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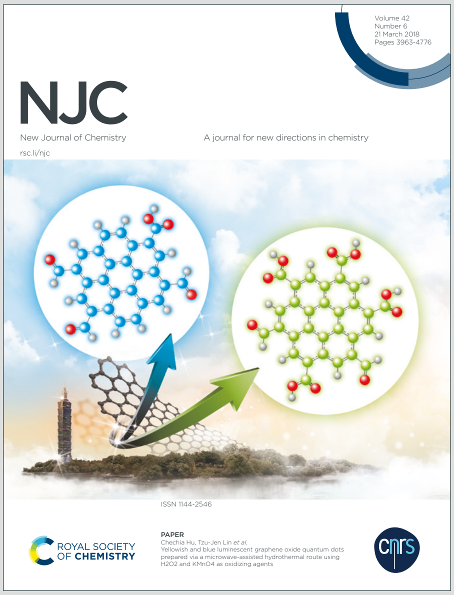

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The use of Enaminones and Enamines as effective synthons for MSA-catalyzed regioselective synthesis of 1,3,4-Tri- and 1,3,4,5-Tetrasubstituted Pyrazoles

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Abstract:

In the present work, an efficient regioselective synthesis of 1,3,4-tri- and 1,3,4,5-tetrasubstituted pyrazoles via Methanesulfonic acid（MSA）-catalyzed reaction of hydrazones with enaminones or enamines is reported. Mechanistically, the formation of the title compounds involves the [2+3] cycloaddition of hydrazones with enaminones or enamines followed by aromatization with acid and oxygen. This convenient method under mild conditions with various hydrazones, enaminones, and enamines was well-tolerated to afford products in good to excellent yields. Compared with literature methods, this strategy has advantages such as materials are available economically, Metal-free catalysis, excellent regioselectivity, and high efficiency.

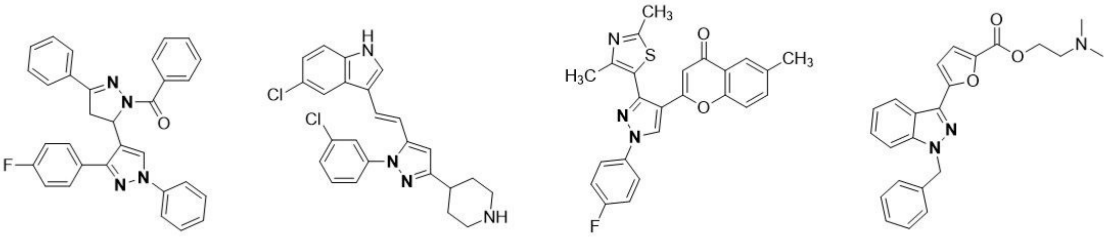

Figure 1. Selected examples of pharmacologically active substances containing pyrazole moiety

Pyrazole is an important building block in drug design (**Figure 1**)[1,2], and can be found in many therapeutic drugs, such as Celebrex, Viagra, and Acomplia, and drugs containing pyrazole moiety have shown a wide spectrum of therapeutic such as anti-inflammatory[3], analgesic[4], antibacterial[5] and anticancer[6]. Due to its importance, there are already so many methods for preparation pyrazole scaffold has been developed. In the 19th century, Knorr prepared 1,3,5-trisubstituted pyrazoles by the condensation reaction of hydrazines and 1,3-diketones for the first time[7]. However, the Knorr reaction lacks regiospecificity. In the past few decades, considerable progress has been achieved in the synthesis of pyrazole. Deng has developed a regioselective synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles by the reaction of electron-deficient N-arylhydrazones with nitroolefins[8]. And Li's group designed a synthetic strategy to synthesize substituted 4-acyl pyrazole derivatives from N-propynylsulfonyl hydrazide and diaryl iodide salts[9]. Recently, Florian, Fan and Tian obtained pyrazole derivatives by the free radical reaction independently, providing an alternative synthetic method for pyrazoles(**Scheme 1**)[10,11,12]. However, there are still some limitations, for example, difficulties in obtaining the

