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NaF-catalyzed efficient one-pot synthesis of dihydropyrano[2,3-*c*]pyrazoles under ultrasonic irradiation *via* MCR approach

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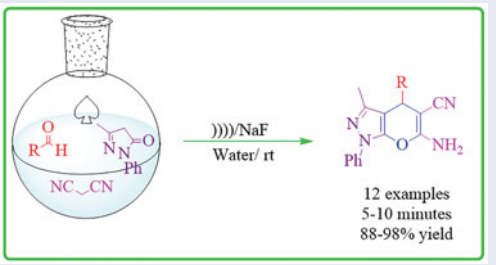
ABSTRACT

Sodium fluoride was identified as an efficient catalyst for the preparation of series of dihydropyrano [2,3-*c*]pyrazoles (**4a–l**) by the three-component condensation of 3-Methyl-1-phenyl-2-pyrazoline-5-one (**1**), aromatic aldehydes (**2**) and malononitrile (**3**) in aqueous methanol at ambient temperature under ultrasonication. The cost and efficacy of the catalyst, mild reaction conditions, simple workup procedure, less reaction time and higher yields of the product with analytical purity keeping this protocol superior to the previously reported ones. Structures of all the compounds were in agreement with their spectroscopic data (^{1}H NMR, ^{13}C NMR) and elemental (CHN) analyses.

GRAPHICAL ABSTRACT



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KEYWORDS
Aqueous ethanol; cavitation effect; multi-component reaction; sodium fluoride; ultrasonication

Introduction

For the last few decades, green synthesis played a vital role in organic synthesis. The twelve green chemistry principles are helpful to improve the safe synthetic methodologies. The Various environmentally benign conditions are developed for the synthesis of organic compounds. Because of the advantages like high reaction rate, isolation by simple filtration etc., and by considering its green credentials, water is growing as competitive reaction media along with the other organic media like ionic liquid, ethanol, PEGs, etc., in green organic synthesis.[1–5] MCRs are also considered as a green

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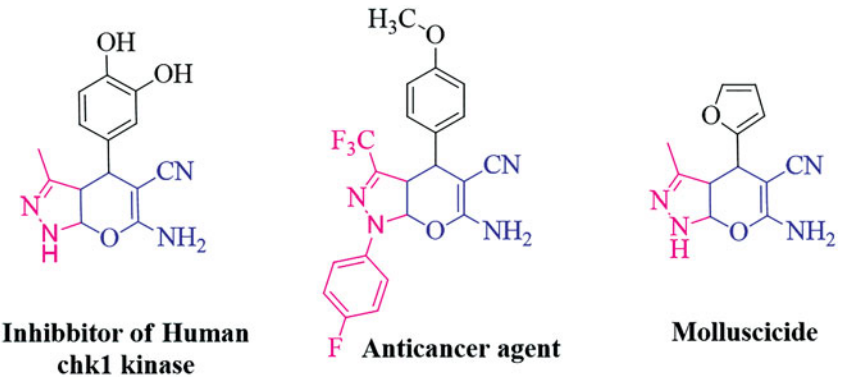
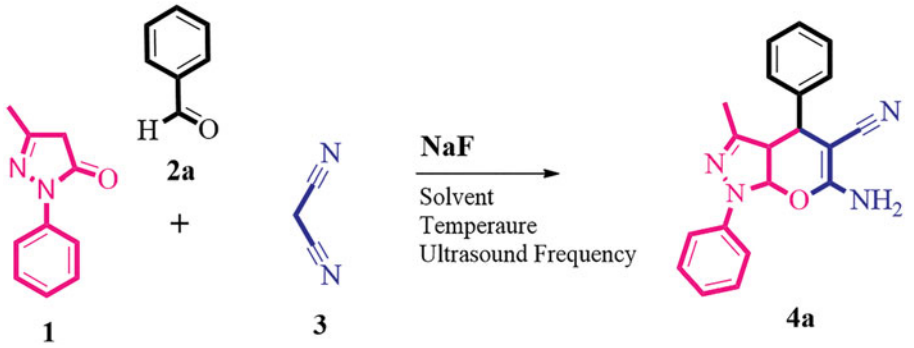


Figure 1. Some of the biologically active molecules with dihydropyrano[2,3-*c*]pyrazole scaffold.

reaction because of the benefits like less reaction time, avoidance of difficult workup procedures, energy saving etc.[6] MCRs are the reaction in which three or more substrates react to synthesis the complex drug-like molecules through several transformations in a single process in one-pot without isolating the intermediate.[7–10] The diversity in the MCRs is achieved by changing one of the reaction components.[11] Hence, MCRs become a very useful tool in the drug discovery.[12] If such MCRs are carried out in the environmentally benign solvents and reusable catalysts, then there is a possibility to prevent the environmental contamination. Several dihydropyrano[2,3-*c*]pyrazoles were prepared by using MCRs efficiently.

