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# Regioselective [3 + 2]-annulation of hydrazonyl chlorides with 1,3-dicarbonyl compounds for assembling of polysubstituted pyrazoles†

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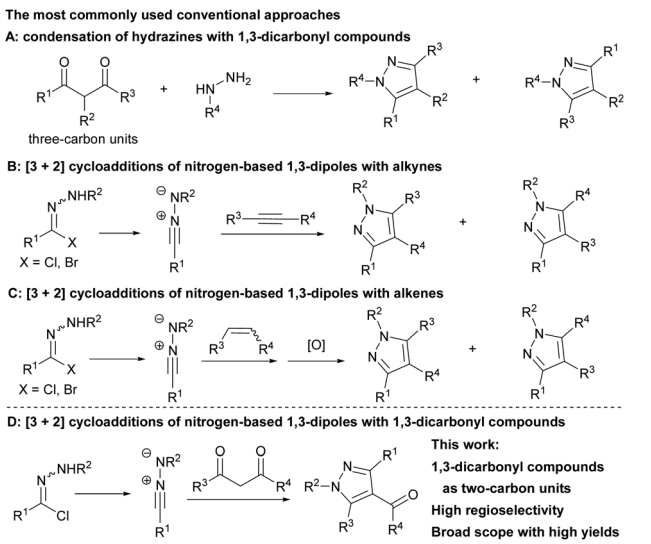
**A facile approach to polysubstituted pyrazoles from hydrazonyl chlorides and 1,3-dicarbonyl compounds has been developed. In the presence of DMAP combined with $Et_3N$, hydrazonyl chlorides reacted with *N*-phenyl-3-oxobutanamides smoothly to afford a series of polysubstituted pyrazoles in 67–98% yields *via* the [3 + 2]-cycloaddition.**

Pyrazoles are fascinating and versatile examples of five-membered heterocycles prevalently found in a wide variety of compounds known to exhibit a broad spectrum of pharmaceutical and agrochemical activities.[1] Moreover, they have also been successfully utilized as units in supramolecular architectures[2] and as ligands in coordination compounds.[3] Owing to the functional diversity of pyrazoles, advanced methodologies for such aza-heterocycles is highly desirable.

Among the methods developed over the past decades for the construction of the pyrazole skeleton,[4] the construction of two C–N bonds by condensation of hydrazines with 1,3-dicarbonyl compounds or their 1,3-dielectrophilic equivalents is one of the conventional approaches, wherein 1,3-dicarbonyl compounds were employed as three-carbon units (Scheme 1A).[5] Another conventional approach involved the generation of one C–N bond and one C–C bond by intermolecular [3 + 2]-cycloadditions of nitrogen-based 1,3-dipoles with alkynes (Scheme 1B)[6] or alkenes (Scheme 1C).[7] Whereas the aforementioned methodologies have realized high efficiency, such procedures often suffer from regioselectivity issues, which greatly reduces their attractiveness. With the aim of increasing the regioselectivity in the preparation of substituted pyrazoles, developing additional methodologies are currently in demand.

We $V_\phi^o$ have successfully developed an organocatalyzed 1,3-dipolar cycloaddition of 3-oxobutanamides with nitrile oxides[8] and azides[9] for the construction of 3,4,5-trisubstituted isoxazoles and 1,4,5-trisubstituted 1,2,3-triazoles in high yields with high regioselectivities. It's no doubt that 1,3-dipolar cycloaddition provides an efficient and facile access to five-membered heterocycles.[10] Based on the applications of 3-oxobutanamides as two-carbon units in the 1,3-dipolar cycloaddition and as a continuation of our efforts in the development of cycloaddition reaction,[11] we here report the 1,3-dipolar cycloaddition reactions of hydrazonyl chlorides and 1,3-dicarbonyl compounds for the regioselective construction of polysubstituted pyrazoles (Scheme 1D).

