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Catalyst-free aza-Michael addition of azole to β,γ-unsaturated-α-keto ester: an efficient access to C–N bond formation

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ABSTRACT

An efficient aza-Michael addition of azoles to β,γ-unsaturated-α-keto esters under room temperature conditions has been developed. In this conjugate addition, no additional catalyst is employed. Azole reacts with β,γ-unsaturated-α-keto ester smoothly to afford new C–N bond adducts in good to excellent yields (up to 96%).

The significance of N-heterocyclic scaffolds has been recognized by their high abundance in nature, as well as broad synthetic applications in pharmaceutical chemistry, biological, and material sciences.[1] In particular, azole moiety is commonly found in drug candidates, such as Voriconazole (antifungal), Fluconazole (antifungal), Losartan (high blood pressure), and INCB018424 (Janus Kinase Inhibitor).[1] The conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds, termed the aza-Michael reaction, is a versatile method for constructing new C–N bonds.[2] This convergent protocol constitutes a key route for the synthesis of diversified bioactive natural products. Over the last several years tremendous progress has been achieved. Seeking of new category of nitrogen nucleophiles, suitable acceptors as well as more efficient catalyst systems for this important transformation are of current interest.[3,4] Nevertheless, most established reports with impressive results were only focused on the aza-Michael addition of hydroxylamines and their derivatives.[5] The organocatalytic aza-Michael addition of the nitrogen nucleophile containing azole groups is rarely reported, either in enantioselective manner[6] or non-enantioselective version.[4d–g]

The majority of organocatalytic reactions are usually based on amine catalysts. These reactions often proceed via enamine or iminium intermediates. Indeed, the amine would also serve as a base. The potential competition between the catalyst and the nucleophile could happen in the organocatalytic aza-Michael addition. The N-heterocyclic compound can act as a dual-role reagent in certain aza-Michael additions.[7] Thus, the appropriate choice of the nitrogen nucleophile represents a crucial factor in the catalytic aza-Michael addition.

β,γ-Unsaturated α-keto ester is a resourceful moiety in synthetically useful building blocks. These unsaturated keto esters have been investigated in several type of reactions, such as aldol reactions,[8] Diels–Alder reactions[9] and Michael–type reactions.[10] Yet, the Michael addition of β,γ-unsaturated α-keto ester has only been limited to carbon nucleophiles. To the best of our knowledge, only one example of the nitrogen nucleophile was reported by Palacios et al. in 2006.[11] It should be noted that this reaction is catalyzed by a metal complex affording 69–88% product yields. Enlightened by our previous research works focusing on unsaturated carbonyl compounds,[8,10] we are attracted to explore a new aza-Michael addition of azole to unsaturated keto ester.

In order to find a suitable N-heterocyclic nucleophile that would give a self-catalytic conjugate reaction, we embarked the aza-Michael addition of pyrrolidine and azoles to methyl 2-oxo-4-phenyl-but-3-enoate (**1a**). Interestingly, pyrrolidine could react with **1a** to afford a product of (*E*)-4-phenyl-1-(pyrrolidin-1-yl)but-3-ene-1,2-dione instead of the Michael adduct. When imidazole was used as the nucleophile, no reaction was observed. To our delight, pyrazole could afford the 1,4-adduct with high conversion. With this initial result in hand, the screening of solvent for aza-Michael addition of pyrazole and **1a** was further carried out and the results are summarized in Table 1. This aza-Michael addition was found to be nearly independent of commonly used organic solvents. Most

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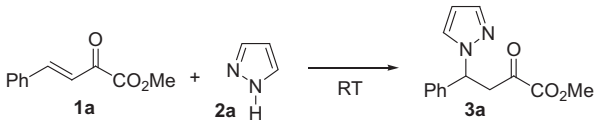
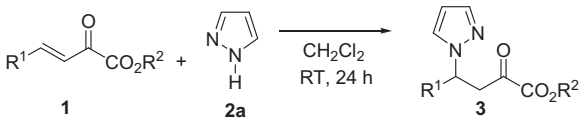
Table 1
Optimization of reaction conditions[a]



Entry	**1a** (mmol)	**2a** (mmol)	Solvent	Time (h)	Conversion[b] (%)
1	0.10	0.30	CH_2Cl_2	18	99
2	0.10	0.30	$CHCl_3$	18	98
3	0.10	0.30	THF	18	90
4	0.10	0.30	EtOAc	18	96
5	0.10	0.30	Toluene	18	98
6	0.10	0.30	MeOH	18	96
7	0.10	0.30	Et_2O	18	97
8	0.10	0.30	MeCN	18	97
9	0.10	0.20	CH_2Cl_2	18	98
10	0.10	0.15	CH_2Cl_2	18	97
11	0.10	0.10	CH_2Cl_2	18	91
12	0.20	0.10	CH_2Cl_2	18	99
13	0.10	0.15	CH_2Cl_2	24	75 (isolated yield)
14	0.10	0.15	CH_2Cl_2 (0.2 mL)	24	91 (isolated yield)
15	0.10	0.15	CH_2Cl_2 (0.1 mL)	24	94 (isolated yield)

[a] Unless noted, the reaction was carried out as following: the mixture of **1a** and **2a** was stirred in the solvent (0.3 mL) at room temperature for the time given.
[b] Determined by HPLC.

