Cs$_2$CO$_3$ catalyzed direct aza-Michael addition of azoles to $\alpha,\beta$-unsaturated malonates†

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A highly efficient method for the synthesis of azole derivatives via a direct aza-Michael addition of azoles to $\alpha,\beta$-unsaturated malonates using Cs$_2$CO$_3$ as a catalyst, has been successfully developed. A series of azole derivatives have been obtained in up to 94% yield and the reaction could be amplified to gram scale in excellent yield in the presence of 10 mol% of Cs$_2$CO$_3$.

Introduction

Azoles and their derivatives are important heterocyclic scaffolds which have been widely found in many natural products, bioactive compounds, and drug candidates. Particularly, the pyrazole constitutes the structural core featured in numerous pharmacologically active molecules. For example, the $\beta$-pyrazolyl acid A has activity toward human GPR40 G-protein coupled receptor (Fig. 1). A prominent example is the Janus kinase (JAK) inhibitor Ruxolitinib (INCB018424), which has been used in the treatment of myelofibrosis (Fig. 1). Therefore, in the past two decades, continuous efforts have been directed towards the development of efficient methods for accessing such pyrazole structures in medicinal chemistry and organic synthesis. To date, numerous concise and robust synthetic methods, mainly including $N$-nucleophilic substitutions, C–N cross-couplings and aza-Michael additions, have been established. Among them, the direct aza-Michael addition of pyrazole has attracted more attention as a highly efficient method for construction of pyrazole derivatives.

As we all know, the pyrazoles via $N$-deprotonation generating active $N$-nucleophiles under base-catalysis, could react with all kinds of Michael receptors to afford pyrazole derivatives. These Michael receptors in aza-Michael addition of pyrazole mainly include methyl acrylate, acrylonitrile, $\beta,\gamma$-unsaturated- $\alpha$-ket esters, nitroalkenes, $\alpha,\beta$-unsaturated ketones or imides and maleic or crotonic acid (Scheme 1a). Specially, several catalytic asymmetric aza-Michael additions of pyrazoles had been successfully realized in which the optically active pyrazole derivatives were obtained. Nevertheless, the development of alternative receptor in aza-Michael addition of azole will be remain as a highly desirable work, owing to their easy accessing other valuable pyrazole derivatives. To the best of our

![Fig. 1 Biologically pyrazole compounds.](https://doi.org/10.1039/d2ra02314h)
knowledge, the α,β-unsaturated malonates, which had been used as Michael receptors in numerous transformations, had their potential in the construction ofazole derivatives via direct aza-Michael addition of azoles.\(^{13}\) Herein, we describe a Cs\(_2\)CO\(_3\) catalyzed direct aza-Michael addition of azoles 2 to α,β-unsaturated malonates 1 to afford azole derivatives 3 (Scheme 1b).

