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Construction of multi-substituted pyrazoles via potassium carbonate-mediated [3 + 2] cycloaddition of *in situ* generated nitrile imines with cinnamic aldehydes†

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A highly efficient potassium carbonate-mediated [3 + 2] cycloaddition reaction of hydrazoneyl chlorides with cinnamic aldehydes to furnish multi-substituted pyrazoles under nontoxic and mild conditions has been developed. A plausible stepwise cycloaddition reaction mechanism is proposed. This protocol featured broad substrate coverage, good functional group tolerance, wide scalability, and operational simplicity, as well as conveniently constructed pyrazole scaffolds.

Pyrazole, as a ubiquitous structural motif found in many natural products and biomolecules possessing significant biological and therapeutic effects, is utilized in various areas of pharmaceutical, agrochemical, and biological research.¹ The multi-substituted pyrazoles, especially 1,3,4-tri, 1,3,5-tri and 1,3,4,5-tetrasubstituted pyrazoles, are the structural basis for a wide range of commercially available drugs, such as celecoxib, used as a cyclooxygenase-2 inhibitor for the treatment of rheumatoid arthritis,² CDPPB, described as the first positive allosteric modulator of human metabotropic glutamate receptor,³ Lonazolac, regarded as an anti-inflammatory and anti-hyperglycemic drug,⁴ and PNU-32945 employed as a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV (Fig. 1).⁵

Considering the therapeutic potential of these moieties, the development of new methods towards their synthesis has attracted substantial interest. The past decades have witnessed the development of a large number of simple and efficient methods for synthesis of various functionalized pyrazoles, including the addition condensation of hydrazines with carbonyl derivatives,⁶ the annulation reaction of hydrazones

with nitroolefins,⁷ cycloadditions of diazo compounds with alkenes, alkynes or 1,3-dicarbonyl compounds,⁸ the synthesis of 5-formyl-1,3,4,5-tetrasubstituted pyrazoles by using alkyne surrogates and the preparation of 4-formyl-1,3,4,5-tetrasubstituted pyrazoles by Pd-catalyzed direct arylation at C-5 position (Scheme 1).⁹

In addition, the cascade reaction of hydrazines to acyl chlorides was catalyzed by palladium *via* Sonogashira coupling reaction *in situ* to prepare pyrazoles.¹⁰ Moreover, TsOH-catalyzed Mannich-type cyclization–oxidation of arylhydrazines, aromatic aldehydes, and terminal arylalkynes has been reported to provide multi-substituted pyrazoles.¹¹ Later, the condensation of α,β -unsaturated ketones with aryl hydrazines afforded the functionalized pyrazoles under the presence of water-soluble metal ion catalyst.¹²

Recently, several approaches of preparing pyrazoles by the [3 + 2] cycloaddition reaction of hydrazoneyl chlorides with active alkynes, bromoalkenes, or ketones bearing an active methylene group at the α -position were developed. For example, the 1,3-

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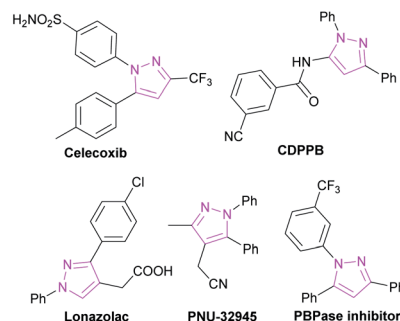
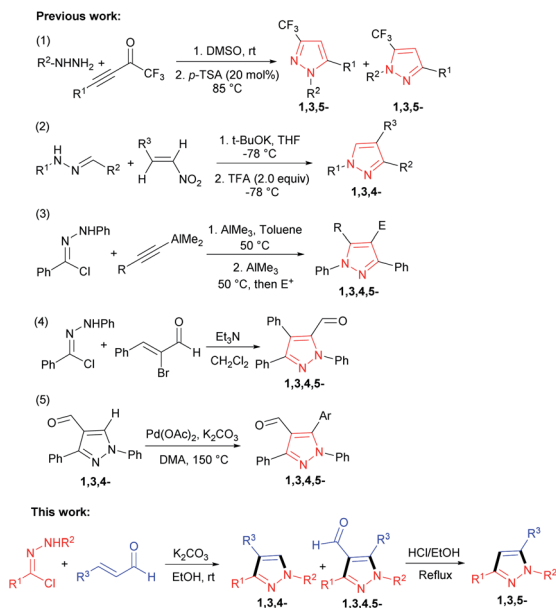


Fig. 1 Example of pyrazole-containing bioactive compounds.





