Catalyst-Free Efficient Aza-Michael Addition of Azoles to Nitroalkenes

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Abstract: An efficient aza-Michael addition of azole to nitroalkene has been developed. In this conjugate addition, no catalyst was employed and azole reacted with nitroolefin smoothly to afford new C–N bond adducts in good to excellent yields.

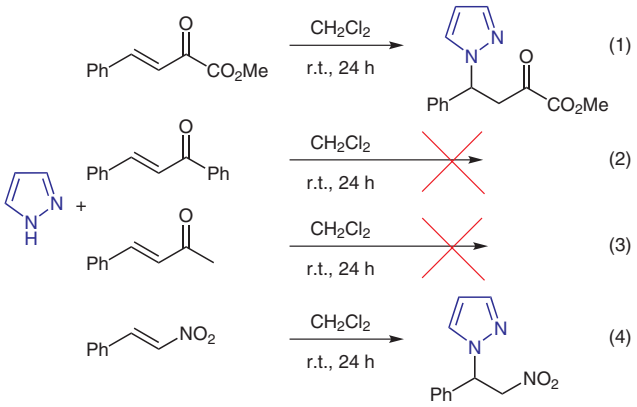
Key words: Michael addition, azole, nitroolefin, nitroalkene, amination

The catalytic aza-Michael addition is an important reaction within synthetic organic chemistry, given the significance of the biologically and synthetically interesting products.[1] Over the last decade, tremendous progress has been achieved by employing new nitrogen nucleophiles and suitable acceptors as well as more efficient catalyst systems for this important transformation.[2,3] Particularly, the catalytic aza-Michael addition of azole remains more attractive because azole moiety is commonly found in drug candidates, such as Losartan (high blood pressure), Voriconazole (antifungal), Fluconazole (antifungal), and INCB018424 (Janus Kinase Inhibitor). However, the catalytic aza-Michael addition of nucleophile containing azole groups has been rare, both in enantioselective manner[4] and in non-enantioselective version.[3d–h] Although several examples of catalyst-free aza-Michael additions of azole have been reported, severe conditions such as high reaction temperature,[5] high pressure[6] and UVA irradiation[7] are required to yield the adducts. The only exception is aza-Michael addition of enone with a limited scope of substrates.[8]

As the nitro group is the most electron-withdrawing group known, nitroalkenes are very attractive among the Michael acceptors.[9] Moreover, the conjugate adduct of nitroalkene retains the nitro function, and therefore, a suitable transformation of the nitro group very often follows the main addition process. The Nef reaction,[10] the nucleophilic displacement,[11] the reduction to an amino group,[12] the Meyer reaction,[13] and the conversion into a nitrile oxide[14] are only some examples of the possible transformations that nitro groups can undergo. Despite the important value of these conjugate adducts, only two examples on aza-Michael addition of nitroalkene were reported by Wang[4b] and Jørgensen.[15] Therefore, development of methodology for this C–N bond-formation reaction is of considerable importance. In this letter, we report our results concerning an efficient aza-Michael addition of azole to nitroalkene without catalyst.

Our initial results showed that the aza-Michael addition of azole to β,γ-unsaturated α-keto ester[16] to afford new C–N bond adducts was feasible (Equation 1 in Scheme 1). On this basis, we wondered whether this approach could be applied to other electron-poor alkenes.

Initially we examined the reaction of pyrazole with several typical Michael acceptors, including chalcone, benzylidene acetone, and β-nitrostyrene. However, reactions between pyrazole and enone were not successful and the conjugate adducts could not be obtained in substantial yields (Equations 2 and 3 in Scheme 1). To our delight, pyrazole reacted with β-nitrostyrene (**1a**) to afford 1,4-adduct in excellent yield (95%, Equation 4 in Scheme 1).[17]



Scheme 1 Aza-Michael additions of pyrazole to Michael acceptors

With this encouraging result, we then optimized the reaction conditions, including screening of solvent and molar ratios of reactants. And the results are displayed in Table 1. It was found that the reaction medium had an impact on the reaction. No more than 50% of conversion was obtained when reaction was carried out in THF, Et_2O and EtOAc (entries 2–4, respectively). The using of MeCN as solvent afforded 87% of conversion (entry 5). Importantly, the reactions in CH_2Cl_2, toluene, MeOH and $CHCl_3$ all proceeded with excellent conversion (entries 1 and 6–8) and the best result, 99% of conversion was obtained in

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CH_2Cl_2 (entry 1). Decreasing amount of pyrazole still afforded more than 90% of conversion (entries 9 and 10). When the ratio of reactants was 1:1, 78% of conversion was obtained (entry 11). When β-nitrostyrene was employed in excess, excellent conversion could also be obtained (entry 12). Reducing the volume of the reaction medium resulted in high conversion within short time (entries 13 and 14).

