


Cite this: *RSC Adv.*, 2022, **12**, 13087

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

Mei-Mei Li, <sup>‡</sup><sup>a</sup> Hui Huang, <sup>‡</sup><sup>a</sup> Wanrong Tian, <sup>a</sup> Yiru Pu, <sup>a</sup> Chaozheng Zhang, <sup>a</sup> Jirui Yang, <sup>a</sup> Qing Ren, <sup>d</sup> Feiyan Tao, <sup>\*c</sup> Yun Deng <sup>\*a</sup> and Jun Lu <sup>\*ab</sup>

Received 17th January 2022  
Accepted 25th April 2022

DOI: 10.1039/d2ra00331g

rsc.li/rsc-advances

A highly efficient potassium carbonate-mediated [3 + 2] cycloaddition reaction of hydrazonoyl 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.<sup>1</sup> 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,<sup>2</sup> CDPPB, described as the first positive allosteric modulator of human metabotropic glutamate receptor,<sup>3</sup> Lonazolac, regarded as an anti-inflammatory and anti-hyperglycemic drug,<sup>4</sup> and PNU-32945 employed as a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV (Fig. 1).<sup>5</sup>

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,<sup>6</sup> the annulation reaction of hydrazones

with nitroolefins,<sup>7</sup> cycloadditions of diazo compounds with alkenes, alkynes or 1,3-dicarbonyl compounds,<sup>8</sup> 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).<sup>9</sup>

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

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

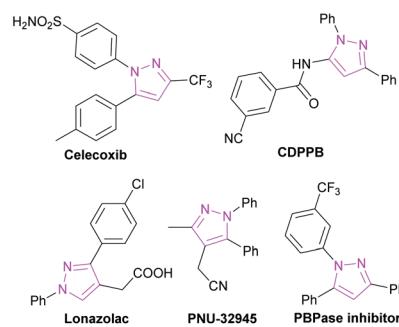


Fig. 1 Example of pyrazole-containing bioactive compounds.

<sup>a</sup>State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China. E-mail: ljaaa111@163.com; dengyun@cdutcm.edu.cn; taofeiyang@163.com

<sup>b</sup>Institute for Advancing Translational Medicine in Bone & Joint Diseases, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, 999077, China

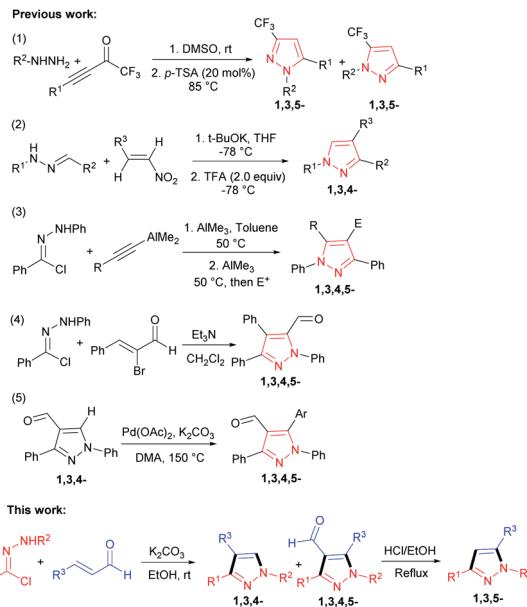
<sup>c</sup>Research and Development Centre, China Tobacco Sichuan Industrial Co., Ltd, Chengdu, 610066, China

<sup>d</sup>School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, 999077, China

<sup>†</sup> Electronic supplementary information (ESI) available. See <https://doi.org/10.1039/d2ra00331g>

<sup>‡</sup> These authors contributed equally.





Scheme 1 Different strategies for synthesis of pyrazoles.

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

cycloaddition of *in situ* formed nitrile imine with 2-bromo-3,3-trifluoropropene was successfully demonstrated for the construction of functionated pyrazoles in simple and mild reaction conditions.<sup>14</sup> Moreover, nitrile imines, generally *in situ* generated by a base-induced dehydrodechlorination of corresponding hydrazoneyl chlorides, are also known for their ability to serve as the prominent [3 + 2] cycloaddition synthons.<sup>15</sup> 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 hydrazoneyl 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<sup>a</sup>

