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Aqueous-mediated Michael Addition of Active Methylene Compounds with Nitroalkenes

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A simple, atom economical and highly efficient green protocol has been developed for the synthesis of Michael adducts of nitroalkenes and 2-amino-2-chromene derivatives by Michael addition of active methylene compounds (such as malononitrile and ethyl cyanoacetate) to nitroalkenes under aqueous-mediated conditions. This green approach provided the desired products in high yields and the reaction scope proved to be quite broad.

Keywords Michael addition, green chemistry, chromenes, nitroalkenes, domino reaction

Introduction

Environmentally benign reactions have become the targets of synthetic organic chemists today. In many synthetic organic processes, organic solvents can cause significant air pollution, land contamination and water pollution. Therefore, the development of efficient synthetic methodologies for organic reactions, in the absence of organic solvents, is an important challenge toward reducing the amount of waste.[1,2] To reduce the use of ecologically hazardous chemicals, it is advantageous to carry out organic reactions in aqueous media because water is an environmentally friendly solvent and exhibits unique reactivity and selectivity, different from those in conventional organic solvents.[3-6] Moreover, the development of efficient transformations in water without any catalyst is highly appreciated. Indeed, great efforts have been implemented in the development of catalyst-free processes to accomplish greener and cleaner syntheses, such as ring opening of epoxides by amines,[7a] Michael addition of thiols or amines to unsaturated compounds,[7b-7e] *N*-*tert*-butyloxy-carbonylation of amines,[7f] Friedel-Crafts alkylation of naphthols or indoles with nitroalkenes[7g,7h] and C-alkylation of 2-hydroxy-1,4-naphthoquinone to nitroalkenes.[7i]

The Michael addition reaction is widely recognized as one of the most versatile C—C bond forming reactions to construct highly functionalized building blocks for the total synthesis of natural and biologically active compounds.[8] Nitroalkenes is a very good Michael acceptors, and Michael adducts of nitroalkene can be readily transformed into different functionalities.[9] The electrophilic property of nitroalkene could be increased when the nitro group is interacted with urea and thiourea through hydrogen bonding,[10] we envisage that the nitro group would also be activated with water through hydrogen bonding without any catalyst. Moreover, there are few reports on conjugate addition of active methylene compounds to nitroalkenes in water without any catalyst.

As part of our ongoing research work on the development of green approaches in organic synthesis,[11] herein we report an efficient, green route to access Michael adducts of nitroalkenes and 2-amino-2-chromene derivatives by aqueous-mediated Michael addition of active methylene compounds to nitroalkenes.

Results and Discussion

We started our original studies by screening a range of solvents for the Michael reaction of malononitrile and nitroalkenes. As shown in Table 1, when toluene, THF, and CH_2Cl_2 were used as solvents, no product was obtained after 12 h at room temperature (Table 1, Entries 1—3). To our delight, Michael addition proceeded in water without any catalyst or additive, giving the desired product in 9% isolated yield after 12 h (Table 1, Entry 6). Then different temperatures were screened and the best yield was obtained when the reaction was carried out at 80 ℃ for 3 h (Table 1, Entry 6). Michael addition also proceeded smoothly in deionized water and similar results were obtained. When the reaction time was extended, the reaction became a little complicated; somewhat low yield was isolated (Table 1, Entry 7). It is worthy of note that catalytic amount of water could promote the reaction and good yield was obtained. On the contrary, low yield was obtained when no water was added (Table 1, Entries 8, 9).