Dihydropyrano[2,3-*c*]pyrazoles, ubiquitous in numerous drug molecules, are important class of heterocyclic moieties, played a vital role in medicinal chemistry because of the various biological activities like antimicrobial,[13] anticancer,[14]anti-inflammatory,[15] inhibition of human Chk1 kinase[16] activities, analgesic, antipyretic, antifungal, antidepressant, anti-HIV,[17] etc., Some of the biologically active molecules containing dihydropyrano[2,3-*c*]pyrazole ring in their core structure were shown in Figure 1.[18–20]

Because of their broad spectrum of biological activities, the synthesis of dihyropyrano[2,3-*c*]pyrazoles are still of interest. Several methodologies were developed for the synthesis of these compounds via three or four-component reactions by using different catalysts like amberlyst,[12] sodium benzoate,[21] L-proline,[9] nano MgO,[22] triethyl amine, β-cyclodextrin,[6] morpholine, piperidine, cetyltrietylammoniumchloride, glycine,[18] lemon juice,[23] $ZnAl_2O_4$NPs[24], uncapped SnO_2 quantum dots,[25] silica coated magnetic $NiFe_2O_4$ nanoparticles supported $H_3PW_{12}O_{40}$ (NFSPWA),[26] cerium ammonium nitrate[27] etc., Even though these methodologies are efficient, some of these methodologies have suffered from high reaction times, usage of toxic and expensive catalyst, strong basic conditions, low yields, difficult isolation procedure of the product etc., According to the literature, the synthesis of dihydropyrano[2,3-*c*]pyrazoles by using NaF as a catalyst was less investigated. Herein, we report the synthesis of dihydropyrano[2,3-*c*]pyrazole (**4a–l**) efficiently *via* one-pot, three-component condensation reaction by using NaF as an efficient catalyst with good to excellent yields in aqueous methanol



Scheme 1. The synthetic pathway of compound **4a**.

Table 1. Optimized reaction conditions for the preparation of compound **4a**.

Entry[a]	Solvent	Ultrasound frequency (kHz)	Bath temperature (°C)	Time	Yield[b] (%)
1	Water	30	25	20	62
2	Methanol	30	25	15	70
3	Water:methanol (1:1 v/v)	30	25	5	85
4	Acetic acid	30	25	10	77
5	Acetonitrile	30	25	10	65
6	Dimethylformamide	30	25	15	60
7	Water:methanol (1:1 v/v)	30	50	5	82
8	Water:methanol (1:1 v/v)	30	75	5	80
9	Water:methanol (1:1 v/v)	50	25	5	98
10	Water:methanol (1:1 v/v)	50	50	5	94
11	Water:methanol (1:1 v/v)	50	75	5	90

[a]Reaction conditions: benzaldehyde **1a**, malononitrile **2** and 3-Methyl-1-phenyl-2-pyrazoline-5-one **3**, ultrasonic irradiation.
[b]Isolated yields in the pure form.

(1:1 v/v) at room temperature under ultrasonic irradiation and an environmentally benign method.

Results and discussion

Inspired from the green chemistry principles and as a part of our endeavor toward the development of new synthetic methodologies, we herein reported the efficient and green protocol for the preparation of 1,4-dihydropyrano[2,3-*c*]pyrazoles by using NaF as a catalyst The schematic representation for the synthesis of title compounds are illustrated in Scheme 1.

In order to find out the optimal reaction conditions, a model reaction was performed by choosing equimolar concentrations of 3-Methyl-1-phenyl-2-pyrazoline-5-one (**1**), benzaldehyde (**2a**) and malononitrile (**3**) as starting materials under various solvents and varying the amounts of NaF as a catalyst at different bath temperatures and ultrasonic frequencies (30 and 50 kHz). From the results, we have observed the optimistic results (yield 98%, reaction time-5 min) at 25 °C, 50 kHz in 1:1 (v/v) water/methanol in the presence of 0.02 g of NaF (Table 1). To highlight the catalytic efficacy of NaF, the same model reaction was also performed in the absence of a catalyst and also by utilizing other different inorganic catalysts (Table 2). The results clearly emphasized the

Table 2. The effect of catalysts on the model reaction.