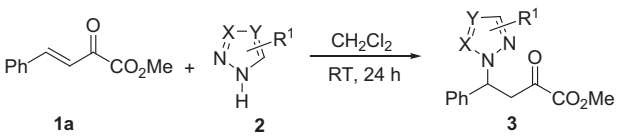
Table 2
Scope of β,γ-unsaturated-α-keto esters[a+]



Entry	R^1	R^2	Adduct	Yield [b] (%)
1	Ph	Me	**3aa**	94
2	Ph	Et	**3ba**	86
3	Ph	*i*-Pr	**3ca**	87
4	2-BrPh	Et	**3da**	85
5	3-BrPh	Et	**3ea**	96
6	3-ClPh	Et	**3fa**	90
7	3-NO_2Ph	Me	**3ga**	91
8	3-NO_2Ph	Et	**3ha**	96
9	3-MePh	Et	**3ia**	83
10	3-MeOPh	Et	**3ja**	90
11	4-FPh	Et	**3ka**	90
12	4-ClPh	Et	**3la**	92
13	4-BrPh	Et	**3ma**	92
14	4-NO_2Ph	Me	**3na**	88
15	4-NO_2Ph	Et	**3oa**	96
16	4-MePh	Et	**3pa**	91
17	4-MeOPh	Et	**3qa**	89
18	5-Methylthiophen-2-yl	Et	**3ra**	34

[a] Unless noted, the reaction was carried out as following: **1** (0.10 mmol) reacted with **2a** (0.15 mmol) in CH_2Cl_2 (0.1 mL) at rt for 24 h.
[b] Isolated yield.

Table 3
Scope of azoles[a]



Entry	R^1	X	Y	Adduct	Yield[b]
1	3,5-Di-Me	CH	CH	**3ab**	84%
2[c]	H	N	CH	**3ac**	37%
3[c]	H	CH	N	**3ad**	42%
4[d]	—	—	—	**3ae**	Trace

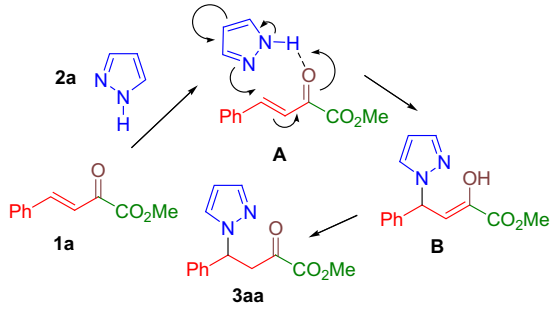
[a] Unless noted, the reaction was carried out as follows: **1** (0.10 mmol) reacted with **2a** (0.15 mmol) in CH_2Cl_2 (0.1 mL) at rt for 24 h.
[b] Isolated yield.
[c] Compound **1a** (0.2 mmol) and N-nucleophile (0.1 mmol) were used.
[d] 1*H*-indazole was used as the nucleophile.

reactions proceeded smoothly with excellent substrate conversions (entries 1–8). The best result was obtained in CH_2Cl_2 (entry 1). The stoichiometry of the reactants was also examined (entries 9–12). Further optimization on the concentration parameter revealed that a more concentrated medium provided a better yield (entries 13–15).

Under the optimized reaction conditions, the aza-Michael addition of pyrazole to β,γ-unsaturated α-keto ester was explored and the results are displayed in Table 2. The reactions between pyrazole and both ethyl and isopropyl esters proceeded smoothly to give adducts in high yields (entries 2 and 3). Both electron-withdrawing (–F, –Cl, –Br, –NO_2, entries 4–8, 11–15) and electron-donating (–Me, –OMe, entries 9–10, 16–17) substituents on the aromatic ring were compatible under this system. Good to excellent product yields were obtained (83–96%). No significant electronic effect on the aromatic moiety was observed. The heteroaromatic containing β,γ-unsaturated α-keto ester was also tested (entry 18).

Apart from the pyrazole, the aza-Michael addition of other azoles to methyl 2-oxo-4-phenylbut-3-enoate (**1a**) was also investigated and the results are shown in Table 3. 3,5-Dimethylpyrazole reacted with methyl 2-oxo-4-phenylbut-3-enoate smoothly to afford the adducts in 84% yield (entry 1). 1,2,3-Triazole and 1,2,4-triazole were found to react slowly, and 37–42% of adduct yields were obtained (entries 2 and 3). When 1*H*-indazole was used as the nucleophile, the aza-Michael addition did not proceed and only a trace amount of adduct was detected by LCMS (entry 4).

We propose the mechanism that the intermediate **A** is initially formed via the hydrogen bonding between the carbonyl oxygen of **1a** and the NH moiety of **2a** (Scheme 1). The enamine nitrogen atom of **2a** then attacks the γ-position of **1a** to afford intermediate **B** in the enolization manner. Finally, the intermediate **B** undergoes a retro-enolization to afford the desired product **3aa**.



Scheme 1. Proposed reaction mechanism.

In conclusion, we have succeeded a general and efficient catalyst-free aza-Michael addition of azoles to β,γ-unsaturated α-keto esters. Particularly noteworthy is that a wide spectrum of β,γ-unsaturated α-keto esters reacts smoothly under mild reaction conditions (room temperature) and gives excellent product yields. Further application of this methodology toward complex heterocycle synthesis is actively in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.132.

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