Scheme 1 Different strategies for synthesis of pyrazoles.

dipolar cycloaddition of hydrazonoyl chloride with *o*-(trimethylsilyl)phenyl triflate to access multi-substituted pyrazoles has been developed by Spiteri *et al.*¹³ Then, the regioselective [3 + 2]

cycloaddition of *in situ* formed nitrile imine with 2-bromo-3,3,3-trifluoropropene was successfully demonstrated for the construction of functionalized pyrazoles in simple and mild reaction conditions.¹⁴ Moreover, nitrile imines, generally *in situ* generated by a base-induced dehydrochlorination of corresponding hydrazonoyl chlorides, are also known for their ability to serve as the prominent [3 + 2] cycloaddition synthons.¹⁵ Herein, we report the first [3 + 2] cycloaddition reaction of *in situ* generated nitrile imines and cinnamic aldehydes under mild conditions, conveniently delivering various multi-substituted pyrazoles in good yields.

With encouragement from the preliminary results, we commenced our exploration using the readily accessible hydrazonoyl chloride and cinnamic aldehyde to investigate the feasibility of the designed [3 + 2] cycloaddition reaction for preparing 1,3,4,5-tetrasubstituted pyrazole. However, our surprise was the achievement of the compound beyond our expectation, the 1,3,4-trisubstituted pyrazole, which was prepared by extremely limited methods, was also presented as a minor substance (Scheme 1). As the potential benefits of this transformation seemed to be promising, we decided to engage in a more thorough investigation.

Subsequently, **1a** and **2a** were used as model substrates to examine the optimal conditions of the annulation reaction in this study. We were delighted to observe that when the reaction was conducted in THF with K_2CO_3 as the base, two products as

Table 1 Optimization of reaction conditions^a

Entry	Base	Solvent	Time (h)	Yield ^b (%) (3aa)	Yield ^b (%) (4aa)
1	K_2CO_3	THF	12	55	27
2	K_2CO_3	1,4-Dioxane	12	51	29
3	K_2CO_3	EtOH	12	53	42
4	K_2CO_3	DCM	12	39	14
5	K_2CO_3	CH_3CN	>72	47	26
6	K_2CO_3	$CHCl_3$	12	34	22
7	K_2CO_3	Toluene	12	48	17
8 ^c	K_2CO_3	Toluene	12	45	16
9 ^d	K_2CO_3	Toluene	12	43	16
10	Na_2CO_3	EtOH	12	47	39
11	$KHCO_3$	EtOH	12	49	33
12	DIPEA	EtOH	12	45	36
13	Et_3N	EtOH	12	49	32
14	CS_2CO_3	EtOH	12	Trace	Trace
15	NaOH	EtOH	12	Trace	Trace
16	DBU	EtOH	12	Trace	Trace
17 ^e	K_2CO_3	EtOH	>72	39	20
18 ^f	K_2CO_3	EtOH	12	49	39
19 ^g	K_2CO_3	EtOH	12	37	27
20 ^h	K_2CO_3	EtOH	12	50	39
21 ⁱ	K_2CO_3	EtOH	12	51	42
22 ^j	K_2CO_3	EtOH	12	52	40

^a The reactions were performed with **1a** (0.2 mmol), **2a** (1.2 equiv.), and base (2.5 equiv.) in the solvent (2.5 mL) at room temperature. ^b Isolated yields. ^c K_2CO_3 was pre-dried. ^d With 4 Å MS in anhydrous toluene. ^e K_2CO_3 (1.0 equiv.) was used. ^f K_2CO_3 (5.0 equiv.) was used. ^g The reaction was carried out at 0 °C. ^h The reaction was carried out at 60 °C. ⁱ DDQ (2.5 equiv.) was added. ^j Under the protection of N_2 .