Entry[a]	Catalyst (0.02 g)	Time (min)	Yield[b] (%)
1	NaF	5	98
2	KF	10	63
3	NaI	5	88
4	KI	10	60
5	$AlCl_3$	10	85
6	$FeCl_3$	5	89
7	$CuCl_2$	10	86
8	CuI	10	82

[a]Reaction conditions: benzaldehyde **1a**, malononitrile **2** and 3-Methyl-1-phenyl-2-pyrazoline-5-one **3**, ultrasonic irradiation (50 kHz), solvent water:methanol (1:1 v/v), at 25 °C bath temperature.
[b]Isolated yields.

unique catalytic property of NaF (Table 2, entry 1) in the preparation of 1,4-dihydropyrano[2,3-*c*]pyrazoles and also the necessity of the catalyst for the rapid transformation of reaction. The effect of other inorganic catalysts on the model reaction is not so appreciable. We also observed form the model reaction that, the effect of temperature and frequency of ultrasonic waves on the percentage of yield of the product and time of the reaction to complete. The increase in yield of the product under ultrasonication can be explained by the cavitation effect.[28] Further increase in the reaction temperature and ultrasonic frequency, gradually decreased the yield of the product, that may be due to the formation of unidentified impurities and due to the lowering of focusing energy on the reaction vessel. The optimized conditions were shown in Table 1.

Utilizing the above optimal conditions, we explored the efficacy of reaction for the preparation of a wide variety of substituted 1,4-dihydropyrano[2,3-*c*]pyrazoles (**4a–l)** and achieved the target compounds in good to excellent yield (88–98%) in 5–10 min (Table 3). The time and yields of the reactions were shown in Table 3. The progress of the reactions was monitored by using TLC. After the completion of the reaction, the separated solid was filtered under vacuum. The residue was washed twice with ethyl acetate (2 × 10 mL) in order to remove unreacted impurities. The plausible mechanism for the NaF-catalyzed formation of dihydropyrano[2,3-*c*]pyrazolones (**4a–l)** was shown in Scheme 2.

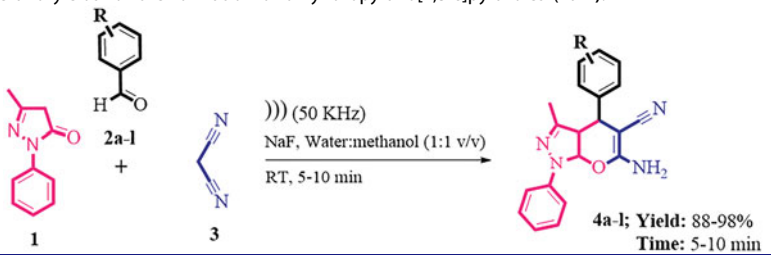
Structures of all the synthesized compounds were characterized by their spectral data. For example, the ^{1}H NMR spectrum of the compound **4l** showed the singlet peaks at δ 1.82 (s, 3H) and 4.94 (s, 1H), which corresponds to the $-CH_3$ (Pyrazole ring) and –CH (Pyran ring) groups respectively and peak at δ 7.83 (broad s, 2H) corresponds to the $-NH_2$ group, whereas in ^{13}C NMR spectrum, the peaks observed at δ 13.03 and 36.90 corresponds to the $-CH_3$ (Pyrazole ring) and –CH (Pyran ring) groups, respectively.

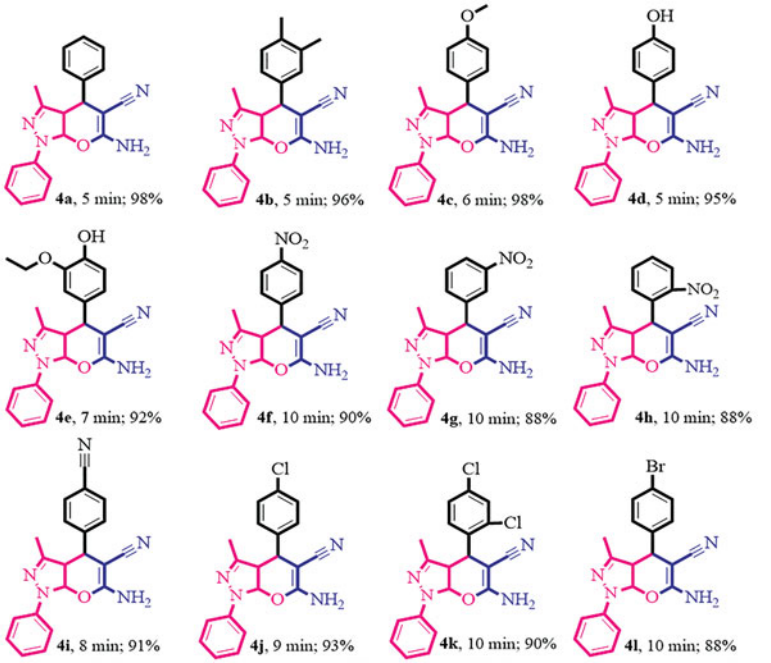
Experimental section

General considerations

All the melting points were recorded by using Stuart SMP30 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker Advance III HD 400 MHz instrument and the chemical shift values were reported in ppm. Progress and purity of the reactions

Table 3. Time and yields for the formation of dihyhdropyrano[2,3-*c*]pyrazoles (**4a–l**).