Results and discussion

In the initial study, dimethyl 2-benzylidene malonate 1a and pyrazole 2a were chosen as the model substrates for the synthesis of pyrazole derivatives via the direct aza-Michael addition. No product was observed without catalyst when stirring in THF at 25 °C for 24 h (Table 1, entry 1). Next, various bases as catalysts were surveyed in THF at 25 °C and trace amount of product 3aa was observed in the presence of 100 mol% of organic base Et\(_3\)N (Table 1, entry 2). Meanwhile, DBU could afford pyrazole derivative 3aa in lower yield (31%, Table 1, entry 3). When the reaction was performed with 100 mol% of inorganic bases, the acceptable yields of 3aa were obtained (Table 1, entries 4–7). Comparatively, the Cs\(_2\)CO\(_3\) exhibited a slight superiority in reactivity toward this aza-Michael addition compared with LiOH, K\(_3\)PO\(_4\), 7H\(_2\)O, and K\(_2\)CO\(_3\) (Table 1, entries 6 vs. 4, 5 and 7). Further optimization of the reaction conditions was then aimed at exploring the efficiency of solvent. Unfortunately, the yield of 3aa decreased slightly in other types of solvents (CH\(_2\)OH, PhCH\(_3\), EtOAc, CH\(_2\)Cl\(_2\), Table 1, entries 6 vs. 8–11), and the THF was still the most suitable solvent for this reaction. The efficiency of temperature was also examined (Table 1, entries 6 and 12–13), and it was found that increasing the temperature to 40 °C had nearly no effect on the yield of 3aa (Table 1, entry 12) but the yield of 3aa decreased when reducing the temperature to 0 °C (Table 1, entry 13). Increasing the amount of pyrazole 2a to 0.3 mmol could further improve the yield of 3aa to 80% (Table 1, entry 14). We were delighted to find that reducing the amount of Cs\(_2\)CO\(_3\) to 10 mol% had no effect on the yield of 3aa (Table 1, entry 15), while the yield of 3aa decreased significantly when reducing the amount of Cs\(_2\)CO\(_3\) to 1 mol% (Table 1, entry 16). Reducing the amount of solvent THF to 0.20 mL, the yield of 3aa increased slightly (Table 1, entry 17). The reaction was amplified to 0.50 mmol scale and also proceeded smoothly, affording 3aa in 84% yield (Table 1, entry 18). Therefore, the optimal conditions were identified as 10 mol% of Cs\(_2\)CO\(_3\) in THF at 25 °C for 24 h.

Under the optimal conditions (Table 1, entry 17), various α,β-unsaturated malonates 1 were evaluated, affording the corresponding pyrazole derivatives 3 in moderate to excellent yields (up to 92%). As shown in Table 2, the reactivity of this direct aza-Michael addition was sensitive to the steric hindrance on the ester group of α,β-unsaturated malonates 1. The substrates 1 containing bulkier ester groups (–CO\(_2\)Et, –CO\(_2\)Pr, and –CO\(_2\)Bu) gave lower yields than its with –CO\(_2\)Me group (Table 2, entries 2–4 vs. 1). For the effects of substituents in the phenyl ring, the reactivity of the direct aza-Michael addition was sensitive to the steric hindrance rather than to the electronic property of α,β-unsaturated malonates 1. The substrates 1 with ortho-substituents gave lower yields than those with para or meta ones (Table 2, entries 7 vs. 5 and 6, 10 vs. 8 and 9, 13 vs. 11 and 12, 17 vs. 15 and 16, 20 vs. 18 and 19). The substrates with 2-F, 2-Cl, 2-Br, 2-Me or 2-OMe substituents on phenyl ring (1g, 1j, 1m, 1q and 1t) were transformed into pyrazole derivatives 3, 3a, 3aa, 3ma, 3qa and 3ja in moderate yields (Table 2, entries 7, 10, 13, 17 and 20). Meanwhile, the fused-ring substrates (1u and 1v) were also tolerable, giving the desired products with 75% and 88% yields, respectively (Table 2, entries 21 and 22). For the thienyl heteroaromatic substrates 1w and 1x, the reaction generated the desired products 3wa and 3xa in 84% and 88% yield (Table 2, entries 23 and 24), while the 2-furyl heteroaromatic substrate 1y afforded the desired product 3ya in 76% yield (Table 2, entry 25). At the same time, the alkyl substituted substrates 1z, 1x, 1β and 1y also gave the corresponding pyrazole derivatives 3za, 3za, 3βa and 3γa in good yields (60–92%, Table 2, entries 26–29).

Next, the use of this catalytic system for aza-Michael addition of a variety of substituted pyrazoles 2 was explored, and the desired pyrazole derivatives 3 were obtained in moderate to excellent yields (up to 94%). As shown in Table 3, the electronic nature of the substituents in pyrazoles 2 had obvious effect on the efficiency of this reaction (Table 3, 3ab–3af). The substrates 2 with electron-donating Me group gave higher yields than those with electron-withdrawing (Cl or Br) substituents (Table 3, 3ae, 3af vs. 3ab, 3ac and 3ad). For indazole substrate 2g, the aza-