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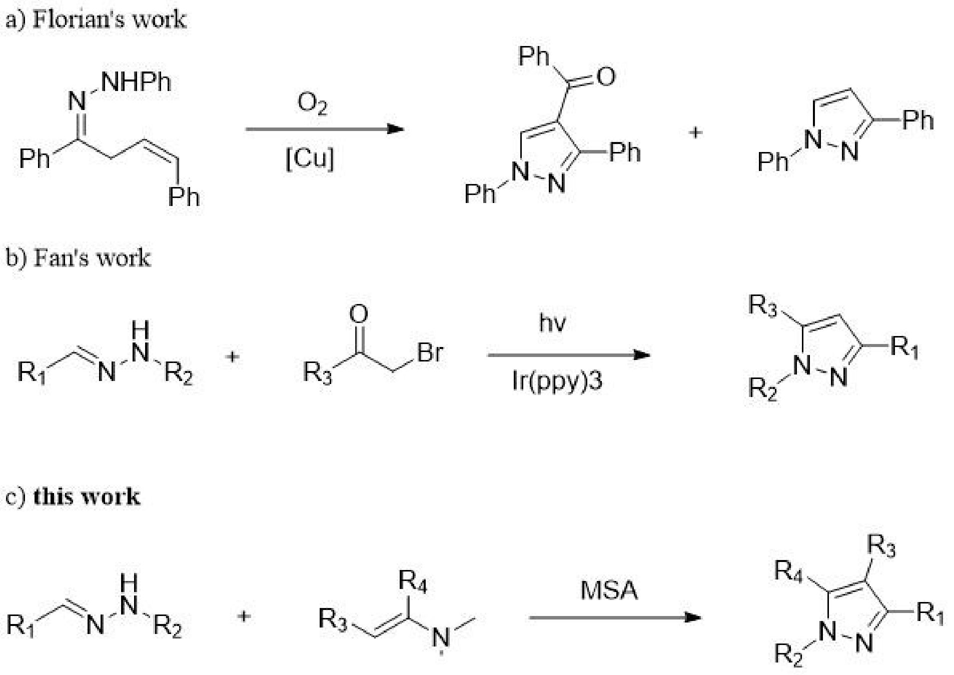
substrates[13,14], poor regioselectivity[15], harsh reaction conditions[16], and need non-oxygen oxidants or metals. Therefore, developing a more selective and versatile method for the preparation of substituted pyrazoles from economical and readily available substrates remains a very challenging subject.

1,3-Dipolar cycloaddition reactions are the basic reaction in organic chemistry[17], and it has always been favored and applied by chemists, and constantly broaden the scope of application. 1,3-Dipolar cycloaddition provides a powerful and reliable synthetic method for obtaining a five-membered heterocyclic ring by means of regional and stereo control[18]. Indeed, the 1,3-dipolar cycloaddition reaction has been described as “the single most important method for the construction of heterocyclic five-membered rings in organicchemistry”[19]. Due to the characteristics of 1,3-dipolar cycloaddition reactions, it is still one of the most interesting topics for chemists to design the reactions which are involved in 1,3-dipolar cycloaddition directly or indirectly.

Unsaturated ketone is a kind of important intermediate is widely used in organic synthesis. It can easily occur in the Michael addition reaction and Diels Alder reaction. Utilizing these characteristics, unsaturated ketone structure was introduced to design enaminones as synthon, it was designed to undergo 1,3-dipolar cycloaddition reaction with hydrazones to construct 1,3,4-trisubstituted pyrazoles. Further, enamines were designed as synthon by removing the carbonyl group of enaminones. Herein, we report a new method for synthesis of 1,3,4-tri- and 1,3,4,5-tetrasubstituted pyrazoles via Methanesulfonic acid（MSA）-catalyzed reaction, excellent regioselectivity can be achieved on the reaction of hydrazones with enaminones or enamines.



Scheme 1. Previous works and this work

Table 1. Exploration of reaction conditions[a].

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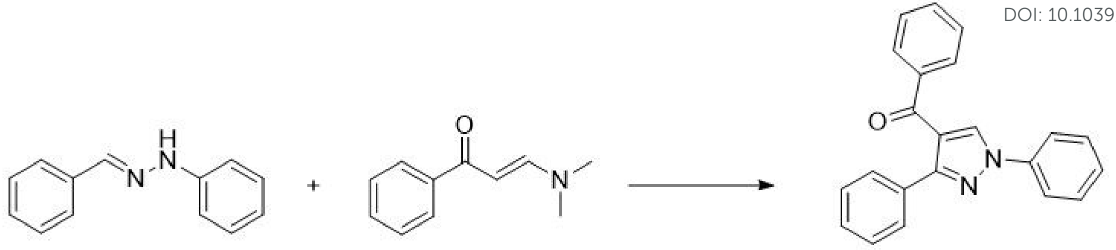

1a **2a** **3aa**

Entry	Catalyst	Solvent	Condition	Yield[b](%)
1	$Sc(CF_3SO_3)_3$	DCM	RT, 5h	trace
2	$Sc(CF_3SO_3)_3$	Toluene	100℃, 5h	7
3	$Ni(CF_3SO_3)$	DCM	RT, 5h	NR
4	$Ag(CF_3SO_3)$	DCM	RT, 5h	NR
5	$Ag(CF_3SO_3)$	Toluene	100℃, 5h	NR
6	$Cu(OAc)_2.H_2O$	DCM	RT, 5h	trace
7	$Mn(OAc)_2$	DCM	RT, 5h	trace
8	$CuCl_2.2H_2O$	DCM	RT, 5h	12
9	$BiCl_3$	DCM	RT, 5h	trace
10	$NiCl_2$	DCM	RT, 5h	NR
11	$MgCl_2$	DCM	RT, 5h	NR
12	$(CF_3COO)_2Cu.H_2O$	DCM	RT, 5h	NR
13	$FeCl_3.6H_2O$	DCM	RT, 5h	18
14[c]	$AlCl_3$	DCM	RT, 5h	28
15[c]	$AlCl_3$	Toluene	100℃, 5h	22
16[d]	$AlCl_3$	DCM	RT, 5h	trace
17	TsOH	DCM	RT, 5h	trace
18	–	DCM	RT, 5h	NR
19	–	Toluene	100℃, 5h	NR

[a]Reaction conditions: 1a (0.10 mmol, 1.0 equiv.), 2a (0.10 mmol, 1.0 equiv.), catalyst (0.10 mmol, 1.0 equiv.), solvent (3.0 mL); [b] Isolated yield; [c] A few drops of water was added; [d] Anhydrous dichloromethane, under N_2 atmosphere; NR: no reaction.