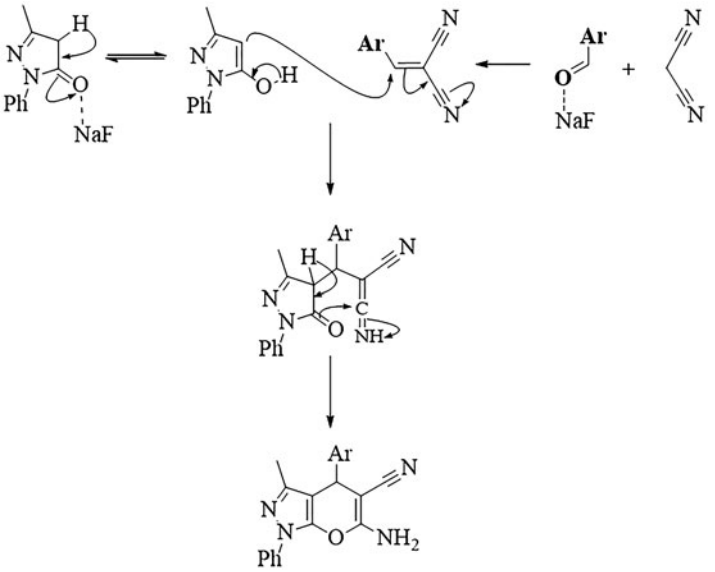


[a]All the reaction were carried out by using equimolar mixture of benzaldehyde 1a, malononitrile 2 and 3-Methyl-1-phenyl-2-pyrazoline-5-one 3 under ultrasonic irradiation method at room temperature.
[b]The progress of all the reactions was monitored by TLC.
[c]All the yields are isolated yields.

were monitored by Thin-Layer chromatography (E. Merck, Mumbai, India) and the developed chromatogram was visualized under UV light and iodine vapors. Unless otherwise stated, all the chemicals and solvents used were of high grade and purchased from Sigma-Aldrich and Spectrochem. Elemental analysis was performed on an Elementar Vario EL III analytical unit and the values were ±0.4% of theoretical values. Sonication was performed on PCi-Analytics-6.5L200H1DTC ultrasonic cleaner (PCi-Analytics, 25 and 50 kHz, the input voltage the range of 170–270 VAC, 50 Hz) (Mumbai, India).

General producer for the synthesis of the dihydropyrano[2,3-c]pyrazoles (4a–l)

An equimolar mixture of methyl-1-phenyl-2-pyrazoline-5-one (**1**, 1 mmol), aromatic aldehydes (**2**, 1 mmol) and malononitrile (**3**, 1 mmol) was taken in a 100 mL



Scheme 2. Proposed mechanism for the synthesis of compounds (**4a–l**).

borosil test-tube initially charged with 0.02 g of NaF and 2 mL water and 2 mL ethanol. The tube in an ultrasonication bath was kept in such a way that the surface of the reactants is just lower than the level of water in a bath. Then the tube was subjected to 50 kHz ultrasonic frequency at ambient temperature for an appropriate time (Table 3). The progress of the reaction was monitored by TLC and the separated product was filtered under vacuum followed by washing with ethyl acetate afforded the pure products in analytical purity with no need of further recrystallization.

Spectral data of the title compounds (4a)

6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a)

White solid; M. P.: 168-170 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.79 (s, 3H), 4.89 (s, 1H), 7.22-7.36 (m, 8H), 7.5 (d, 2H, $J = 7.6$ Hz), 7.8 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR (100 MHz, DMSO) δ: 159.90, 145.75, 144.36, 144.08, 138.02, 129.80, 129.00, 128.25, 127.52, 126.63, 120.43, 99.11, 58.68, 37.23, 13.03. Anal. Calcd. For $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06; found: C, 73.37; H, 4.98; N, 17.29.

Conclusions

In conclusion, we have developed a facile and green protocol for the synthesis of dihydropyrano[2,3-*c*]pyrazoles (**4a–l**) by employing MCR strategy. This method offers several advantages over previously reported protocols including, mild reaction conditions, higher yields, lower reaction times, low energy consumption and using a low-cost catalyst. We believe that our methodology may useful for the large-scale production in industries.

Acknowledgments

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