As we all known, hydrazonyl chlorides could easily generate reactive intermediate 1,3-dipolar in the presence of base to




**Scheme 1** Conventional approaches for the construction of pyrazole skeletons.

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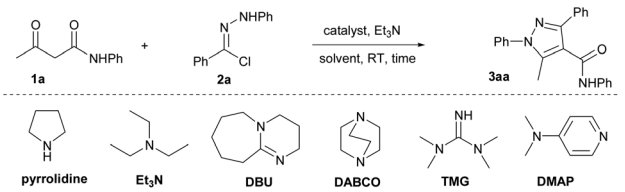
react with partners to furnish the desired product. Accordingly, we started our investigations by screening a series of catalyst combined with triethylamine ($Et_3N$) as base for the model [3 + 2]-annulation reaction of hydrazonyl chloride (**2a**) with 3-oxo-*N*-phenylbutanamide (**1a**) in $CHCl_3$ at room temperature for 12 h and the representative results were listed in Table 1. To our delight, all the tested organocatalysts combined with $Et_3N$ could accelerate the annulation to generate the desired 5-methyl-*N*,1,3-triphenyl-1*H*-pyrazole-4-carboxamide **3aa** in the moderate yield, respectively (entries 1–6). In particular, **3aa** with 60% yield was obtained in the presence of **DMAP** combined with $Et_3N$ (entry 6). Further screening of reaction media indicated that solvent affected the yield significantly (entries 7–10) and the yield was improved to 64% when the reaction was carried out in $CH_2Cl_2$ (entry 7). An enhancement of yield was achieved when the reaction time was prolonged (entries 11–13) and **3aa** with 92% yield was obtained after 48 h (entry 13). In consideration of cost, replacing DMAP with $Et_3N$ was surveyed and product **3aa** was obtained in 80% yield when the reaction was carried out in $CH_2Cl_2$ after 48 h (entry 14). Importantly, a yield of 87% was still obtained with a catalyst loading of 10 mol% after 72 h (entry 15).

Under the optimal reaction conditions, the 1,3-dipolar cycloadditions of hydrazonyl chlorides and 1,3-dicarbonyl compounds were explored. The results of these reactions were shown in Table 2. The scope of hydrazonyl chlorides **2** was examined. The 1,3-dipolar cycloaddition of **1a** and **2a** furnished pyrazole **3aa** in 87% yield (entry 1). Pleasingly, various substituted hydrazonyl chlorides, regardless of the electronic properties, steric hindrances, and substitution positions on the aromatic ring, were broadly tolerated, furnishing pyrazoles **3ab–af** in 83–98% yields (entries 2–6). Notably, the reaction of 1-(chloro(naphthalen-2-yl)methylene)-2-phenylhydrazine also afforded the desired pyrazole **3ag** in 90% yield (entry 7). The hetero hydrazonyl chloride was also compatible to furnish product **3ah** in 67% yield (entry 8). The using of 1-(chloro(phenyl)methylene)-2-(3-fluorophenyl)hydrazine and 1-(chloro(phenyl)methylene)-2-(2-chlorophenyl)hydrazine also resulted in the formation of **3ai** and **3aj** in good yields (entries 9 and 10). To our delight, if we changed $R^2$ as i-Pr, the desired product **3ak** was obtained with 56% yield (entry 11). It was found that no reaction occurred between 1-(1-chloroethylidene)-2-phenylhydrazine and **1a** (entry 12).

To further explore the 1,3-dipolar cycloaddition of hydrazonyl chlorides and 1,3-dicarbonyl compounds, the scope of 1,3-dicarbonyl compounds was then surveyed (Table 3). Pleasingly, a variety of 3-oxo-*N*-arylbutanamide substrates with different substitution patterns on their aromatic ring were tolerated, affording the corresponding pyrazoles **3ba–ga** in 74–86% yields (entries 1–6). Importantly, we did not observe any discernible electronic effects or steric hindrance effects on the aromatic moiety. It should be noted that 4-methyl-3-oxo-*N*-phenylpentanamide was found to be compatible to afford the desired product **3ha** in 92% yield (entry 7). Furthermore, 3-oxo-*N*,3-diphenylpropanamide was also compatible to furnish the corresponding pyrazole **3ia** in 90% yield (entry 8). In particular, the reaction partner could extend to 1,3-diketones. The 1,3-dipolar cycloaddition of 1,3-diphenylpropane-1,3-dione furnished the corresponding product **3ja** in 97% yield (entry 9). The reaction of pentane-2,4-dione also furnished the desired product **3ka** in good yield (79%, entry 10). However, no reaction occurred if $R^4$ was replaced with ester group (entry 11).