Initial reactions were progressed with enaminones and hydrazones as model substrates. At the beginning, we investigate the effects of Lewis acid on the reaction. However, the catalytic amount (5.0 mol％) of Lewis acid did not make the reaction proceed smoothly at room temperature (**Table 1, Entry 1, 3, 4**). And raising the temperature of the reaction, the results are still not good enough (**Table 1, Entry 2, 5**). To our surprise, we found that the reaction occurred by using the equivalent of $CuCl_2.2H_2O$ and $FeCl_3.6H_2O$ as catalysts, although the reaction yield is low (**Table 1, Entry 8, 13**). Then we control the reaction using $AlCl_3$ as a catalyst with the N_2 atmosphere and anhydrous dichloromethane to afford the product in trace yield (**Table 1, Entry 16**). When a few drops of water were added, the yield was improved significantly (**Table 1, Entry 14**). Based on the above results, we assumed that hydrogen ion may promote the reaction. Subsequently, diverse Protonic Acid was used as the catalysis, and their effects on the reaction were evaluated.

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Table 2. Optimization of reaction conditions[a].

Entry	Catalyst	Solvent	Condition	Yield[b](%)
1	AcOH	DCM	RT, 5h	18
2[c]	HCl	DCM	RT, 5h	21
3[d]	H_2SO_4	DCM	RT, 5h	20
4	CF_3COOH	DCM	RT, 5h	42
5	CF_3SO_3H	DCM	RT, 5h	28
6	**CH_3SO_3H**	**DCM**	RT, 5h	**73**
7	$(CF_3SO_3)_2NH$	DCM	RT, 5h	18
8	Naphthalene-1-sulphonic acid	DCM	RT, 5h	30
9	$(CF_3SO_3)_2O$	DCM	RT, 5h	19
10	Et_3N	DCM	RT, 5h	NR
11	Et_3N	Toluene	100℃, 5h	NR
12	CH_3SO_3H	DCM	RT, 24h	70
13	CH_3SO_3H	DCM	reflux, 5h	71
14	CH_3SO_3H	Et_2O	RT, 5h	15
15	CH_3SO_3H	THF	RT, 5h	60
16	CH_3SO_3H	DMF	RT, 5h	29
17	CH_3SO_3H	Toluene	RT, 5h	52
18	CH_3SO_3H	Dioxane	RT, 5h	58
19	CH_3SO_3H	Dioxane	100℃, 5h	60
20	CH_3SO_3H	MeCN	RT, 5h	27
21	CH_3SO_3H	MeOH	RT, 5h	36

[a]Reaction conditions: 1a (0.10 mmol, 1.0 equiv.), 2a (0.10 mmol, 1.0 equiv.), catalyst (0.10 mmol, 1.0 equiv.), solvent (3.0 mL); [b] Isolated yield; [c] conc. HCl; [d] conc. H_2SO_4; NR: no reaction.

To further verify our hypothesis and improve reaction efficiency. We selected some organic and inorganic acids and examined the effect of acid on this reaction (**Table 2, Entries 1-9**). From the results we can see, CF_3COOH and CH_3SO_3H gave higher yields of 3aa than $AlCl_3$ (**Table 2, Entry 4, 6**), while the strong acidic H_2SO_4, $(CF_3SO_3)_2NH$ and $(CF_3SO_3)_2O$ as catalysts, the target compound was obtained at lower yields (**Table 2, Entry 3, 7, 9**). Furthermore, under the condition of triethylamine as a base, no reaction was observed (**Table 2, Entry 10, 11**). The results show that the most effective catalyst was methanesulfonic acid (MSA), which afforded the target product in 73% yield in DCM at room temperature (**Table 2, Entry 6**). Rising the temperature has

