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HBF_4/ACN: A simple and efficient protocol for the synthesis of pyrazoles under ambient reaction conditions

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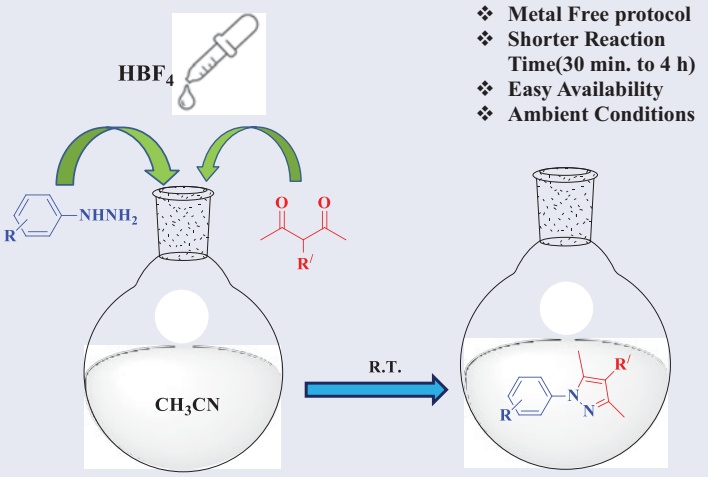
ABSTRACT

An efficient and novel protocol for pyrazole synthesis has been developed by using fluoroboric acid as the acid catalyst. Simple and easily available 1,3-diketone and hydrazine derivatives are taken as the substrates for this purpose. The reaction entails mild reaction conditions and produces desired pyrazoles in good to excellent yields. Easy accessibility, easy handling, broad substrate scope, evading metal catalyst and economic viability make this protocol advantageous to most of the previously reported literature.

GRAPHICAL ABSTRACT



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KEYWORDS
Pyrazole; fluoroboric acid; hydrazine; 13-diketone; metal free

Introduction

Along with the fast developing world, due to the revolution in lifestyles and rapid changes in environment and climate, different diseases and disordernesses have become the major issues of an unwealthy and unhealthy life span over the last few decades.[1]

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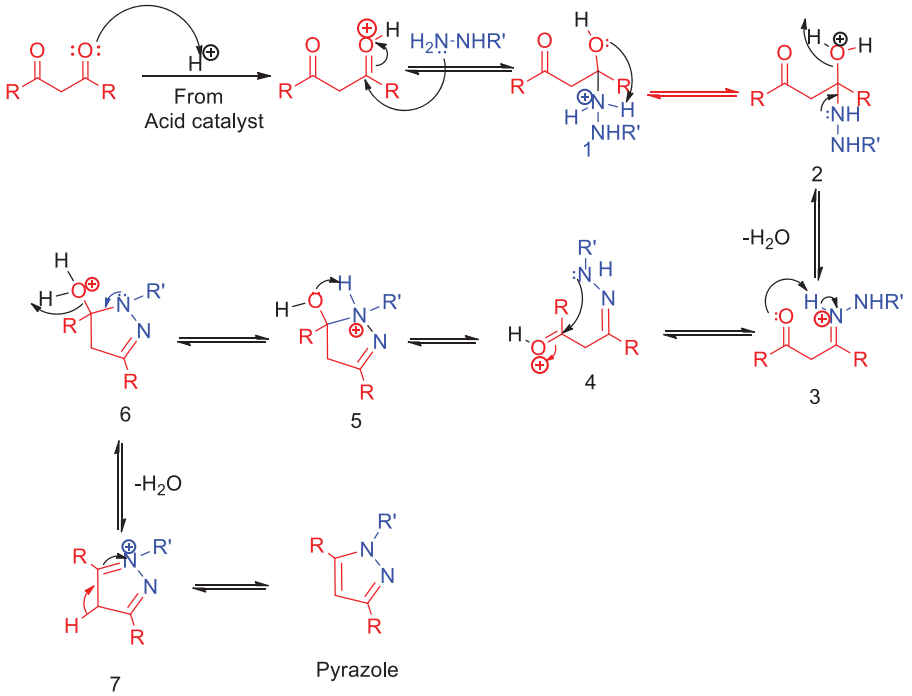
To overcome these difficulties, scientists are able to design varieties of drug molecules. Despite the keen efforts to develop small molecules with enhanced therapeutic properties, the scientific community are still in a hunt for new drug molecules with improved efficiency, selectivity and proper safety.[2] In this regards, N-heterocyclic compounds are prominent choices for researchers as they are universally acknowledged for displaying a broad range of biological properties.[3]