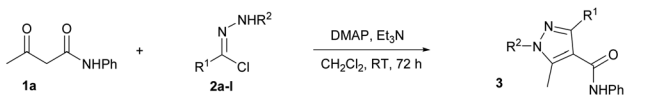
**Table 1** Optimization of reaction conditions[a]




| Entry | Catalyst | Time (h) | Solvent | Isolated yield (%) |
|---|---|---|---|---|
| 1 | Pyrrolidine | 12 | $CHCl_3$ | **3aa**, 57 |
| 2 | $Et_3N$ | 12 | $CHCl_3$ | **3aa**, 57 |
| 3 | DBU | 12 | $CHCl_3$ | **3aa**, 57 |
| 4 | DABCO | 12 | $CHCl_3$ | **3aa**, 51 |
| 5 | TMG | 12 | $CHCl_3$ | **3aa**, 45 |
| 6 | DMAP | 12 | $CHCl_3$ | **3aa**, 60 |
| 7 | DMAP | 12 | $CH_2Cl_2$ | **3aa**, 64 |
| 8 | DMAP | 12 | $CH_3CN$ | **3aa**, 55 |
| 9 | DMAP | 12 | EtOH | **3aa**, 34 |
| 10 | DMAP | 12 | DMSO | **3aa**, 14 |
| 11 | DMAP | 24 | $CH_2Cl_2$ | **3aa**, 72 |
| 12 | DMAP | 36 | $CH_2Cl_2$ | **3aa**, 81 |
| 13 | DMAP | 48 | $CH_2Cl_2$ | **3aa**, 92 |
| 14 | $Et_3N$ | 48 | $CH_2Cl_2$ | **3aa**, 80 |
| 15 | DMAP (10 mol%) | 72 | $CH_2Cl_2$ | **3aa**, 87 |

[a] Unless noted, a mixture of **1a** (0.05 mmol), **2a** (0.10 mmol), $Et_3N$ (0.10 mmol), catalyst (20 mol%) in the solvent (0.30 mL) was stirred at room temperature for the time given.

**Table 2** Substrate scope of hydrazonyl chlorides[a]

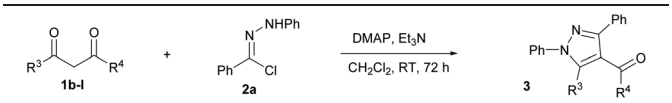



| Entry | $R^1$ | $R^2$ | Isolated yield (%) |
|---|---|---|---|
| 1 | Ph | Ph | **3aa**, 87 |
| 2 | 4-$MeC_6H_4$ | Ph | **3ab**, 95 |
| 3 | 4-$MeOC_6H_4$ | Ph | **3ac**, 98 |
| 4 | 4-$FC_6H_4$ | Ph | **3ad**, 92 |
| 5 | 3-$MeC_6H_4$ | Ph | **3ae**, 90 |
| 6 | 2-$BrC_6H_4$ | Ph | **3af**, 83 |
| 7 | 2-Naphthyl | Ph | **3ag**, 90 |
| 8 | 2-Furanyl | Ph | **3ah**, 67 |
| 9 | Ph | 3-$FC_6H_4$ | **3ai**, 72 |
| 10 | Ph | 2-$ClC_6H_4$ | **3aj**, 77 |
| 11[b] | Ph | i-Pr | **3ak**, 56 |
| 12 | Me | Ph | — |

[a] Unless noted, reactions were performed with **1a** (0.05 mmol), **2a–l** (0.10 mmol), $Et_3N$ (0.10 mmol), **DMAP** (10 mol%) in $CH_2Cl_2$ (0.30 mL) at room temperature for 72 h. [b] The reaction was performed in $CHCl_3$ at 80 °C for 48 h.

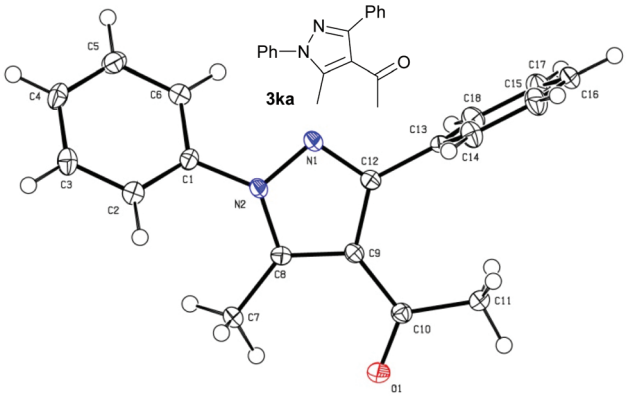
 

Table 3 Substrate scope of 1,3-dicarbonyl compounds[a]