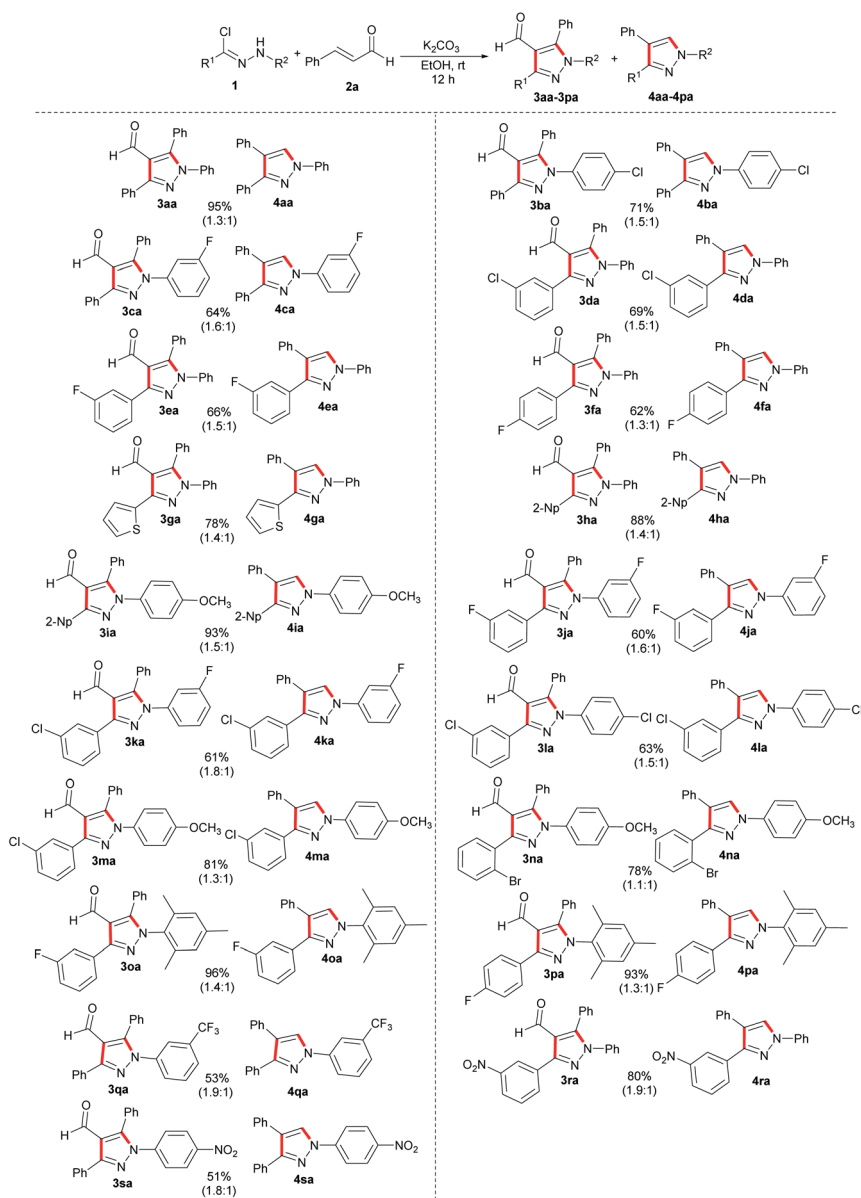


3aa and **4aa** were isolated in 55% and 27% yields, respectively (Table 1, entry 1). As a result of the solvent screening, it was found that ethanol was the most effective solvent with a drastic increase in total yield (95%) (Table 1, entry 3), and oxygenated solvent, such as tetrahydrofuran, 1,4-dioxane or ethanol, could have a detrimental effect on the reaction, affording moderate to excellent yields of the two products (Table 1, entries 1–3). Upon further screening of other solvents, additional improvements in reaction efficiency were not obtained even with prolonged time (Table 1, entries 4–9). Accordingly, different types of bases were screened in order to enhance the yields (Table 1, entries 10–16). To our delight, K_2CO_3 , Na_2CO_3 , $KHCO_3$, DIPEA, Et_3N could provide moderate to excellent yields (81–95%) (Table 1, entries 3, 10–13). Unfortunately, those bases, such as Cs_2CO_3 , NaOH or DBU, displayed no efficacies for this reaction (Table 1, entries

14–16). An obvious decrease in yield has been observed with a decrease in the amount of K_2CO_3 (Table 1, entry 17), while the doubled amount of the base resulted in a slight reduction of the total yield (Table 1, entry 18).