| Entry           | Base       | Solvent            | Time (h) | Yield <sup>b</sup> (%) ( <b>3aa</b> ) | Yield <sup>b</sup> (%) ( <b>4aa</b> ) |
|-----------------|------------|--------------------|----------|---------------------------------------|---------------------------------------|
| 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 <sub>3</sub> CN | >72      | 47                                    | 26                                    |
| 6               | $K_2CO_3$  | CHCl <sub>3</sub>  | 12       | 34                                    | 22                                    |
| 7               | $K_2CO_3$  | Toluene            | 12       | 48                                    | 17                                    |
| 8 <sup>c</sup>  | $K_2CO_3$  | Toluene            | 12       | 45                                    | 16                                    |
| 9 <sup>d</sup>  | $K_2CO_3$  | 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 <sup>e</sup> | $K_2CO_3$  | EtOH               | >72      | 39                                    | 20                                    |
| 18 <sup>f</sup> | $K_2CO_3$  | EtOH               | 12       | 49                                    | 39                                    |
| 19 <sup>g</sup> | $K_2CO_3$  | EtOH               | 12       | 37                                    | 27                                    |
| 20 <sup>h</sup> | $K_2CO_3$  | EtOH               | 12       | 50                                    | 39                                    |
| 21 <sup>i</sup> | $K_2CO_3$  | EtOH               | 12       | 51                                    | 42                                    |
| 22 <sup>j</sup> | $K_2CO_3$  | EtOH               | 12       | 52                                    | 40                                    |

<sup>a</sup> 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. <sup>b</sup> Isolated yields. <sup>c</sup>  $K_2CO_3$  was pre-dried. <sup>d</sup> With 4 Å MS in anhydrous toluene. <sup>e</sup>  $K_2CO_3$  (1.0 equiv.) was used. <sup>f</sup>  $K_2CO_3$  (5.0 equiv.) was used. <sup>g</sup> The reaction was carried out at 0 °C. <sup>h</sup> The reaction was carried out at 60 °C. <sup>i</sup> DDQ (2.5 equiv.) was added. <sup>j</sup> Under the protection of  $N_2$ .

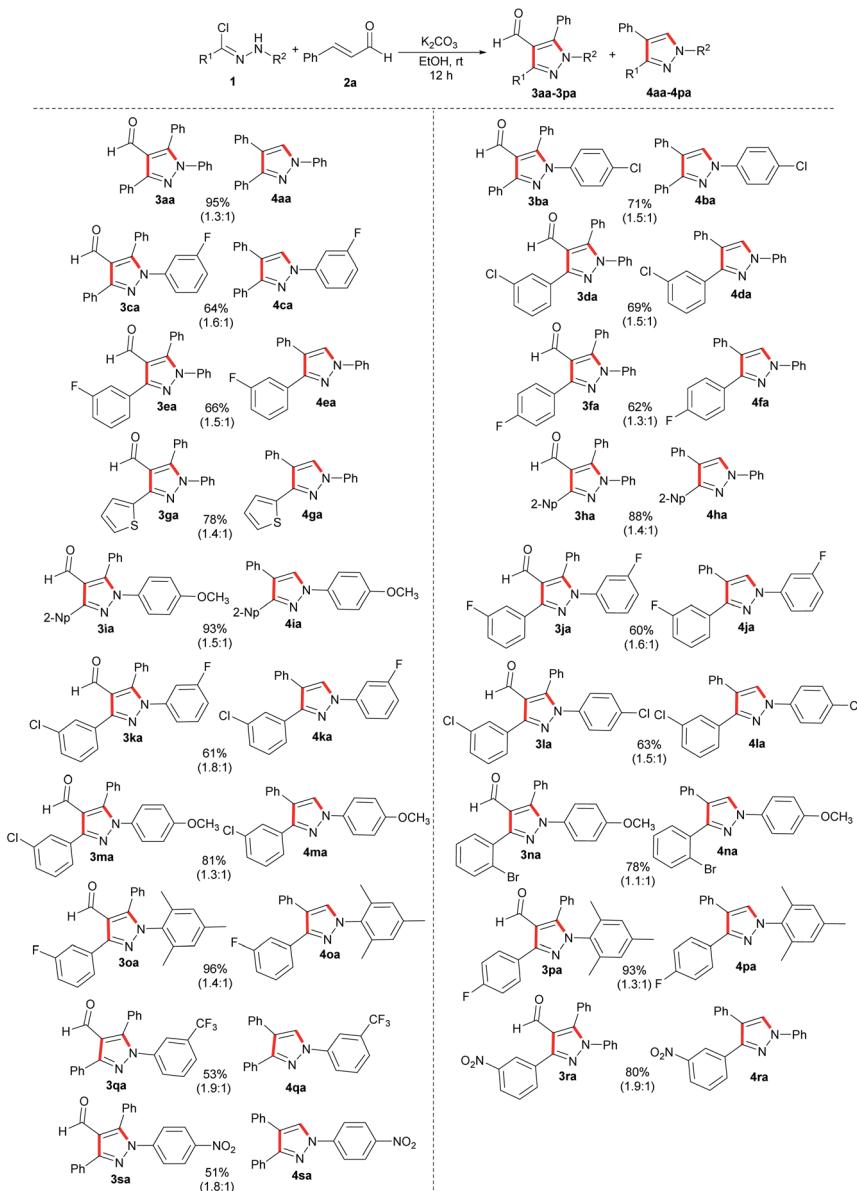


**3aa** and **4aa** were isolated in 55% and 27% yields, respectively (Table 1, entry 1). As a result of the solvent screening, it was found that ethanol was the most effective solvent with a drastic increase in total yield (95%) (Table 1, entry 3), and oxygenated solvent, such as tetrahydrofuran, 1,4-dioxane 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 hydrazoneyl chlorides exhibited good