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**Table 1** Optimization of the reaction conditions\(^{a}\)

| Entry | Base | Solvent | \(T\) (°C) | Yield\(^{b}\) (%) |
|-------|------|---------|-------------|-----------------|
| 1     | —    | THF     | 25          | 0               |
| 2     | Et\(_3\)N | THF     | 25          | Trace           |
| 3     | DBU  | THF     | 25          | 31              |
| 4     | LiOH \(\cdot\)H\(_2\)O | THF     | 25          | 60              |
| 5     | K\(_3\)PO\(_4\) \(\cdot\)7H\(_2\)O | THF     | 25          | 58              |
| 6     | Cs\(_2\)CO\(_3\) | CH\(_3\)OH | 25          | 69              |
| 7     | K\(_2\)CO\(_3\) | THF     | 25          | 53              |
| 8     | Cs\(_2\)CO\(_3\) | PhCH\(_3\) | 25          | —               |
| 9     | Cs\(_2\)CO\(_3\) | EtOAc   | 25          | 48              |
| 10    | Cs\(_2\)CO\(_3\) | CH\(_2\)Cl\(_2\) | 25          | 61              |
| 11    | Cs\(_2\)CO\(_3\) | THF     | 40          | 67              |
| 12    | Cs\(_2\)CO\(_3\) | THF     | 0           | 50              |
| 13    | Cs\(_2\)CO\(_3\) | THF     | 25          | 80              |
| 14\(\dagger\) | Cs\(_2\)CO\(_3\) | THF     | 25          | 79              |
| 15\(\ddagger\) | Cs\(_2\)CO\(_3\) | THF     | 25          | 55              |
| 16\(\ddagger\) | Cs\(_2\)CO\(_3\) | THF     | 25          | 83              |
| 17\(\ddagger\) | Cs\(_2\)CO\(_3\) | THF     | 25          | 84              |

\(^{a}\) Reaction conditions: 1a (0.20 mmol), 2a (0.20 mmol), base (100 mol%), solvent (1.0 mL), 24 h. \(^{b}\) Isolated yield. \(^{\dagger}\) 0.30 mmol of 2a was used. \(^{\ddagger}\) 0.2 mL of THF was used. \(^{\ddagger\ddagger}\) 0.5 mmol of Cs\(_2\)CO\(_3\) was used. \(^{\dagger\dagger}\) 0.2 mL of THF was used.
Michael addition generated the desired product 3ag in 52% yield (Table 3, entry 7).  

Then, the use of this catalytic system for the direct aza-Michael addition of triazoles 2 to dimethyl 2-benzylidenemalonate 1a was explored, and the desired N1-substituted triazole derivative 3ah was obtained in 71% yield for the 1,2,4-triazole 2h, while the N2-substituted triazole derivative 3ai was obtained in 61% yield for the 1,2,3-triazole 2i (Scheme 2). For the substrate 1H-benzotriazole 2j, the reaction generated triazole derivatives 3aj and 3aj′ in 57% and 18% yields, simultaneously (3aj/3aj′ = 3.2/1, based on the isolated yields, Scheme 3) under the optimal conditions.  

Besides, the direct aza-Michael additions of imidazole and pyrrole to dimethyl 2-benzylidene-malonate 1a were also explored, unfortunately, no desired products were observed under the optimal conditions.

On account of the synthetic potential of this method, the reaction was amplified to gram scale. As shown in Scheme 4, the direct aza-Michael addition of pyrazole 2a (1.02 g, 15.0 mmol) to methyl dimethyl 2-benzylidenemalonate 1a (2.20 g, 10.0 mmol) proceeded smoothly under the optimal conditions, affording the pyrazole derivative 3aa in 75% yield (Scheme 4a). Delightfully, the yield of 3aa could be improved to 94% when the reaction concentration was increased twice as much in the gram scale synthesis (Scheme 4b).