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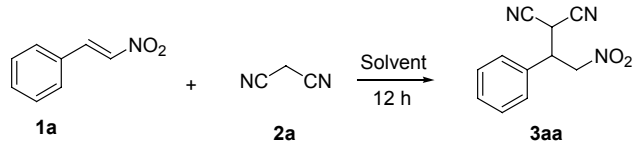
Table 1 Reaction of nitroalkene **1a** and malononitrile under different conditions[a]



1a **2a** **3aa**

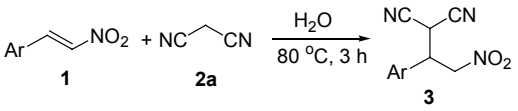
Entry	Solvent	Temp./℃	Yield[b]/%
1	Toluene	25	Trace
2	THF	25	Trace
3	CH_2Cl_2	25	Trace
4	H_2O[c]	25	9
5	H_2O[c]	60	31
6[d]	H_2O[c]	80	81
7[e]	H_2O[c]	80	70
8	—	80	11
9[f]	—	80	73

[a] Unless noted otherwise, reactions performed with 0.50 mmol of **1a**, 0.60 mmol of malononitrile in 2 mL solvent. [b] Isolated yield. [c] Tap water. [d] 3 h. [e] 4 h. [f] Catalytic amount of water (0.1 mmol) was added.

Consequently, an array of various substituted nitroalkenes **1** was explored in the reactions with malononitrile to establish the general utility of this new methodology (Table 2). Several points are noteworthy: (1) In general, the desired product can be prepared in good to excellent yields under standard conditions from the corresponding nitroalkenes and malononitrile. Nitroalkenes with electron withdrawing substituents on the *ortho*, *meta* or *para* positions have a little effect on the yields (Table 2, Entries 5—7). (2) It turned out that the substituents on the phenyl group of nitroalkenes had a little influence on the yields under the optimized conditions (Table 2, Entries 2—11). Excellent yields were obtained when there were strong electron-withdrawing groups on the phenyl group of nitroalkenes (Table 2, Entries 10, 11). (3) For the reactions of malononitrile, good yields were achieved with nitroalkenes bearing various heteroaryl substitutions (Table 2, Entries 12, 13). Unfortunately, no product was observed when other Michael acceptors (such as α,β-unsaturated ketones, esters and cinnamonitrile) were used, as well as other Michael donors (such as ethyl cyanoacetate **2b**, acetylacetone and malonates) were used.

Chromene derivatives are an important class of heterocycles, widely present in plants, including edible vegetables and fruits.[12] And they are of considerable interest as they possess a wide range of biological properties.[13] Different approaches towards the synthesis of 2-amino-2-chromene derivatives have been reported.[14] Having succeeded in synthesizing Michael adducts, we turned our attention to the possible synthesis of Chromenes. Gratifyingly, the domino Michael addition/intramolecular cyclization reaction of functionalized nitroalkenes with malononitrile proceeded smoothly in water without any catalyst or additive at 40 ℃ for 12 h, and 2-amino-2-chromene derivatives were obtained with good to excellent yields. As summarized in Table 3, high yields were obtained in the domino reactions of **2a** and electron-withdrawing substituent on aryl ring of functionalized nitroalkenes **1q**—**1s** (Table 3, Entries 4—6). On the contrary, an electron-donating substituent on aryl ring of functionalized nitroalkenes **1o—1p** tended to decrease the reactivity (Table 3, Entries 2, 3). The reactions of ethyl cyanoacetate **2b** with functionalized nitroalkenes also found to be successful while the reaction temperature should be increased, and 2-amino-2-chromene derivatives were obtained with moderate to good yields (Table 3, Entries 7—9). No product was observed when other Michael donors (such as acetylacetone and malonates) were used in this reaction.

Table 2 Reaction of different nitroalkenes **1a**—**1m** and malononitrile[a]