Pyrazoles, belonging to N-heterocyclic compounds are widely found as the core structure in a wide variety of organic compounds. After Knorr, who first synthesized and exposed the biological activities of pyrazole, its pathological voyage instigates toward a demanding future.[4–5]

Pyrazoles show some potent pharmaceutical properties against inflammation,[6a] cancer,[6b] obesity,[6c] gastric[6d] etc. In agricultural field, pyrazole moiety is usually considered as an important active component of some insecticidal,[7a] acaricidal,[7b] fungicidal,[7c,d] and antiviral[7e] molecules. Along with these pharmaceutical properties, pyrazoles can also act as ligands in different organic reactions, some pyrazoles are used in supra-molecular[8a] and polymer chemistry,[8b] food industry,[8c] cosmetic colorings[8d] and UV stabilizers,[8e] while some have liquid crystal properties.[8f] Therefore, development of efficient methodology of its construction has turned out to be an important issue in synthetic organic chemistry. Acid catalyzed pyrazole synthesis turns out to be a promising concept throughout this expedition.

Though there exists a numerous traditional metal free procedures for pyrazole synthesis,[9–12] most of them require vigorous conditions, high loading or longer reaction times as shown in Scheme 1. Therefore, new synthetic strategies for pyrazole are still



Scheme 1. Some literature based reports with the present work.

highly desirable. Hence, we cast our interest in search of a simple acid catalyst which behaves as an efficient catalyst in shorter reaction time compared to the previous catalysts at ambient reaction conditions.

Fluoroboric acid and its salts were first studied in the earliest of 1809 and it is basically used as a precursor to synthesize some other fluoroborate salts.[13,14] This acid is a solution of boron trifluoride in hydrogen fluoride which has super acidic property. But the solution of HBF_4 in HF is not suitable for glassware due to its corrosive nature. Therefore, we are using aqueous fluoroboric acid in our protocol which exists and is stable only as a solvated ion pair $[H_3O^+][BF_4^-]$. H_3O^+ acts as the cation and the tetrahedral BF_4^- acts as the anion and they bind through strong hydrogen bond which brings extra stability to this solvated ion pair (Fig. 1).[15]

The solution of BF_3 in HF is supremely acidic, with an approximate speciation of $[H_2F^+][BF_4^-]$ and having a Hammett acidity function of –16.6 at 7 mol % BF_3, which easily declares fluoroboric acid as super acid.[16] Due to its easy handling, comparable acid strength with that of hydrochloric acid and sulfuric acid, aqueous fluoroboric acid is a better choice to the researchers.

Results and discussion

We initiated our investigation by taking 2,4-dinitrophenyl hydrazine (**1a**) and acetyl acetone (**2a**) as the model substrates for the desired pyrazole (**3a**) synthesis. Initially, we investigated with various organic acids (Table 1**, entries 1–5**) and moved toward inorganic acids (Table 1**, entries 6–10**) as no prominent results were obtained with the organic acids in our investigation. Among the inorganic acids we have screened, fluoroboric acid (Table 1**, entry 6**) came out to be superior to the others and gave upto 95% yield in acetonitrile within 4 h. The presence of most electronegative fluorine atoms makes fluoroboric acid supremely acidic which is confirmed by Hammet acidity function which is already discussed.[15] Therefore, it behaves as the efficient catalyst among the screened catalysts. After optimizing the catalyst, we extended our interest to improve the yield of the reaction by varying other parameters one at a time.

In this investigation, it was observed that the reaction gave superior results in polar aprotic solvents such as CH_3CN (Table 2**, entry 7**) and THF (Table 2**, entry 8**) as compared to polar protic solvents such as CH_3OH (Table 2**, entry 2**), C_2H_5OH (Table 2**, entry 3**) and non-polar solvents such as toluene (Table 2**, entry 10**). Also we tried some green solvents such as H_2O (Table 2**, entry 1**), ethylene glycol (Table 2**, entry 11**)