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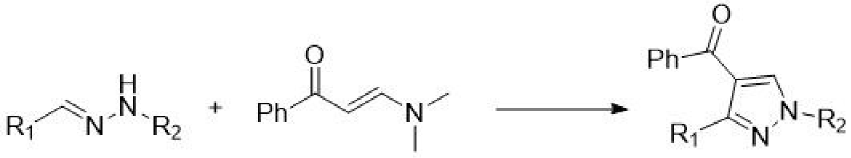
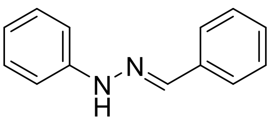
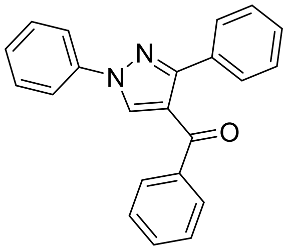
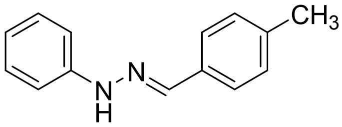
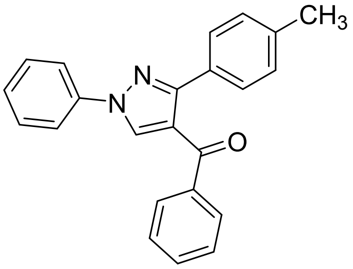
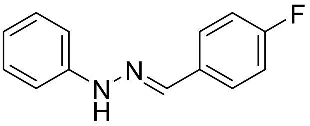
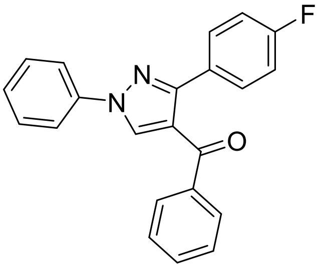
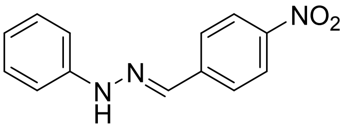
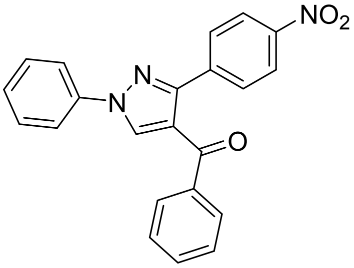
almost no effect on the yield of the reaction (**Table 2, Entry 13, 19**). Prolonging the reaction time to 12 h could not improve the yield (**Table 2, Entry 12**). Under this condition, the solvent screening showed that DCM is optimal, dioxane, tetrahydrofuran, and toluene were also favorable (**Table 2, Entry 15, 17, 18**).

Table 3. The scope of various Hydrazons[a].



Entry	Hydrazon	Product	Yield[b]
1			73% **(3aa)**
2			70% **(3ab)**
3			63% **(3ac)**
4			54% **(3ad)**

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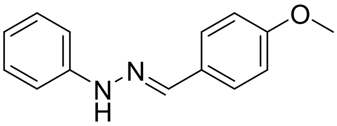
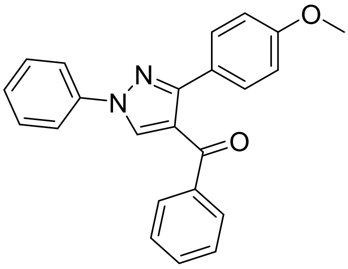
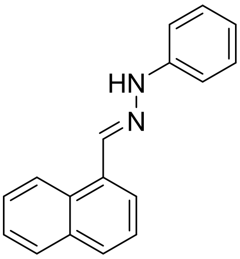
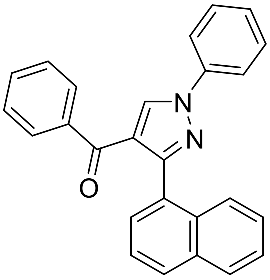
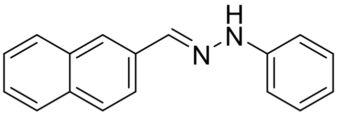
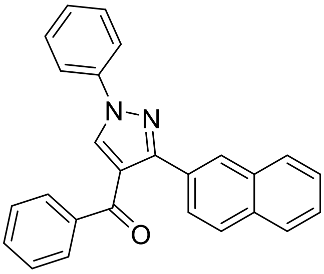
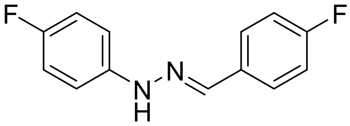
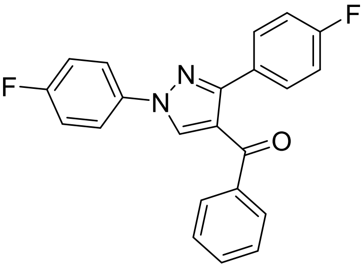
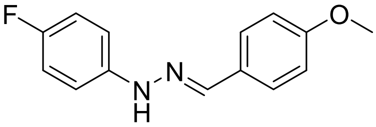
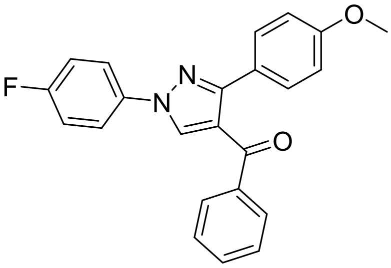
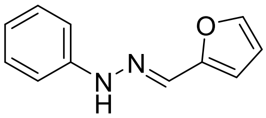
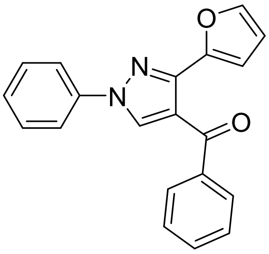
5			64% **(3ae)**
6			68% **(3af)**
7			70% **(3ag)**
8			57% **(3ah)**
9			59% **(3ai)**
10			76% **(3aj)**

