	85
3	3st run	16	81
4	4st run	17	79

[a] Isolated yield.

Then the first mechanism (Scheme 2) is more acceptable than the second mechanism (Scheme 3).

In another study, recyclability of the catalyst was examined upon the condensation of hydrazine hydrate (2.2 mmol) ethyl acetoacetate (2 mmol), malononitrile (2 mmol) and benzaldehyde (2 mmol). After completion the reaction, the catalyst was extracted by water and separated from the reaction mixture. Water was removed and the recovered catalyst used for another reaction. We observed that the catalytic activity of the catalyst was restored within the limits of the experimental errors for four successive runs (Table 5).

Conclusions

In summary, we have reported the synthesis of 6-amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4- dihydropyrano[2,3-*c*]pyrazoles using isonicotinic acid as a dual, biological and reusable organocatalyst in a green media. The promising points for the presented methodology are efficiency, generality, high yield, relatively short reaction time, low cost, cleaner reaction profile, ease of product isolation, simplicity, and finally compliance with the green chemistry protocols.

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23 General procedure: a mixture of aromatic aldehyde (2 mmol), malononitrile (0.132 g, 2 mmol), ethyl acetoacetate (0.26 g, 2 mmol) hydrazine hydrate (2.5 mmol) and isonicotinic acid (0.2 mmol) (0.0246 g, 10 mol%) was added to a test tube, and stirred at 85 °C. After the completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature. Water was added to the reaction mixture to dissolve the catalyst and the aqueous layer was separated from the reaction mixture. Water was removed and the recovered catalyst was reused for up to four times without any significant changes in the yield and the reaction time. Afterward the solid residue (crude product) was triturated by a mixture of ethanol and water (9/1) to give the pure product.