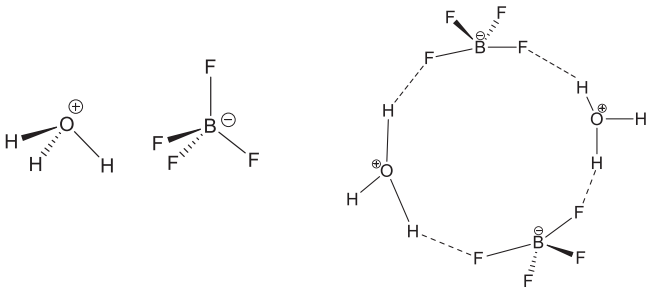
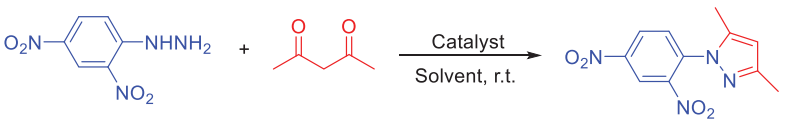


Figure 1. H-bonding of fluoroboric acid in water.

Table 1. Optimization of catalyst.[a]

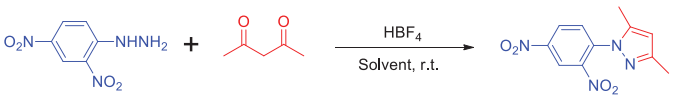


1a 2a 3a

Sl. No.	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Cyanuric acid	CH_3CN	6	50
2	Citric acid	CH_3CN	6	40
3	Acetic acid	CH_3CN	6	30
4	Anthranilic acid	CH_3CN	6	60
5	Gallic acid	CH_3CN	6	40
6	**Fluoroboric acid**	**CH_3CN**	**4**	**95**
7	Boric acid	CH_3CN	6	40
8	Phosphoric acid	CH_3CN	6	60
9	Tungstic acid	CH_3CN	6	60
10	Molybdic acid	CH_3CN	6	60

[a]Reaction conditions: 2,4-dinitrophenyl hydrazine (1 mmol), Acetyl acetone (1.2 mmol), catalyst (20 mol%), solvent (2 mL), room temperature.
[b]Isolated yield.
Bold indicates the optimized value.

Table 2. Solvent optimization.[a]