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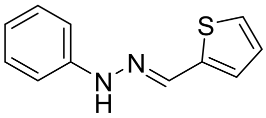
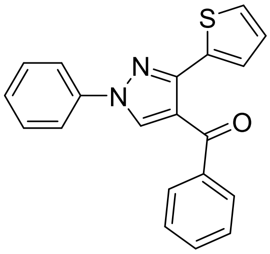
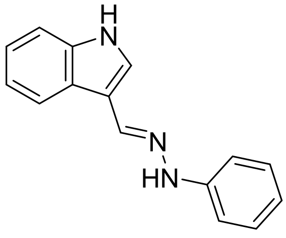
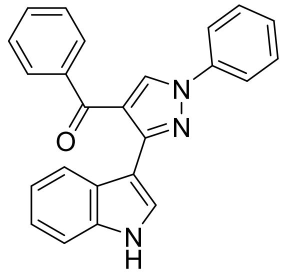
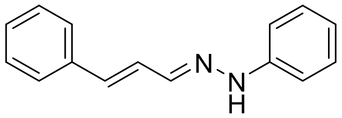
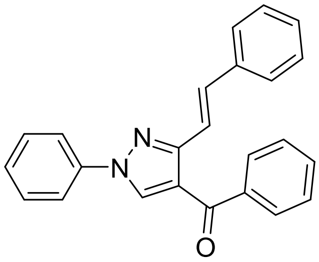
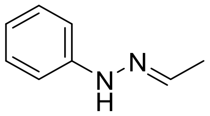
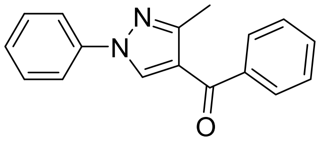
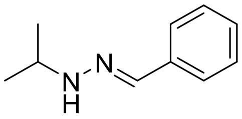
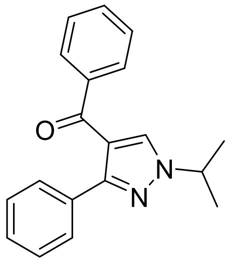
11			74% **(3ak)**
12			62% **(3al)**
13			64% **(3am)**
14			76% **(3an)**
15			72% **(3ao)**

[a]Reaction conditions: 1a (0.10 mmol, 1.0 equiv.), 2a (0.10 mmol, 1.0 equiv.), catalyst (0.10 mmol, 1.0 equiv.), solvent (3.0 mL); [b] Isolated yield.

With the optimized conditions in hand, the scope of this reaction with various enaminones and hydrazones was investigated. As shown in **Table 3**, the reactions of enaminones and hydrazones bearing an electron-donating or electron-withdrawing group proceeded smoothly to give the corresponding product in 54–76% yields. The electron-donating groups, such as 4-OMe, 4-Me, attached to phenyl rings exhibited good reactivity (**Table 3, 3ab and 3ae**), and the electron-withdrawing groups, such as 4-NO_2, could obviously decrease the yield slightly (**Table 3, 3ad**), which suggested that the electron density of two benzene rings of hydrazone has little effect on the reaction efficiency. Then we replace R_1 with 1 and 2-naphthyl, the reaction gave a good yield, indicating the bulky structure did not affect the proceeding of the reaction significantly

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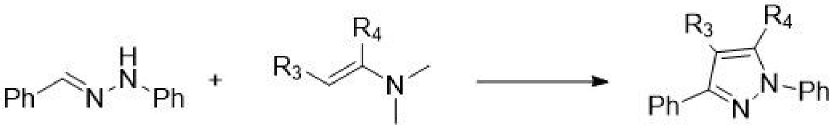
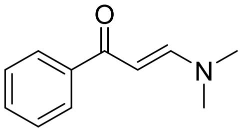
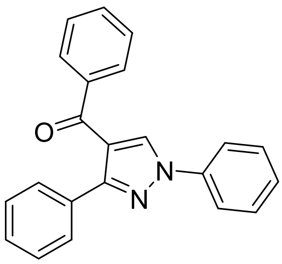
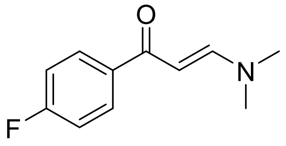
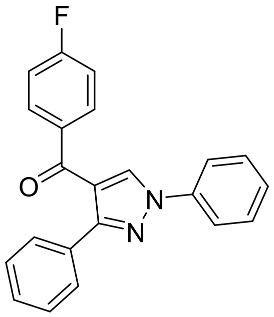
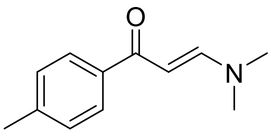
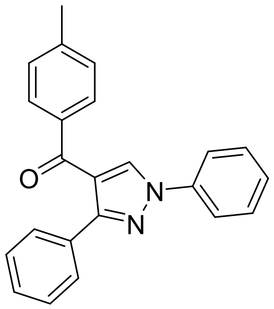
(**Table 3, 3af and 3ag**). And when a double bond was inserted between C and N in the hydrazone, the reaction can also proceed smoothly (**Table 3, 3am**). Notably, hydrazone with aromatic heterocyclic rings, such as furan, thiophene, and indole also formed the corresponding products in good yield (**Table 3, 3aj-3al**). In addition to arylhydrazones, representative alkylhydrazones were tested, which suggested that the reactivity of alkylhydrazones was also very good, rendering target products readily (**Table 3, 3an and 3ao**).