Furthermore, we attempted to conduct the reaction in a precooled ice bath at 0 °C with a considerably decreased total yield (Table 1, entry 19) and in a preheated oil bath at 60 °C with a slightly decreased total yield (Table 1, entry 20). Finally, a combination of an oxidant, such as DDQ, or protection under inert gas, such as N_2 , failed to provide better results (Table 1, entries 21 and 22).

Subsequently, we conducted a systematic evaluation of the substrate scope of nitrile imines in this [3 + 2] annulation reaction under optimal reaction conditions (Scheme 2). Generally, various hydrazonoyl chlorides exhibited good



Scheme 2 Substrate scope of hydrazonoyl chlorides.



functional group tolerance, and the desired multi-substituted pyrazole derivatives were synthesized in moderate to excellent yields (51–96%). The hydrazoneyl chlorides bearing none or electron-rich substituents on the phenyl ring of the R¹ moiety reacted with **2a** and provided higher total yields (**3aa/4aa**, **3ha/4ha** and **3ia/4ia**), compared with that bearing electron-deficient groups, such as fluoro, chloro and bromo at *para*-, *meta*-, and *ortho*-positions of the phenyl ring R¹ (**3da/4da**, **3ea/4ea** and **3fa/4fa**). The *para*-position with electron-withdrawing substituents on R¹ displayed a subtler negative effect on the total yields compared to the *meta*-position (**3ea/4ea** to **3fa/4fa**, **3oa/4oa** to **3pa/4pa**). Substrates with electron-donating groups in the aryl ring at R², such as methoxy- and methyl-, were all directly converted into desired products in excellent yields (**3ia/4ia**, **3ma/4ma**, **3na/4na**, **3oa/4oa** and **3pa/4pa**). Although the electron-withdrawing substituents of R² on hydrazoneyl chlorides can also transform efficiently, an overall slight decline in yields of the corresponding products was observed (**3ba/4ba**, **3ca/4ca**, **3ja/4ja**, **3ka/4ka**, **3la/4la** and **3qa/4qa**, **3sa/4sa**). Interestingly, no matter what type of electron properties a substituent on the R¹ has, the electron-donating substituents on the R² could contribute to an increase in the yields of products. Moreover, the optimal condition was also applicable for heteroaryl hydrazoneyl chlorides, such as *N*-phenylthiophene-2-carbohydrazoneyl chloride, affording the desired multi-

substituted pyrazoles **3ga** and **4ga** in 45% and 33% yields, respectively.