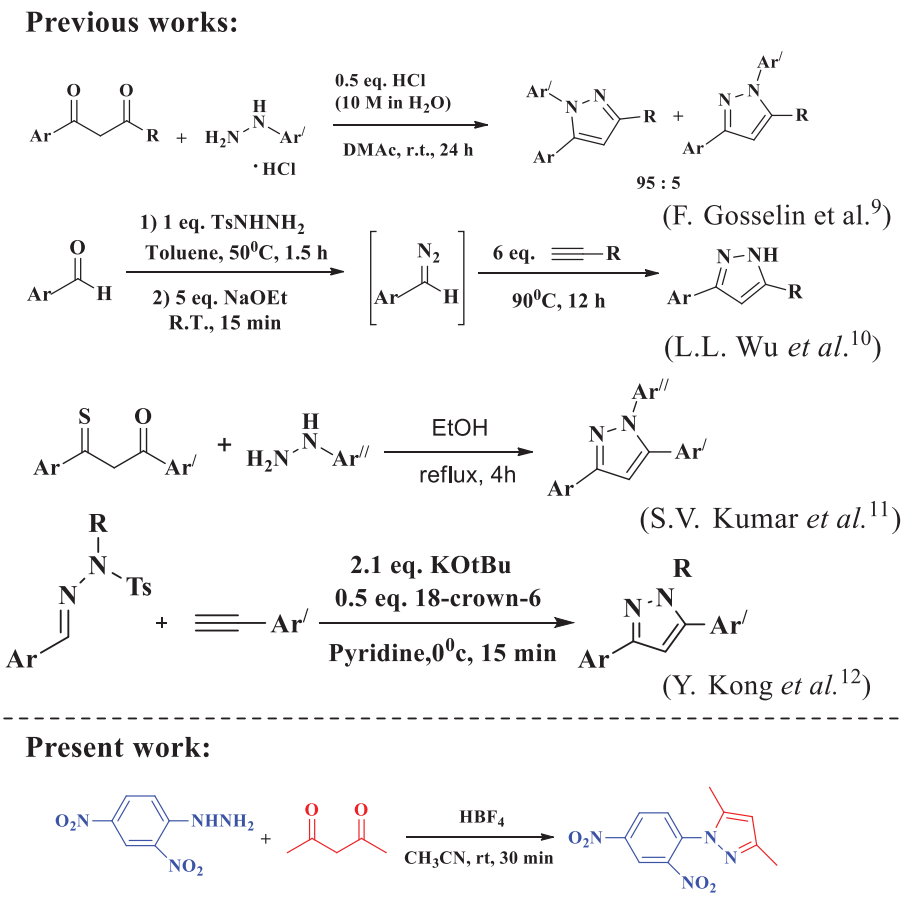


Sl. No.	Solvent	Time (h)	Yield[b] (%)
1	H_2O	6	–
2	CH_3OH	6	60
3	C_2H_5OH	6	60
4	CH_3CN	3	95
5	CH_3CN	2	95
6	CH_3CN	1	93
7	**CH_3CN**	**0.5**	**92**
8	THF	1	70
9	DMF	6	30
10	Toluene	6	40
11	Ethylene glycol	6	30
12	Polyethylene glycol	6	30

[a]Reaction conditions: 2,4-dinitrophenyl hydrazine (1 mmol), Acetyl acetone(1.2 mmol), catalyst (20 mol%) in solvent (2 mL) were stirred at room temperature.
[b]Isolated yield.
Bold indicates the optimized value.

and PEG (Table 2, **entry 12**) but the results were not convincing. The possible reason may be, in aprotic solvent there is no scope of hydrogen bonding of the catalyst with the solvent and therefore the hydrogen is readily available for abstraction by the carbonyl group which is shown in the mechanism (Scheme 2). Among all the screened solvents, it was found that HBF_4 in acetonitrile catalyzed the reaction very fast and it took only 30 min for completion of the reaction and it turned out to be the best reaction condition for our study.

To justify the optimized reaction condition and to extend the scope of the reaction, we investigated the reaction with various hydrazines with different substituted acetyl

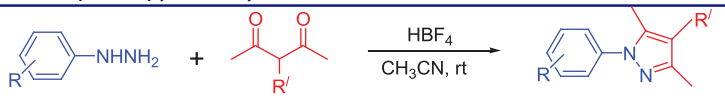


Scheme 2. Mechanistic pathway.

acetones under the same optimized reaction condition and the results are presented in Table 3. The expected products were obtained in reasonable reaction times with good to excellent yields without the formation of any other side product. The yields and reaction times are satisfactorial irrespective of the functional group present in both the hydrazine and diketone derivatives.

We have further studied the tolerance of our catalytic protocol toward fused ring as well as heteroatom bearing hydrazines and higher substituted 1,3-dicarbonyl compounds and the reactions proceeded smoothly and gave satisfactory yields in reasonable time periods. The results are shown in Table 4 **(entries 1–5)**. We have also tried to extend our protocol by using 1,3-unsymmetrical and 1,3-cyclic diketones but the production of regio-isomers in case of unsymmetrical diketone and very negligible yield for cyclic diketone were observed. (Table 4**, entries 6–7**).

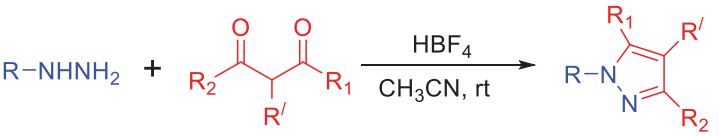
Table 3. Substrate scope for pyrazole synthesis.[a]

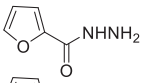
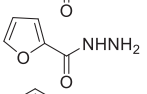
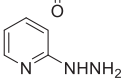
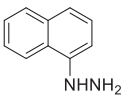
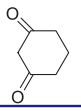


Sl. NO.:	R	R/	Time (h)	Yieldb (%)
1	2,4-dinitro	H	0.5	92
2	3-NO_2	H	2	95
3	3-NO_2	CH_3	2	90
4	4-Br	H	3	88
5	4-Br	CH_3	3	85
6	3-NO_2	C_2H_5	3	87
7	4-CN	CH_3	3	83
8	4-NO_2	H	1	95
9	3-NO_2	Cl	4	90
10	4-OCH_3	H	2	90
11	4-Cl	CH_3	3	85
12	4-OCH_3	CH_3	3	88
13	4-Cl	Cl	4	90
14	4-CH_3	Cl	4	82
15	4-NO_2	Cl	3	76
16	H	CH_3	2	90
17	4-CN	Cl	4	81
18	4-CF_3	H	2	90
19	4-CH_3	CH_3	3	80

[a]Reaction conditions: hydrazine derivatives(1 mmol), 1,3-diketones(1.2 mmol), HBF_4 (20 mol%) was stirred at room temperature.
[b]Isolated Yield.

