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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 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.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. Moreover, TsOH-catalyzed Mannich-type cyclization-oxidation of arylhydrazines, aromatic aldehydes, and terminal arylalkynes has been reported to provide multi-substituted pyrazoles. Later, the condensation of α,β -unsaturated ketones with aryl hydrazines afforded the functionalized pyrazoles under the presence of water-soluble metal ion catalyst.

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 α -position were developed. For example, the 1,3-

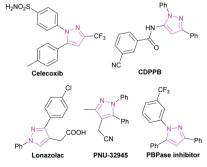


Fig. 1 Example of pyrazole-containing bioactive compounds.

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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 functionated pyrazoles in simple and mild reaction conditions. ¹⁴ Moreover, nitrile imines, generally *in situ* generated by a base-induced dehydrodechlorination 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 K₂CO₃ 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	$\mathrm{CH_{3}CN}$	>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 K₂CO₃ was pre-dried. ^d With 4 Å MS in anhydrous toluene. ^e K₂CO₃ (1.0 equiv.) was used. ^f K₂CO₃ (5.0 equiv.) was used. ^g The reaction was carried out at 0 °C. ^h The reaction was carried out at 60 °C. ^l DDQ (2.5 equiv.) was added. ^j Under the protection of N₂.

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, K2CO3, Na2CO3, KHCO3, DIPEA, Et3N could provide moderate to excellent yields (81-95%) (Table 1, entries 3, 10-13). Unfortunately, those bases, such as Cs₂CO₃, 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 K₂CO₃ (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 N2, 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 hydrazonoyl 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 hydrazonoyl 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 hydrazonoyl chlorides, such as N-phenylthiophene-2carbohydrazonoyl chloride, affording the desired multi-

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

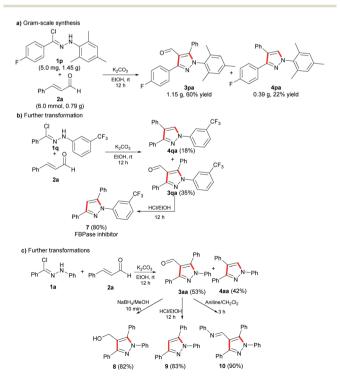
Entry	$1\left(R^{1},R^{2}\right)$	2 (Ar)	Product, yield ^b
1	Ph, Ph	4 -BrC $_6$ H $_4$	3a, 54%; 4a, 29%
2	Ph, Ph	4-ClC ₆ H ₄	3b, 59%; 4b, 28%
3	Ph, Ph	4-OMeC_6H_4	3c, 48%; 4c, 27%
4	3-FC ₆ H ₄ , Ph	4-BrC ₆ H ₄	3d, 57%; 4d, 24%
5	3-FC ₆ H ₄ , Ph	4-ClC_6H_4	3e, 59%; 4e, 22%
6	3-FC ₆ H ₄ , Ph	4-OMeC_6H_4	3f, 50%; 4f, 25%
7	$4-FC_6H_4$, Ph	4-ClC_6H_4	3g, 55%; 4g, 27%
8	4-FC ₆ H ₄ , Ph	$4\text{-BrC}_6\mathrm{H}_4$	3h, 50%; 4h, 27%
9	3-ClC ₆ H ₄ , Ph	4-ClC_6H_4	3i, 54%; 4i, 27%
10	3-ClC ₆ H ₄ , Ph	$4\text{-BrC}_6\mathrm{H}_4$	3j, 44%; 4j, 29%
11	3-ClC ₆ H ₄ , 4-OMeC ₆ H ₄	4-OMeC_6H_4	3k, 52%; 4k, 29%
12	2-BrC ₆ H ₄ , 4-OMeC ₆ H ₄	4-ClC_6H_4	3l, 48%; 4l, 47%
13	2-Np, 4 -OMeC ₆ H ₄	$4\text{-ClC}_6\text{H}_4$	3m, 56%; 4m, 30%
14	2-Np, 4 -OMeC ₆ H ₄	4-OMeC_6H_4	3n, 54%; 4n, 32%
15	2-Np, Ph	4-ClC ₆ H ₄	30 , 54%; 40 , 31%
16	$3-FC_6H_4$, 2,4,6-triMeC ₆ H ₂	4-ClC_6H_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_6H_4	3r, 60%; 4r, 28%
19	2-Thiophenyl, Ph	4-ClC_6H_4	3s, 59%; 4s, 21%
20	Ph, Ph	$4-NO_2C_6H_4$	3t, 52%; 4t, 24%
21	Ph, $3\text{-}\mathrm{CF}_3\mathrm{C}_6\mathrm{H}_4$	$4\text{-NO}_2\text{C}_6\text{H}_4$	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.

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 hydrazonoyl 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 electronwithdrawing 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 (31/41 = 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.



Scheme 3 Gram-scale synthesis and further transformations.

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$$\begin{array}{c} \begin{array}{c} Ph \\ NNH \\ N$$

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,** his 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 hydrazonovl chloride 1a in situ in the presence of K₂CO₃. 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 NO2. 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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