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$BF_3.CH_3CN$ As a Novel Catalyst for One Pot Solvent Free Synthesis of Pyrazole Derivatives.

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ABSTRACT
Solvent free synthesis is receiving tremendous attention in recent times and is an integral part of research especially in green synthesis. Development of catalyst and establishing a new catalyst in synthesis is also the current trend of research. $BF_3.CH_3CN$ is one of such rarely explored catalyst. The $BF_3.CH_3CN$ has been found as an efficient effective catalyst for synthesis of substituted in pyrazole. It is first report of combination of $BF_3.CH_3CN$ in solvent free reaction condition to yield pyrazole derivatives. The main advantage of this protocol is establishing $BF_3.CH_3CN$ as a catalyst, shorter reaction time, high atom economy and simple work-up procedure.

KEYWORDS
$BF_3.CH_3CN$, Pyrazole, Green synthesis, Solvent Free, Atom economy.

1. INTRODUCTION

Heterocyclic chemistry is very important topic of research in the Pharmaceutical and Organic Chemistry. Among the various heterocyclic molecules discovered and developed, the nitrogen containing compounds show great applications due to its varied biological activities.[1-3] Pyrazole is a well-known heterocycles, privileged in medicinal chemistry owing to various biological activities such as antibacterial [1-2], anticancer [3], antifungal [4], anti- antioxidant [4-5], antidepressant [6],anti-HIV [7].

Pyrazole synthesis is reported [8-18]using various reagents such as {[HMIM]$C(NO_2)_3$}[8], CuO/ZrO_2[9], $Sc(OTf)_3$[10],$Ti(NMe_2)_2(PyPyr)_2$[11], [BMIM]OH [12], ZrO_2 nanoparticles [13]and Fe_3O_4.Si.MoO_2[14].Pyrazole synthesis mainly reported by three component coupling of aromatic aldehydes, malononitrile and phenylhydrazine under various reaction conditions [15-18].But reported pyrazole synthesis have several drawbacks such as long reaction times, need of expensive catalyst, tedious work-up. Therefore, there are need for improvement and development of generalized methods for the synthesis of these vital scaffolds. But these methods require diverse solvents, are often time consuming, requiring costly reagents, employing non eco-friendly reaction conditions, with need of elevated reaction temperature and cumbersome work-up procedure.

The obtained product yields of most of these reactions are significant, but still there is scope for improvements. The focus of researchers is on developing environment friendly reaction protocol which will be with high yield, cost effective and less time consuming. For these reasons, we chose the synthesis of pyrazole heterocycles keeping in mind environment-friendly conditions. In recent times solvent free synthesis is gaining importance especially in green synthesis. Due to the harmful effects of organic solvents on the environment and humans, solvent-free reactions have received a widespread attention in research. Furthermore, solvent-free reactions have several benefits compared with reaction using solvents, such as faster reaction rate; less reaction time, less energy requirement, easy separation, formation of product with fewer impurities and high yields. Establishing a new catalyst in synthesis is also the current trend of research in pharmaceutical industries and academics. Boron trifloro acetonitrile [$BF_3.CH_3CN$] is one of such rarely explored catalyst.

Considering the above requirement we decided to explore $BF_3.CH_3CN$ as a catalyst. $BF_3.CH_3CN$ has several advantages for organic transformations; it is convenient, economic environment friendly and ease of handling. As part of our ongoing efforts to achieve new routes for the synthesis of heterocyclic compounds, herein we report a one-pot Multicomponent synthesis of highly functionalized pyrazole derivatives by condensing malononitrile, aryl aldehyde and phenyl hydrazine in the presence of catalytic amounts of $BF_3.CH_3CN$ as a proficient and viable catalyst (Scheme 1).

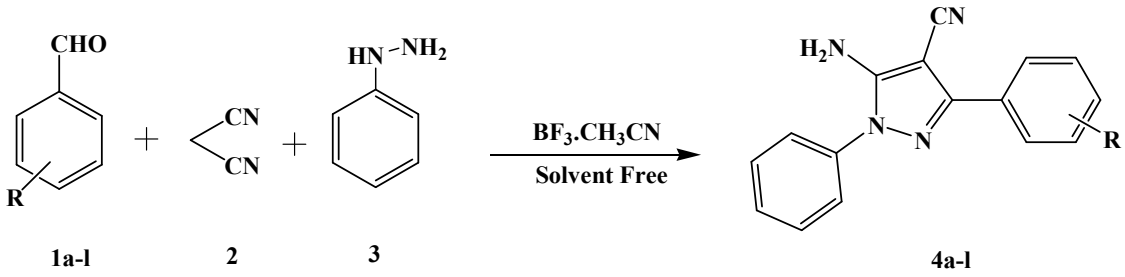
2. MATERIALS AND METHODS

All the chemicals were purchased from Sigma Aldrich and used as received without further purification. All the melting points were determined on Labstar melting point apparatus and are uncorrected. The IR spectra were run on a Perkin-Elmer FTIR-1600 Spectrophotometer and the

data expressed in cm (KBr). The ^{1}H NMR (400.13) and ^{13}C NMR (100.62 MHz) were recorded on a Bruker spectrometer (δ in ppm). Mass spectra were recorded on a Agilent spectrometer. The synthesized compounds were analyzed, matched and confirmed with literature data for Melting point, IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry.