According to the previous studies on the reactive properties of azoles in literatures, a reasonable catalytic cycle was proposed in Fig. 2. Because the pKa value of N1–H in azole is less that of H2CO3, pKₐ(N1–H) = 2.49, pKₐ(H₂CO₃) = 6.37, the N1-deprotonation of azoles 2 could be promoted by the conjugated base CO₃⁻, which had been from the ionization of Cs₂CO₃. First, the active N-nucleophiles I and HCO₃⁻ were generated via the N1-deprotonation of azoles 2. Then the N-nucleophiles I attacked the α,β-unsaturated malonates 1 at β-positions, forming the enolate intermediates II. Next, the HCO₃⁻ transferred the H⁺ to the enolate oxygen of intermediates II due to that the pKa value of HCO₃⁻ is less than that of enolates, providing the enol type azole derivatives 3. Meanwhile, the CO₃⁻ could regenerate and participate in the next round of catalytic cycle.

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**Table 2** Substrate scope of α,β-unsaturated malonates

| Entry | R₁   | R₂   | Yield (%) |
|-------|------|------|-----------|
| 1     | Ph   | Me   | 3aa 84    |
| 2     | Ph   | Et   | 3ba 68    |
| 3     | Ph   | tPr  | 3ca 67    |
| 4     | Ph   | tBu  | 3da 69    |
| 5     | 4-F   | Me   | 3ea 84    |
| 6     | 3-F   | Me   | 3fa 73    |
| 7     | 2-F   | Me   | 3ga 66    |
| 8     | 4-Cl  | Me   | 3ha 92    |
| 9     | 3-Cl  | Me   | 3ia 87    |
| 10    | 2-Cl  | Me   | 3ja 64    |
| 11    | 4-Br  | Me   | 3ka 74    |
| 12    | 3-Br  | Me   | 3la 71    |
| 13    | 2-Br  | Me   | 3ma 52    |
| 14    | 4-F   | C₆H₄  | 3na 81    |
| 15    | 4-Me  | C₆H₄  | 3oa 63    |
| 16    | 3-Me  | C₆H₄  | 3pa 91    |
| 17    | 2-Me  | C₆H₄  | 3qa 55    |
| 18    | 4-MeO | C₆H₄  | 3ra 77    |
| 19    | 3-MeO | C₆H₄  | 3sa 87    |
| 20    | 2-MeO | C₆H₄  | 3ta 65    |
| 21    | 2-Naphthyl | Me | 3ua 75    |
| 22    | 1-Naphthyl | Me | 3va 88    |
| 23    | 3-Thienyl | Me | 3wa 84    |
| 24    | 2-Thienyl | Me | 3xa 81    |
| 25    | 2-Furyl | Me | 3ya 76    |
| 26    | tPr  | Me   | 3za 85    |
| 27    | tBu  | Me   | 3za 92    |
| 28    | tBu  | Me   | 3βa 60    |
| 29    | 4-CH₃ | Me   | 3γa 74    |

* Reaction conditions: 1 (0.50 mmol), 2 (0.75 mmol), Cs₂CO₃ (10 mol%), THF (0.5 mL), 25 °C, 24 h.  

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**Table 3** Substrate scope of azoles

| Entry | Yield (%) |
|-------|-----------|
| 1a    | 94%       |
| 2a    | 37%       |
| 3aa   | 75%       |
| 3ab   | 68%       |
| 3ac   | 77%       |
| 3ad   | 59%       |

* Reaction conditions: 1 (0.30 mmol), 2 (0.75 mmol), Cs₂CO₃ (10 mol%), THF (0.5 mL), 25 °C, 24 h.  

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Finally, the azole derivatives 3 were obtained via the tautomerism of the enol type azole derivatives 3'.

Conclusions

We have developed a highly efficient method for the synthesis of azole derivatives via a direct aza-Michael addition of azoles to α,β-unsaturated malonates using Cs₂CO₃ as catalyst. A series of azole derivatives (38 examples) have been obtained in up to 94% yield. The reaction could be amplified to gram scale in excellent yield (94%) in the presence of 10 mol% of Cs₂CO₃, which had shown the potential value of the catalytic system for practical synthesis. Further study on an enantioselective version of this direct aza-Michael addition is still in progress.

Conflicts of interest

There are no conflicts to declare.

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