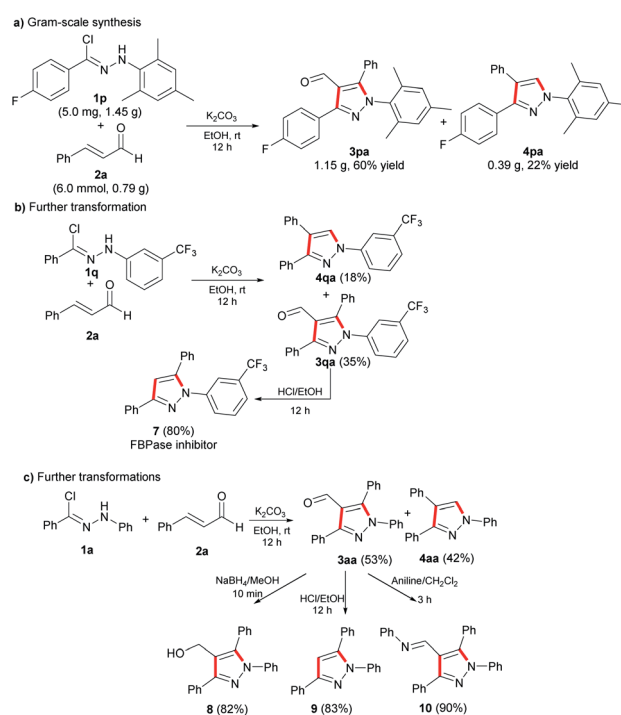
In addition, we investigated how the substituted cinnamic aldehydes could be employed as substrates for the optimum conditions established previously (Table 2). The protocol worked efficiently regardless of the electronic nature of substituted groups on cinnamic aldehydes. The cinnamic aldehyde derivatives with electron-withdrawing groups, such as nitro, chloro and bromo, or electron-donating groups, such as methoxy, on the phenyl ring could react with a variety of hydrazoneyl chlorides to afford the desired products in good to excellent yields (73–96%) (entries 1–21). Interestingly, a systematic comparison showed the electron-donating group on cinnamic aldehyde has a slightly detrimental effect on the reaction efficiency with a lessened yield compared to electron-withdrawing groups (entries 1–3, 4–6, 13–14, 17–18 and 20). In addition, the reaction of *p*-chlorocinnamaldehyde with **1n** afforded an equal proportion of the annulation products (**3l/4l** = 1 : 1) (entry 12). During the reaction with *p*-chlorocinnamaldehyde, it was found that when **1g** was substituted for **1o**, this optimal condition resulted in the highest total yield (96%) (entry 16). Furthermore, the positions of the substituent on the phenyl ring R¹ exhibited no apparent influence on the total yields (entries 4 and 8, 5 and 7, 16–17).

To determine the possibility of using the optimal reaction condition to produce multi-substituted pyrazoles on a gram scale, we carried out the cycloaddition reaction of **1p** and **2a**, which proceeded smoothly and gave the corresponding products of **3pa** and **4pa** in 60% yield and 22% yield, respectively (Scheme 3). The result indicated that the total yield was slightly decreased compared to the milligram-scale reaction.

Table 2 Substrate scope of the synthesis of multi-substituted pyrazoles^a

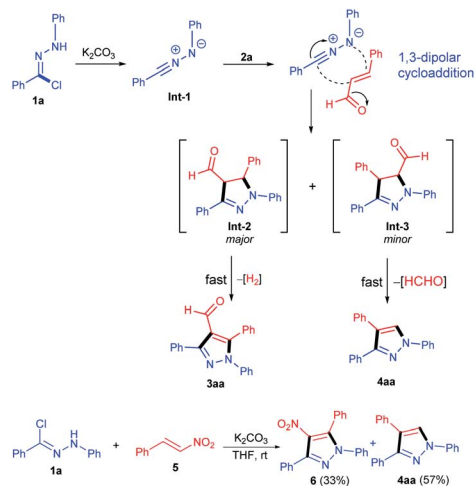
Entry	1 (R ¹ , R ²)	2 (Ar)	Product, yield ^b
1	Ph, Ph	4-BrC ₆ H ₄	3a , 54%; 4a , 29%
2	Ph, Ph	4-ClC ₆ H ₄	3b , 59%; 4b , 28%
3	Ph, Ph	4-OMeC ₆ H ₄	3c , 48%; 4c , 27%
4	3-FC ₆ H ₄ , Ph	4-BrC ₆ H ₄	3d , 57%; 4d , 24%
5	3-FC ₆ H ₄ , Ph	4-ClC ₆ H ₄	3e , 59%; 4e , 22%
6	3-FC ₆ H ₄ , Ph	4-OMeC ₆ H ₄	3f , 50%; 4f , 25%
7	4-FC ₆ H ₄ , Ph	4-ClC ₆ H ₄	3g , 55%; 4g , 27%
8	4-FC ₆ H ₄ , Ph	4-BrC ₆ H ₄	3h , 50%; 4h , 27%
9	3-ClC ₆ H ₄ , Ph	4-ClC ₆ H ₄	3i , 54%; 4i , 27%
10	3-ClC ₆ H ₄ , Ph	4-BrC ₆ H ₄	3j , 44%; 4j , 29%
11	3-ClC ₆ H ₄ , 4-OMeC ₆ H ₄	4-OMeC ₆ H ₄	3k , 52%; 4k , 29%
12	2-BrC ₆ H ₄ , 4-OMeC ₆ H ₄	4-ClC ₆ H ₄	3l , 48%; 4l , 47%
13	2-Np, 4-OMeC ₆ H ₄	4-ClC ₆ H ₄	3m , 56%; 4m , 30%
14	2-Np, 4-OMeC ₆ H ₄	4-OMeC ₆ H ₄	3n , 54%; 4n , 32%
15	2-Np, Ph	4-ClC ₆ H ₄	3o , 54%; 4o , 31%
16	3-FC ₆ H ₄ , 2,4,6-triMeC ₆ H ₂	4-ClC ₆ H ₄	3p , 67%; 4p , 29%
17	4-FC ₆ H ₄ , 2,4,6-triMeC ₆ H ₂	4-ClC ₆ H ₄	3q , 65%; 4q , 30%
18	4-FC ₆ H ₄ , 2,4,6-triMeC ₆ H ₂	4-OMeC ₆ H ₄	3r , 60%; 4r , 28%
19	2-Thiophenyl, Ph	4-ClC ₆ H ₄	3s , 59%; 4s , 21%
20	Ph, Ph	4-NO ₂ C ₆ H ₄	3t , 52%; 4t , 24%
21	Ph, 3-CF ₃ C ₆ H ₄	4-NO ₂ C ₆ H ₄	3u , 45%; 4u , 29%

