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Introduction

Azoles and their derivatives are important heterocyclic scaffolds which have been widely found in many natural products, bioactive compounds, and drug candidates.^{1,2} Particularly, the pyrazole constitutes the structural core featured in numerous pharmacologically active molecules.³ For example, the β-pyrazolyl acid A has activity toward human GPR40 G-protein coupled receptor (Fig. 1).⁴ A prominent example is the Janus kinase (JAK) inhibitor Ruxolitinib (INCB018424), which has been used in the treatment of myelofibrosis (Fig. 1).⁵ 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.⁶⁻¹¹ To date, numerous concise and robust synthetic methods, mainly including N-nucleophilic substitutions,⁶ C-N cross-couplings7,8 and aza-Michael additions,9,10 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.^{10,11}



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Cs₂CO₃ catalyzed direct aza-Michael addition of azoles to α , β -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 α , β -unsaturated malonates using Cs₂CO₃ 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 Cs₂CO₃.

As we all know, the pyrazoles *via N*-deprotonation generating active *N*-nucleophiles under base-catalysis,¹² 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,^{10c,dj,k} acrylonitrile,^{10c,j} β , γ -unsaturated- α -keto esters,^{10f} nitroalkenes,^{10e} α , β -unsaturated ketones^{10a-c} or imides¹⁰ⁱ and maleic or crotonic acid^{10g,h} (Scheme 1a). Specially, several catalytic asymmetric aza-Michael additions of pyrazoles had been successfully realized in which the optically active pyrazole derivatives were obtained.¹¹ 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



Scheme 1 Commonly encountered aza-Michael addition of azoles.

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knowledge, the α , β -unsaturated malonates, which had been used as Michael receptors in numerous transformations, had their potential in the construction of azole derivatives *via* direct aza-Michael addition of azoles.¹³ Herein, we describe a Cs₂CO₃ 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-benzylidenemalonate 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 Et₃N (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 Cs₂CO₃ exhibited a slight superiority in reactivity toward this aza-Michael addition compared with LiOH·H₂O, K₃PO₄·7H₂O, and K_2CO_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

Table	1 Optimization of t	he rea	action cond	ditions ^a		
	Ph COOMe + COOMe 1a	N N H 2a	base solvent, 25 °C, 24 h			
Entry	Base		Solvent	Т (°С)	Yield ^b (%	
1	_		THF	25	0	
2	Et_3N		THF	25	Trace	
3	DBU		THF	25	31	
4	$LiOH \cdot H_2O$		THF	25	60	
5	K ₃ PO ₄ ·7H ₂ O		THF	25	58	
6	Cs_2CO_3		THF	25	69	
7	K_2CO_3		THF	25	53	
8	Cs_2CO_3		CH ₃ OH	25	_	
9	Cs_2CO_3		PhCH ₃	25	62	
10	Cs_2CO_3		EtOAc	25	48	
11	Cs_2CO_3		CH_2Cl_2	25	61	
12	Cs_2CO_3		THF	40	67	
13	Cs_2CO_3		THF	0	50	
14^c	Cs_2CO_3		THF	25	80	
$15^{c,d}$	Cs_2CO_3		THF	25	79	
16 ^{<i>c</i>,<i>e</i>}	Cs_2CO_3		THF	25	55	
$17^{c,e,f}$	Cs_2CO_3		THF	25	83	
18^g	Cs_2CO_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. ^{*c*} 0.30 mmol of **2a** was used. ^{*d*} 10 mol% of Cs_2CO_3 was used. ^{*e*} 1 mol% of Cs_2CO_3 was used. ^{*f*} 0.2 mL of THF was used. ^{*g*} **1a** (0.50 mmol), **2a** (0.75 mmol), Cs_2CO_3 (10 mol%), THF (0.5 mL), 24 h.