2.1. General procedure for the preparation of pyrazole derivatives (4a-l)

A mixture of malononitrile (1 mmol), aldehyde (1 mmol), phenyl hydrazine (1 mmol) and $BF_3.CH_3CN$ (10 mol %) was treated at 30°C till the completion of reaction, monitored by TLC. After completion of the reaction, as monitored by TLC *n*-hexane/ethyl acetate (5:3), ethyl acetate (5.0 mL) and water (2.0mL) was added to reaction mixture, stirred for 5 min, separate the organic layer and distilled to get residue. The obtained crude product was purified by column chromatography over silica gel (EtOAc/*n*-hexane) to give pure functionalized pyrazole product (Table 3).



Scheme 1. Preparation of pyrazole derivatives (4a-l).

3. RESULTS AND DISCUSSION

Initially, a mixture of benzaldehyde, malononitrile and phenyl hydrazine in ethanol in the presence of catalytic amount of $BF_3.CH_3CN$ (Table 1, Entry 1) obtain the corresponding pyrazole derivative. The product was obtained in good yield (88%). Solvent optimization studies of the above reaction were carried out and are summarized in Table 1, the effect of different solvents on reaction rate as well as yields of products was investigated and the results are summarized in Table 1. It was observed the reaction proceeded excellently in solvent free condition (Table 1, Entry 5). It was further observed that reaction proceeds very well at ambient temperature (30 °C) and does not require elevated temperatures.

Catalyst optimization studies of the above reaction were carried out and are summarized in Table 2. When catalyst was used from 5 to 10 mol% both yield and rate of the reaction was increased (Table 2, Entries 1, 2). However, further increment of catalyst amount (above 10 mol %) does not affect the yield and rate of the reaction (Table 2, Entries 3, 4, 5). Finally, among all the experimental variations the 10 mol% $BF_3.CH_3CN$ solvent free condition at ambient temperature gave the best results with 95% yield (Table 2, Entry 2).To check the generality and scope of the optimized reaction, the methodology was evaluated by employing different aromatic aldehyde,

malononitrile and phenyl hydrazine. The resultant corresponding functionalized pyrazole (4a-l) were obtained in good to excellent yields (Table 3).

Table 1. Solvent Optimization for one-pot synthesis of Pyrazole[a].

Sr. No.	$BF_3.CH_3CN$ (mole %)	Solvent	Time(Min)	Yield (%)[b]
1	10	Ethanol	25	88
2	10	Methanol	20	85
3	10	Water	20	75
4	10	Ethanol: Water (50%)	35	81
5	10	Solvent free	5	95

[a]Experimental conditions: Benzaldehyde (1 mmol), Malononitrile (1 mmol), Phenyl hydrazine (1 mmol), ambient temperature (30 °C). [b]Isolated yield

Table 2. Catalyst Optimization for one-pot synthesis of Pyrazole[a].

Sr. NO.	$BF_3.CH_3CN$ Catalyst mole %	Time(min)	Yield (%)[b]
1	5	25	75
2	10	5	95
3	15	5	95
4	20	5	95
5	25	5	95

[a]Experimental conditions: Benzaldehyde (1 mmol), Malononitrile (1 mmol), Phenyl hydrazine (1 mmol), ambient temperature (30 °C). [b]Isolated yield.

Table 3. Synthesis of functionalized pyrazoles (1-12) with different aryl aldehydes, malonitrile and phenyl hydrazine[a].

Sr. No.	Aldehyde	Time (min)	Yield (%)[b]	Melting point (°C)	Reported Melting point (°C)
4a	Benzaldehyde	5	95	159-160	160-161[19]
4b	3-Nitro benzaldehyde	25	92	128-130	129-130[19]
4c	4-Nitro benzaldehyde	20	91	163-164	164-165[20]
4d	4-Cholro benzaldehyde	30	85	128-130	129-130[20]
4e	2,3,4,5,6- pentafluoro benzaldehyde	20	90	159-160	158-160[14]
4f	5-fluoro-2-hydroxybenzaldehyde	24	87	161-162	161-163[14]
4g	pyrrole-2-carbaldehyde	20	85	260-262	260-262[14]
4h	4-Methoxybenzaldehyde	15	88	112-113	112-114[21]
4i	1-naphthaldehyde	15	86	163-164	163-165[11]
4j	Furan-2-carbaldehyde	20	81	168-170	168-170[14]
4k	Thiophene-2-carbaldehyde	25	82	163-165	163-165[14]
4l	4-Pyridinecarboxaldehyde	15	89	219-220	218-220[14]

[a]Experimental conditions: Arylaldehyde (1 mmol), Malononitrile (1 mmol), Phenyl hydrazine (1 mmol), ambient temperature (30 °C). [b]Isolated yield.

4. CONCLUSION

In summary, an efficient solvent mild protocol for the synthesis highly functionalized pyrazole derivatives using $BF_3.CH_3CN$ as a catalyst has been demonstrated. This protocol is first report of solvent free $BF_3.CH_3CN$ catalysed pyrazole synthesis. This protocol offers several significant advantages including operational simplicity, superior atom-economy, short reaction time and good to excellent yields.

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