Table 4. The scope of various Enaminones and Enamines[a]



Entry	Enamine	Product	Yield[b]
1			73% **(3aa)**
2			70% **(3ap)**
3			66% **(3aq)**

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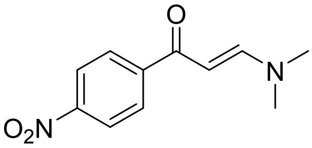
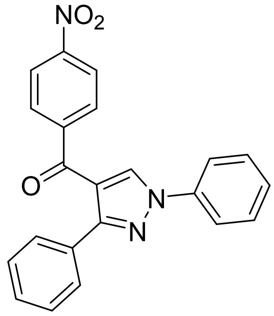
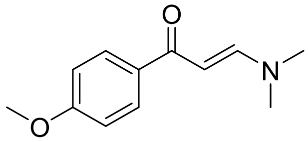
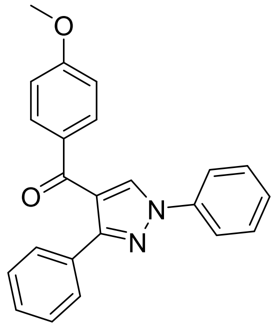
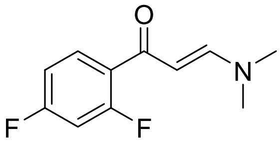
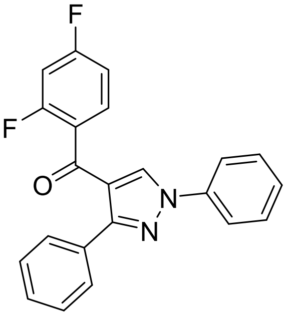
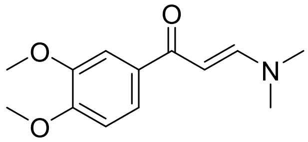
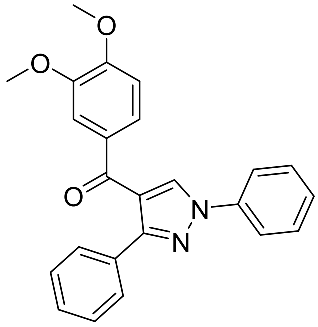
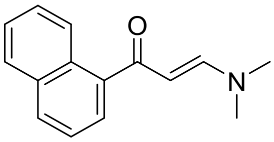
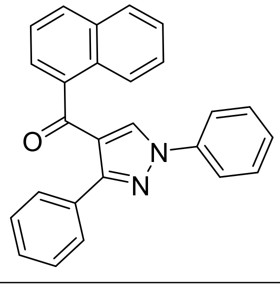
4			82% **(3ar)**
5			66% **(3as)**
6			64% **(3at)**
7			62% **(3au)**
8			71% **(3av)**

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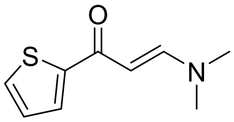
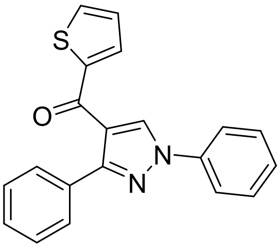
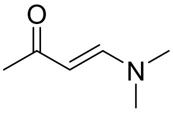
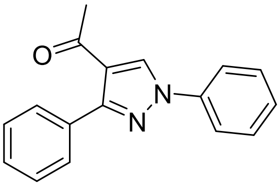
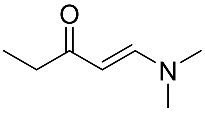
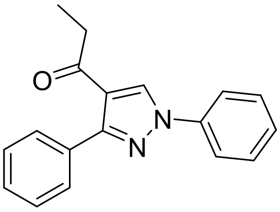
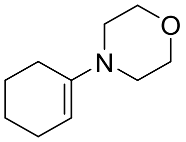
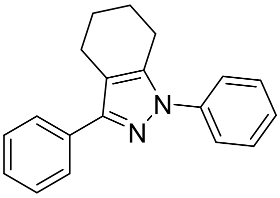
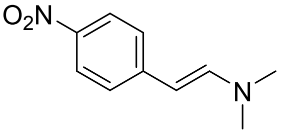
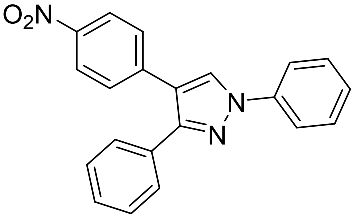
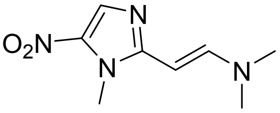
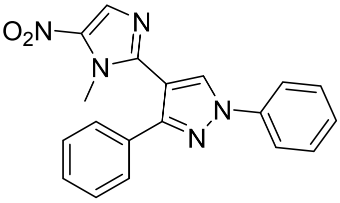
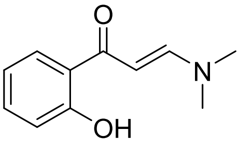
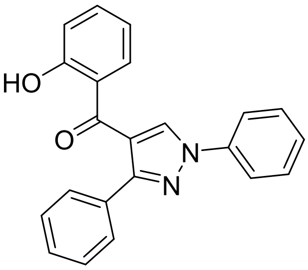
9			81% **(3aw)**
10			43% **(3ax)**
11			41% **(3ay)**
12[c]			68% **(3ba)**
13[c]			72% **(3bb)**
14[c]			64% **(3bc)**
15			70% **(3az)**