Table 4. Effect of fused ring, heteroatom bearing hydrazines and higher substituted 1,3-dicarbonyl compounds on pyrazole synthesis.[a]



Sl. No.	Hydrazine derivatives	R/, R_1, R_2	Time(h)	Yield[b](%)
1	4-CF_3PhNHNH$_2$	R/=H, R_1=C_2H_5, R_2=C_2H_5	4	90
2		R/=Cl, R_1=CH_3 ,R_2=CH_3	4	74
3		R/=H, R_1=C_2H_5, R_2=C_2H_5	3	88
4		R/=C_2H_5, R_1=CH_3, R_2=CH_3	4	81
5		R/=H, R_1=CH_3, R_2=CH_3	1	90
6	4-CF_3PhNHNH$_2$	R/=H, R_1=CH_3, R_2=OC_2H_5	4	70[c]
7	4-OCH_3PhNHNH$_2$		4	–

[a]Reaction conditions: hydrazine derivatives(1 mmol), 1,3-diketones(1.2 mmol), HBF_4 (20 mol%) was stirred at room temperature.
[b]Isolated Yield.
[c]Regio-isomers are formed.

Proposed mechanism

Based on the literature reports, the mechanism of acid catalyzed pyrazole synthesis can be discussed as listed in Scheme 2 which was initially proposed by Knorr himself.[17] It starts with abstraction of the proton (from catalyst) by one of the nucleophilic carbonyl groups of the symmetrical diketone which is then attacked by the free nitrogen atom of the hydrazine derivative. The same oxygen again attacks the proton on the attached hydrazine to give intermediate **2** from where a water molecule is lost. The molecule is then cyclized (intermediate **4**) and subsequent loss of water finally gives the product.

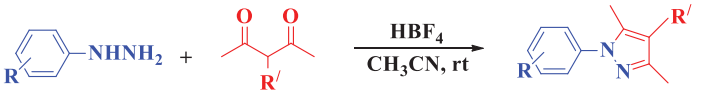
Conclusions

In summary, a simple, efficient protocol is presented for the acid catalyzed pyrazole synthesis which gives good to excellent yields in shorter periods of time. To the best of our knowledge, the reaction portrayed in Scheme 1 is the first synthetic procedure of pyrazole using Fluoroboric acid in Acetonitrile as the catalytic system. Easy handling, easy accessibility, shorter reaction times, ambient reaction conditions are the advantages of our protocol. We anticipate that the current method will be a more practical alternative to the other existing procedures.

Experimental

All reactions were performed under atmospheric conditions using oven dried glassware. All reagents and solvents were purchased from common commercial sources and used without further purification unless otherwise stated. All reported yields are isolated yields. Thin layer chromatography (TLC) was carried out using aluminum sheets precoated with silica gel 60 F_{254} (Merck) and was visualized under 254 nm UV light. Column chromatography was performed on silica gel (120–230 mesh). ^{1}H &^{13}C NMR spectra were recorded on 500 MHz and 125 MHz spectrometer using TMS as an internal standard. Chemical shifts are reported in parts per million (ppm, δ).

General experimental procedure for synthesis of pyrazoles using HBF_4 as catalyst room temperature



In a round bottom flask a mixture of hydrazine derivative (1 mmol) and 1,3-diketone (1.2 mmol) was taken and Fluoroboric acid (20 mol%) was added to it and then allowed to stir at room temperature for the given time period as mentioned in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with ethyl acetate (3 × 10 mL), washed with distilled water and brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography to get the desired product.

Spectral data for the selected compounds

1-(2,4-Dinitro-phenyl)-3,5-dimethyl-1*H*-pyrazole (Table 3, entry 1): Yield = 92%; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.80$ (d, $J = 2.5$ Hz, 1 H), 8.54 (dd, $J = 8.7$, 2.5 Hz, 1 H), 7.71 (d, $J = 8.7$ Hz, 1 H), 6.11 (s, 1 H), 2.31–2.23 (m, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 152.36$ (s), 146.24 (s), 145.64 (s), 140.92 (s), 137.94 (s), 129.36 (s), 127.35 (s), 121.00 (s), 108.89 (s), 13.47 (s), 11.61 (s).

Supporting information

General Information, Experimental and Analytical data, ^{1}H and ^{13}C NMR spectra and characterization data all are found in the "Supplementary Content" section of this article's webpage.

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