decreased slightly in other types of solvents (CH₃OH, PhCH₃, EtOAc, CH₂Cl₂, 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 Cs₂CO₃ 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_2CO_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 3a in 84% yield (Table 1, entry 18). Therefore, the optimal conditions were identified as 10 mol% of Cs₂CO₃ 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 $(-CO_2Et, -CO_2^{i}Pr, and -CO_2^{t}Bu)$ gave lower yields than its with -CO₂Me group (Table 2, entries $2-4 \nu s.$ 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 orthosubstituents 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 3ga, 3ja, 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, 1 α , 1 β and 1 γ also gave the corresponding pyrazole derivatives 3za, 3αa, 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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	$R_1 + COOR_2 + H$ $COOR_2 + H$ $1 = 2a$	Cs ₂ CO ₃ (1 THF, 25 °	Cs ₂ CO ₃ (10 mol%) THF, 25 °C, 24 h R1 COOR ₂ 3		
Entry	R_1	R_2	3	Yield ^b (%)	
1	Ph	Ме	3aa	84	
2	Ph	Et	3ba	68	
3	Ph	ⁱ Pr	3ca	67	
4	Ph	^t Bu	3da	69	
5	4-FC ₆ H ₄	Me	3ea	84	
6	$3-FC_6H_4$	Me	3fa	73	
7	$2-FC_6H_4$	Me	3ga	66	
8	4-ClC ₆ H ₄	Me	3ha	92	
9	$3-ClC_6H_4$	Me	3ia	87	
10	$2-ClC_6H_4$	Me	3ja	64	
11	$4\text{-BrC}_6\text{H}_4$	Me	3ka	74	
12	$3-BrC_6H_4$	Me	3la	71	
13	$2\text{-BrC}_6\text{H}_4$	Me	3ma	52	
14	$4 - F_3 CC_6 H_4$	Me	3na	81	
15	$4-MeC_6H_4$	Me	30a	63	
16	$3-MeC_6H_4$	Me	3ра	91	
17	$2-MeC_6H_4$	Ме	3qa	55	
18	4-MeOC ₆ H ₄	Me	3ra	77	
19	$3-MeOC_6H_4$	Ме	3sa	87	
20	$2-MeOC_6H_4$	Ме	3ta	65	
21	2-Naphthyl	Ме	3ua	75	
22	1-Naphthyl	Me	3va	88	
23	3-Thienyl	Ме	3wa	84	
24	2-Thienyl	Ме	3xa	81	
25	2-Furyl	Ме	3ya	76	
26	ⁿ Pr	Ме	3za	85	
27	ⁱ Pr	Ме	3œa	92	
28	ⁱ Bu	Ме	3βa	60	
29	${}^{n}C_{9}H_{19}$	Ме	3үа	74	

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

Michael addition generated the desired product 3ag in 52% yield (Table 3, entry 7).14

Then, the use of this catalytic system for the direct azaof triazoles dimethyl 2-Michael addition 2 to benzylidenemalonate 1a was explored, and the desired N1substituted 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.¹⁵ Besides, the direct aza-Michael additions of imidazole and pyrrole to dimethyl 2benzylidene-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

Table 3 Substrate scope of azoles.^{*a,b*}

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 a Reaction conditions: 1 (0.50 mmol), 2 (0.75 mmol), Cs₂CO₃ (10 mol%), THF (0.5 mL), 25 $^{\circ}$ C, 24 h. b Isolated yield.

the pyrazole derivative 3aa in 75% yield (Scheme 4a). Delightly, 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,^{9,12} a reasonable catalytic cycle was proposed in Fig. 2. Because the pK_a value of N1-H in azole is less that of $H_2CO_3 [pK_a (N1-H) = 2.49, pK_{a1} (H_2CO_3) = 6.37]$, the N1deprotonation of azoles 2 could be promoted by the conjugated base CO_3^{2-} , which had been from the ionization of Cs_2CO_3 . 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 HCO_3^{-} is less than that of enolates, providing the enol type azole derivatives 3'. Meanwhile, the CO_3^{2-} could regenerate and participate in the next round of catalytic cycle.



Scheme 2 Direct aza-Michael addition of triazoles 2h and 2i to dimethyl 2-benzylidenemalonate 1a



Scheme 3 Direct aza-Michael addition of benzotriazole 2j to dimethyl 2-benzylidenemalonate 1a.



Scheme 4 Preparative scale synthesises of selected compound.



Fig. 2 Proposed catalytic cycle.

Finaly, 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 a zole derivatives *via* a direct aza-Michael addition of a zoles 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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