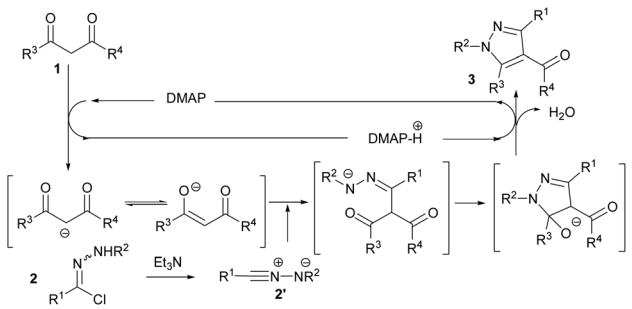

| Entry | $R^3$ | $R^4$ | Isolated yield (%) |
|---|---|---|---|
| 1 | Me | 4-Me$C_6H_4$NH | **3ba**, 80 |
| 2 | Me | 4-MeO$C_6H_4$NH | **3ca**, 74 |
| 3 | Me | 2,4-$Me_2C_6H_3$NH | **3da**, 78 |
| 4 | Me | 2-Me$C_6H_4$NH | **3ea**, 86 |
| 5 | Me | 2-MeO$C_6H_4$NH | **3fa**, 77 |
| 6 | Me | 2-Cl$C_6H_4$NH | **3ga**, 74 |
| 7 | i-Pr | PhNH | **3ha**, 92 |
| 8 | Ph | PhNH | **3ia**, 90 |
| 9 | Ph | Ph | **3ja**, 97 |
| 10 | Me | Me | **3ka**, 79 |
| 11 | Me | OMe | — |

[a] Unless noted, reactions were performed with **1b–l** (0.05 mmol), **2a** (0.10 mmol), $Et_3N$ (0.10 mmol), **DMAP** (10 mol%) in $CH_2Cl_2$ (0.30 mL) at room temperature for 72 h.

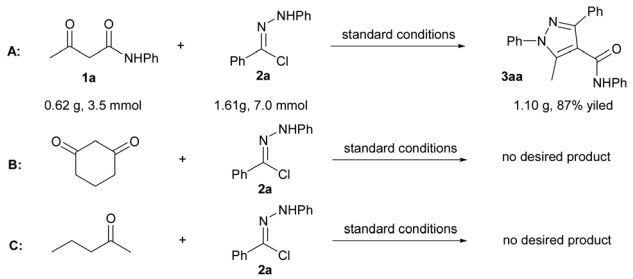



Scheme 2 X-ray of **3ka**.

The configuration of the polysubstituted pyrazole was unambiguously determined based on the X-ray crystal structure of **3ka** (Scheme 2).[12] Accordingly, a possible reaction pathway was suggested as shown in Scheme 3. Catalyzed by DMAP, 1,3-dicarbonyl compounds **1** generated the nucleophile to react with the nitrilimines **2′** formed *in situ* from hydrazonyl




Scheme 3 Reaction mechanism.




Scheme 4 Synthetic potential.

chlorides **2** in the presence of $Et_3N$ to give the desired products **3** *via* cascade reactions.

To highlight the synthetic potential of this methodology, we evaluated the gram-scale synthesis of **3aa.** Under the standard conditions, 3.5 mmol of **1a** reacted smoothly with 7.0 mmol of **2a** to afford **3aa** in 87% yield (1.10 g, Scheme 4A). Furthermore, we also tried the 1,3-dipolar cycloadditions of hydrazonyl chloride **2a** with 1,3-cyclohexanedione (Scheme 4B) and 2-pentanone (Scheme 4C) under the standard conditions, respectively. However, the reactions were sluggish and almost no desire product was obtained.

## Conclusions

In conclusion, we have developed a regioselective 1,3-dipolar cycloaddition between hydrazonyl chlorides and 1,3-dicarbonyl compounds for the construction of polysubstituted pyrazoles. In the presence of DMAP combined with $Et_3N$, the reactions between hydrazonyl chlorides and 1,3-dicarbonyl compounds proceeded smoothly to furnish a wide range of pyrazoles in 67–98% yields *via* a 1,3-dipolar cycloaddition. Practically, synthesis of pyrazoles compounds was achieved through the 1,3-dipolar cycloaddition with high regioselectivity.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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