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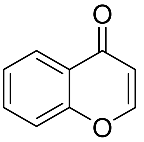
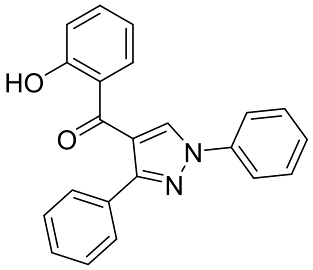
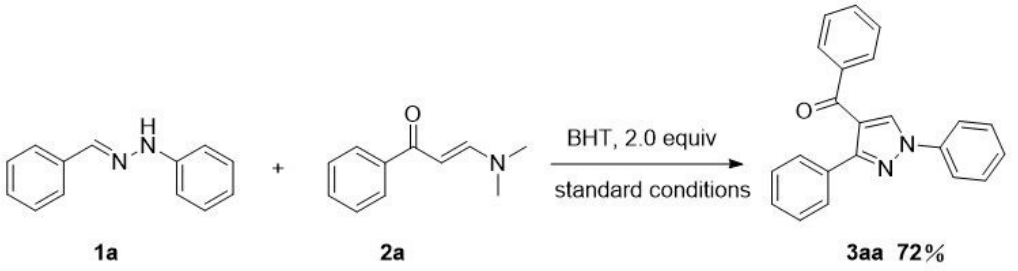
16[c]			80% **(3az)**

[a]Reaction conditions: 1a (0.10 mmol, 1.0 equiv.), 2a (0.10 mmol, 1.0 equiv.), catalyst (0.10 mmol, 1.0 equiv.), solvent (3.0 mL); [b] Isolated yield; [c] the reaction temperature was 100℃ in toluene.

To further expand the scope of the substrates, diversity of enaminone and enamine was investigated. As shown in **Table 4**, first enaminones were used as reactants, compared with the electron-donating groups, enaminones containing the electron-withdrawing groups, such as 4-NO_2 attached to phenyl rings exhibited good reactivity (**Table 4, 3ap-3au**). And the substrates containing other aromatic rings such as thiofuran and naphthalene afforded the corresponding products in good yield (**Table 4, 3av and 3aw**). However, lower yields were observed when enaminone was substituted by alkyl rather than aromatic ring (**Table 4, 3ax and 3ay**). The carbonyl group in enaminones was removed considering that the carbonyl group did not change after the reaction, then enamines we used as reactants. In order to verify the versatility of the reaction and the diversity of substrates, we selected several enamines which containing cyclohexene, substituted benzene and imidazole moiety respectively. However, it was found that the reaction did not proceed under standard conditions. Based on previous results, toluene was used as a solvent and heated to 100°C, target compounds were obtained to our satisfaction (**Table 4, 3ba-3bc**). Indeed, the reaction of enamines and hydrazones confirmed the diversity of substrates and the broadness of the reaction. Furthermore, we have known from the literature[20] that Chromone can be prepared by **2az** under acidic conditions. Then Chromone is used instead of **2az** as substrate under standard conditions. To our delight, the ring-opening reaction proceeds smoothly, target product **3az** was obtained in high yield conveniently (**Table 4 Entry 16**).

In summary, our results are hydrazones (1.0 equiv), enaminones (1.0 equiv), methanesulfonic acid (1.0 equiv) as a catalyst in DCM at room temperature gave the best yield after 5 h, and hydrazones (1.0 equiv), enamines (1.0 equiv), methanesulfonic acid (1.0 equiv) as a catalyst in toluene at 100℃ gave the best yield after 5 h.



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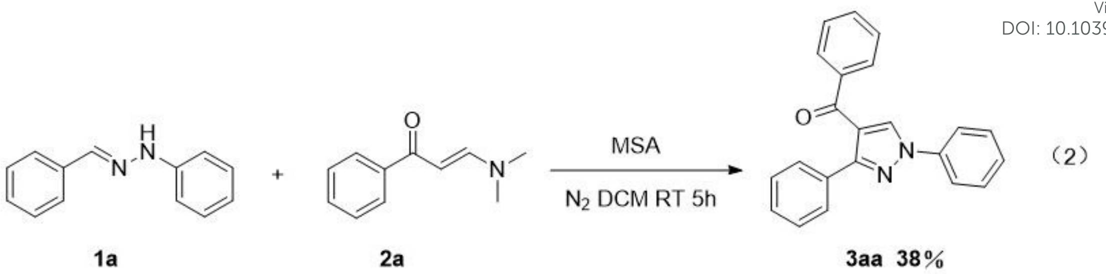

Scheme 2. Control experiments

To explore the reaction mechanism, several control experiments were employed. We performed an experiment when a radical scavenger (butylated hydroxytoluene, BHT) was added under the standard conditions (**Scheme 2, Eq. 1**). But the yield of reaction has almost no changed. This result suggested that a radical process may not be involved in this transformation. Then we performed an experiment in the absence of oxygen (**Scheme 2, Eq. 2**), the yield of the reaction decreased significantly. Based on the above results and previous literature and studies, a plausible mechanism for this cyclization reaction is proposed in **Scheme 3**. First, Hydrazone undergoes a conjugate addition with enamine to afford adduct **A**. Next, an intramolecular nucleophilic addition occurs to afford tetrahydropyrazole **B**. Finally, **B** is converted into final product **3** via successive and rapid oxidative dehydrogenation and acid dehydrogenation reaction. It can be inferred from the reaction mechanism that the carbonyl of enaminones participates in the reaction and the reaction activity was higher than that of enamines. Therefore, enaminones reacted with hydrazone under mild conditions, while enamines require higher temperatures (**Table 4 Entries** 12-16).