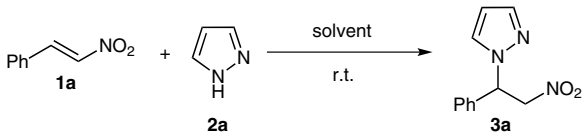
Under the optimal reaction conditions, aza-Michael additions of pyrazole to a variety of nitroalkenes were surveyed, and the results are presented in Table 2.

The reaction between β-nitrostyrene (**1a**) and pyrazole (**2a**) afforded **3aa** in 78% yield after 12 hours. To our delight, up to 98% yield was obtained when the reaction time was increased to 24 hours (entry 1). It should be noted that both electron-withdrawing (halogen atom) and electron-donating substituents (Me, MeO, CF_3O, BnO) could be introduced into the aromatic ring, with only a small effect on the yield of the reaction. And no significant electronic effect on the aromatic moiety was observed. Thus, halogen-substituted nitroalkenes reacted with pyrazole efficiently, and Michael adducts **3ba–da** were formed in more than 90% yields (entries 2–4) with the exception of **3ea**, which was obtained in 82% yield (entry 5). Moreover, Michael adducts **3fa–ha** could also be obtained with more than 90% yields from reactions between pyrazole and nitroalkenes with electron-donating substituents (entries 6–8). Thus, the Michael addition of more sterically congested **1i** also resulted in good yield (81%, entry 9). The BnO-substituted nitroalkenes **1j** and **lk** were found to react quite slowly and adducts **3ja** and **3ka** were obtained with lower yields (entries 10 and 11).

Apart from pyrazole, the aza-Michael additions of other N-nucleophiles to β-nitrostyrene were also investigated (Scheme 2). Up to 98% yield was obtained from the aza-Michael addition of 3,5-dimethylpyrazole (**2b**) to **1a** (Equation 1 in Scheme 2).[18] Particularly noteworthy was that the aza-Michael addition of indoline (**2c**) to **1a** also resulted in 87% yield (Equation 2 in Scheme 2).[19] However, imidazole was found to be incompatible under these reaction conditions and no adduct was obtained (Equation 3 in Scheme 2).

In conclusion, we have succeeded in showing a general and efficient aza-Michael addition between azoles and nitroalkenes.[20] It should be noted that no additional catalyst was employed in this system. The azole serves as both organocatalyst and N-nucleophile in the reaction system. Particularly noteworthy is that a wide spectrum of nitroalkenes reacts smoothly and most compounds containing azole group could be obtained in more than 90% yield

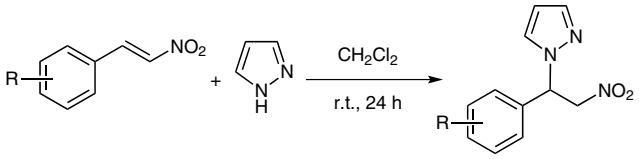
Table 1 Optimization of Reaction Conditions[a]



Entry	**1a** (mmol)	**2a** (mmol)	Solvent	Time	Conversion[b]
1	0.10	0.20	CH_2Cl_2	24 h	99%
2	0.10	0.20	THF	24 h	35%
3	0.10	0.20	Et_2O	24 h	44%
4	0.10	0.20	EtOAc	24 h	50%
5	0.10	0.20	MeCN	24 h	87%
6	0.10	0.20	toluene	24 h	94%
7	0.10	0.20	MeOH	24 h	96%
8	0.10	0.20	$CHCl_3$	24 h	98%
9	0.10	0.15	CH_2Cl_2	24 h	98%
10	0.10	0.13	CH_2Cl_2	24 h	93%
11	0.10	0.10	CH_2Cl_2	24 h	78%
12	0.20	0.10	CH_2Cl_2	24 h	99%
13	0.10	0.13	CH_2Cl_2 (0.2 mL)	12 h	95%
14	0.10	0.13	CH_2Cl_2 (0.1 mL)	12 h	98%