**Scheme 2** Substrate scope of hydrazoneyl chlorides.



functional group tolerance, and the desired multi-substituted pyrazole derivatives were synthesized in moderate to excellent yields (51–96%). The hydrazoneoyl chlorides bearing none or electron-rich substituents on the phenyl ring of the R<sup>1</sup> 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 R<sup>1</sup> (**3da/4da**, **3ea/4ea** and **3fa/4fa**). The *para*-position with electron-withdrawing substituents on R<sup>1</sup> 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 R<sup>2</sup>, 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 R<sup>2</sup> on hydrazoneoyl 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 R<sup>1</sup> has, the electron-donating substituents on the R<sup>2</sup> could contribute to an increase in the yields of products. Moreover, the optimal condition was also applicable for heteroaryl hydrazoneoyl chlorides, such as *N*-phenylthiophene-2-carbohydrazoneoyl chloride, affording the desired multi-

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

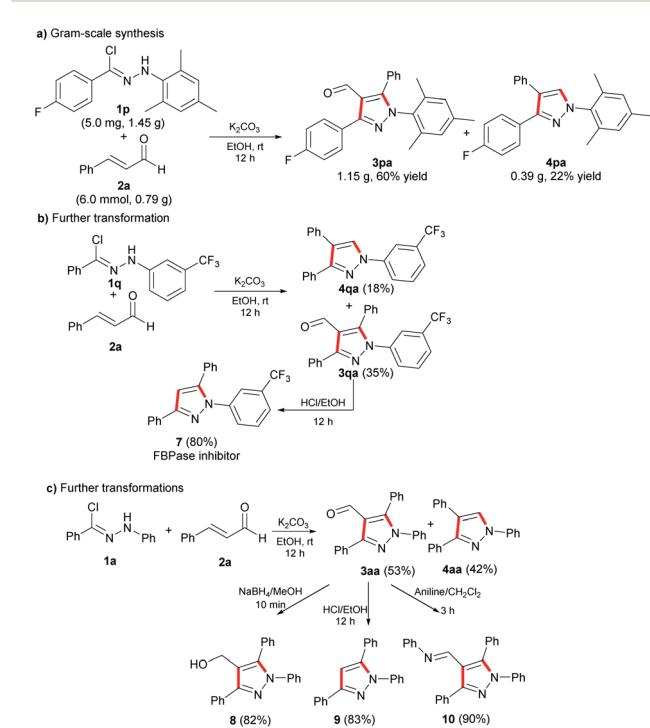
In addition, we investigated how the substituted cinnamic aldehydes could be employed as substrates for the optimum conditions established previously (Table 2). The protocol worked efficiently regardless of the electronic nature of substituted groups on cinnamic aldehydes. The cinnamic aldehyde derivatives 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 hydrazoneoyl 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 R<sup>1</sup> 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<sup>a</sup>

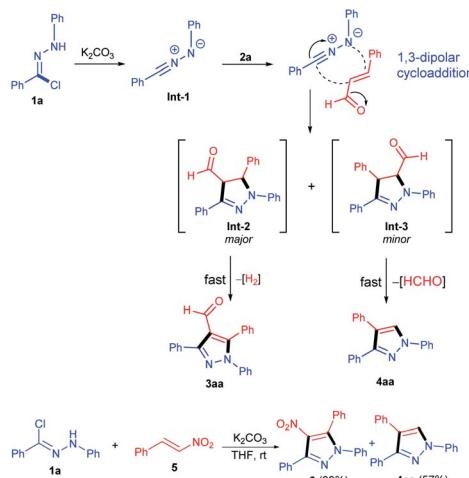
| Entry | <b>1</b> (R <sup>1</sup> , R <sup>2</sup> )                                 | <b>2</b> (Ar)                                   | Product, yield <sup>b</sup>      |
|-------|---|---|----------------------------------|
| 1     | Ph, Ph  | 4-BrC <sub>6</sub> H <sub>4</sub>               | <b>3a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

<sup>a</sup> The reaction of **1** (0.2 mmol) with **2** (0.24 mmol) was carried out in the presence of K<sub>2</sub>CO<sub>3</sub> (0.5 mmol) in EtOH (2.5 mL) at room temperature for 12 h. <sup>b</sup> 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**,<sup>16</sup> 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.

## Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. 81803374), Xinglin Scholar Research Promotion Project of Chengdu University of Traditional Chinese Medicine (No. BJRC2020002, No. BSH2019027), China Postdoctoral Science Foundation (2020M673565XB) and Scientific Research Foundation of the Science & Technology Department of Sichuan Province (Grant No. 2018JY0599).

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