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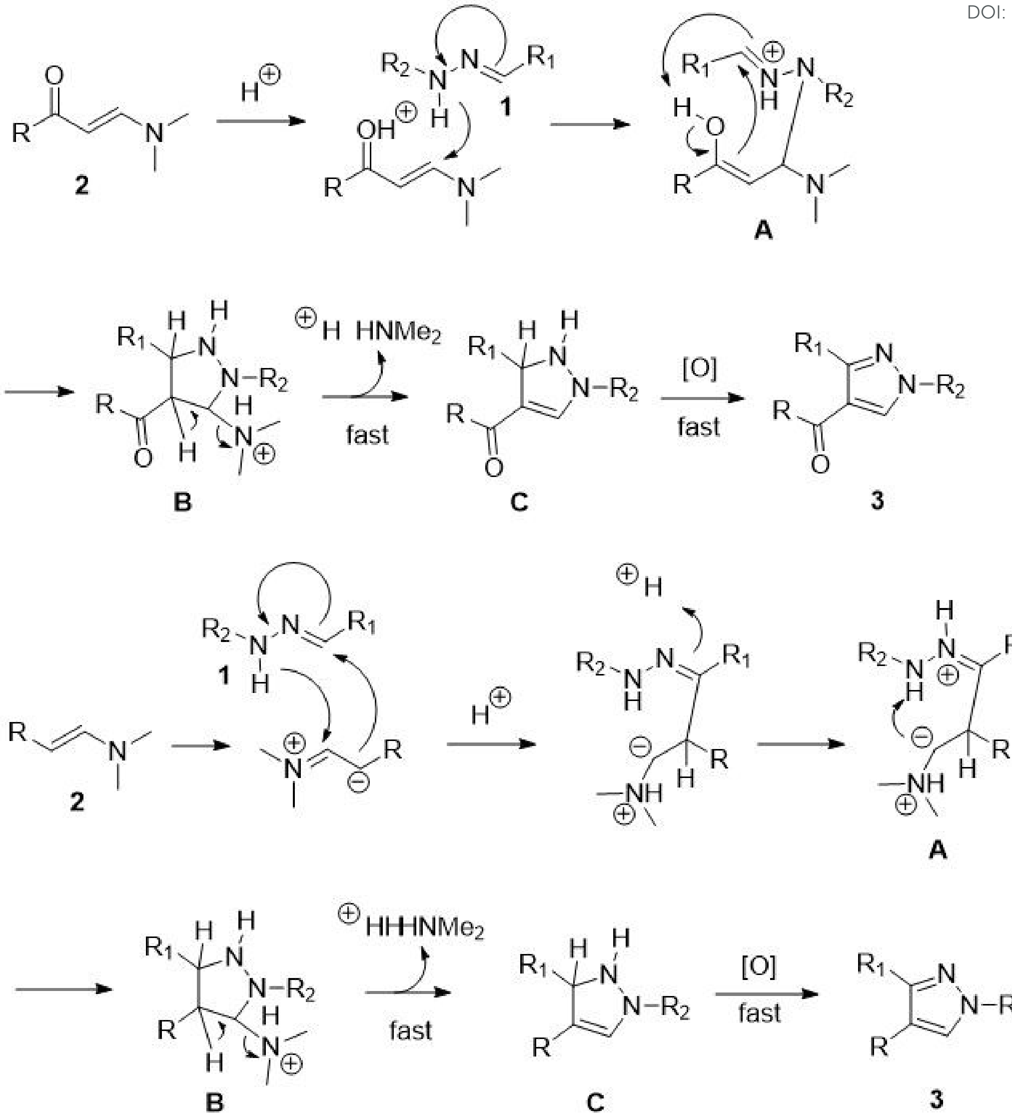

Scheme 3. Plausible mechanism of the reaction

In conclusion, a practical and regioselective synthesis of 1,3,4tri- or 1,3,4,5-tetrasubstituted pyrazoles from hydrazones and enamines has been demonstrated. A plausible mechanism through the methanesulfonic acid-catalyzed was conjectured and explained the regioselective. A range of various hydrazones and enamines were well-tolerated while affording products in good yields. With advantages such as Metal-free catalysis, materials are available economically, excellent regioselectivity and high efficiency. This new synthetic strategy is expected to be widely used in the fields of organic chemistry and medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the Program for Innovative Research Team of the Ministry of Education, The Program of Liaoning Revitalization Talents Program (XLYC1808037). We also gratefully acknowledge a Syngenta Postgraduate Fellow-ship awarded to L.-C.D. and for financial support. (see in Supporting Information, SI).

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