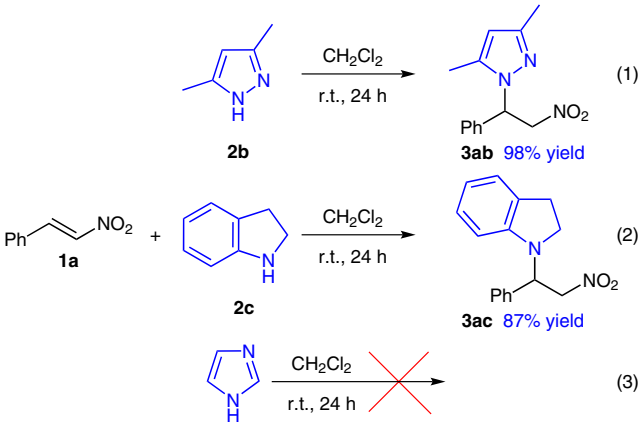
[a] Unless otherwise noted, the reaction was carried out as following: the mixture of **1a** and **2a** was stirred in the solvent (0.3 mL) for the time given.
[b] Determined by HPLC.

Table 2 Scope of Nitroalkenes[a]



Entry	R	Adduct	Yield[b]
1	H, **1a**	**3aa**	98% (78%)[c]
2	2-F, **1b**	**3ba**	96%
3	4-F, **1c**	**3ca**	93%
4	2-Cl, **1d**	**3da**	97%
5	4-Br, **1e**	**3ea**	82%
6	4-Me, **1f**	**3fa**	98%
7	4-MeO, **1g**	**3ga**	91%
8	4-CF_3O, **1h**	**3ha**	97%
9	2,3-$(MeO)_2$, **1i**	**3ia**	81%
10	2-BnO, **1j**	**3ja**	56%
11	4-BnO, **1k**	**3ka**	58%

[a] Unless otherwise noted, the reaction was carried out as following: the mixture of **1a** and **2a** was stirred in CH_2Cl_2 (0.1 mL) for 24 h.
[b] Isolated yield.
[c] Reaction time was 12 h.



Scheme 2 Aza-Michael additions of other N-nucleophiles

via this methodology. Further applications of these reactions in pharmaceutical synthesis are currently underway.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) ^{1}H NMR data of adduct: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1 H), 7.43 (d, *J* = 2.0 Hz, 1 H), 7.36–7.38 (m, 3 H), 7.28–7.30 (m, 2 H), 6.29 (t, *J* = 1.8 Hz, 1 H), 6.12 (dd, *J* = 4.8, 9.6 Hz, 1 H), 5.63 (dd, *J* = 9.6, 14.0 Hz, 1 H), 4.87 (dd, *J* = 4.8, 14.0 Hz, 1 H).

(18) ^{1}H NMR data of adduct: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.36 (m, 3 H), 7.22–7.24 (m, 2 H), 5.96 (dd, *J* = 4.4, 10.0 Hz, 1 H), 5.83 (s, 1 H), 5.67 (dd, *J* = 9.8, 14.2 Hz, 1 H), 4.81 (dd, *J* = 4.4, 14.0 Hz, 1 H), 2.23 (m, 3 H), 2.18 (m, 3 H).

(19) ^{1}H NMR data of adduct: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.39 (m, 5 H), 7.05–7.12 (m, 2 H), 6.67–6.71 (m, 2 H), 5.63 (dd, *J* = 6.8, 8.4 Hz, 1 H), 5.03 (dd, *J* = 8.8, 12.0 Hz, 1 H), 4.92 (dd, *J* = 10.6, 12.2 Hz, 1 H), 3.42–3.48 (m, 1 H), 3.13–3.20 (m, 1 H), 2.86–3.01 (m, 2 H).

(20) Unless noted otherwise, the reaction was carried out as following: to a solution of CH_2Cl_2 (0.1 mL) were added nitroalkene **1** (0.1 mmol) and azole **2** (0.13 mmol). The reaction mixture was stirred at r.t. for 24 h and then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel to yield the desired Michael adducts **3**.