^a The reaction of **1** (0.2 mmol) with **2** (0.24 mmol) was carried out in the presence of K₂CO₃ (0.5 mmol) in EtOH (2.5 mL) at room temperature for 12 h. ^b Isolated yield.



Scheme 3 Gram-scale synthesis and further transformations.





Scheme 4 Plausible reaction mechanism for two multi-substituted pyrazoles.

Furthermore, we demonstrated the synthetic utility by transforming trifluoromethyl-substituted nitrile imine **1q** in two steps to the fructose 1,6-bisphosphatase (FBPase) inhibitor **7**,¹⁶ which could decrease high blood glucose levels. In order to explore the utility of the final compounds, the aldehyde group on the product **3aa** was transformed into hydroxyl, hydrogen and imine *via* reduction reaction, elimination reaction and aldimine condensation, respectively, to provide the corresponding multi-substituted pyrazole derivatives **8**, **9** and **10**.

Although inconclusive, these results indicated that when a strong electron-withdrawing group was attached to the olefins, the stable aromatization products were obtained after the rapid elimination of small molecules, without 1,3-dipolar cycloaddition products being observed. A tentative reaction pathway is outlined in Scheme 4. Initially, nitrile imine specie **Int-1** was generated from hydrazonoyl chloride **1a** *in situ* in the presence of K_2CO_3 . Subsequently, Michael addition reaction of nitrile imine to cinnamic aldehyde **2a** led to the formation of intermediate **Int-2** and **Int-3**. **Int-2** underwent oxidative dehydrogenation to generate fully substituted pyrazole **3aa**, and **Int-3** underwent an elimination of HCHO to give 1,3,4-trisubstituted pyrazole **4aa**, driven by the strongly electron-withdrawing groups such as CHO and NO_2 . For the reaction intermediates **Int-2** and **Int-3**, whether the elimination of formaldehyde or hydrogen is the priority, the main consideration may be the stability of the elimination product. In order to prove this proposed mechanism, when we applied nitrile imine **1a** and nitroolefin **5** as the raw materials, which successfully underwent the previous process of our optimal cycloaddition condition to afford the desired 4-nitro-pyrazole **6** and 1,3,4-trisubstituted pyrazole **4aa** in a good total yield (90%).

Conclusions

In summary, we have developed an efficient cycloaddition reaction of nitrile imine and cinnamic aldehyde, which allow expedient access to 1,3,4,5-tetra and 1,3,4-trisubstituted

pyrazoles under mild conditions without transition metals. In addition, the products could be efficiently converted to other different types of pyrazoles *via* the reduction, oxidation, or elimination reaction. Furthermore, we have analyzed the possible mechanism of this [3 + 2] cycloaddition. The further exploration for the construction of pyrazole scaffold and the potential application of these compounds are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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