1 **2a** **3**

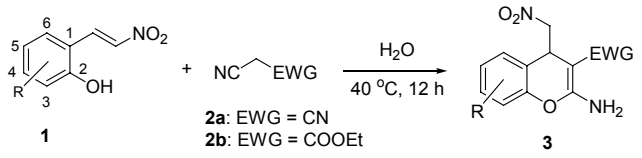
Entry	Ar	**3**	Yield[b]/%
1	Ph (**1a**)	**3aa**	81
2	*p*-$CH_3OC_6H_4$ (**1b**)	**3ba**	88
3	*p*-$CH_3C_6H_4$ (**1c**)	**3ca**	89
4	*p*-FC_6H_4 (**1d**)	**3da**	91
5	*p*-ClC_6H_4 (**1e**)	**3ea**	87
6	*o*-ClC_6H_4 (**1f**)	**3fa**	86
7	*m*-ClC_6H_4 (**1g**)	**3ga**	90
8	*p*-BrC_6H_4 (**1h**)	**3ha**	89
9	*o*-BrC_6H_4 (**1i**)	**3ia**	88
10	*p*-$NO_2C_6H_4$ (**1j**)	**3ja**	92
11	*o*-$NO_2C_6H_4$ (**1k**)	**3ka**	94
12	Furyl (**1l**)	**3la**	70
13	Thienyl (**1m**)	**3ma**	85

[a] Unless noted otherwise, reactions performed with 0.50 mmol of **1**, 0.60 mmol of malononitrile in 2 mL water at 80 ℃. [b] Isolated yield.

A plausible mechanistic proposal considering all data obtained is shown in Scheme 1. The reaction proceeds faster in water than that in organic solvents without catalyst (Table 1, Entries 1—10), since hydrogen atom of water could activate nitroalkenes by the hydrogen-bond between water and oxygen atom of the nitroolefin, increasing electrophilic property of the β-carbon, whereas the hydrogen bond between water and hydrogen atom of the active methylene compounds increases the nucleophilic property of active methylene compounds.[15] Thus, water could activate both donors and acceptors to increase reactivity simultaneously through hydrogen bond formation.

CHINESE JOURNAL OF CHEMISTRY

Table 3 Reaction of functionalized nitroalkenes **1n**—**1r** and active methylene compounds[a]



Entry	R	2	3	Yield[b]/%
1	H (**1n**)	**2a**	**3na**	81
2	5-Me (**1o**)	**2a**	**3oa**	79
3	4-MeO (**1p**)	**2a**	**3pa**	72
4	5-F (**1q**)	**2a**	**3qa**	89
5	5-Cl (**1r**)	**2a**	**3ra**	87
6	5-Br (**1s**)	**2a**	**3sa**	85
7[c]	H (**1n**)	**2b**	**3nb**	84
8[c, d]	5-Me (**1o**)	**2b**	**3ob**	54
9[c]	5-Br (**1s**)	**2b**	**3sb**	85

[a] Unless noted otherwise, reactions performed with 0.50 mmol of **1**, 0.60 mmol of **2** in 2 mL water at 40 ℃. [b] Isolated yield. [c] 80 ℃, 3h. [d] 24 h.

Conclusions

In summary, we have developed a facile and efficient synthesis of Michael adducts of nitroalkenes by Michael addition of malononitrile with nitroalkenes. The reaction scope proved to be quite broad. Notably, this methodology aslo provides facile access to various multifunctional 2-amino-2-chromene derivatives which may serve as a platform for further manipulation leading to structurally unique chromenes and other pharmaceutically intriguing compounds. Additionally, the reaction can be carried out in water as a cheap and environmentally benign solvent and can be conducted on a larger scale at low cost making it an ideal alternative to existing methods.

Experimental

All commercial reagents were used as received unless otherwise mentioned. Various substituted nitroalkenes were synthesized by aldehyde and CH_3NO_2. Purification of reaction products was carried out by column chromatography using Qingdao silica gel (200—300 mesh). Analytical thin-layer chromatography (TLC) was performed on silica gel GF254 (Qingdao, China) with ethyl acetate and petroleum ether (60—90 ℃) and detected by UV light or iodine vapor. Melting points were recorded on an Elemental digital melting points apparatus and were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 400 spectrometer, using $CDCl_3$ or DMSO as solvent and TMS as internal reference, IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR. ESI-HRMS spectrometer was measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer.

General procedure for Michael addition of malononitrile to nitroalkenes

A mixture of malononitrile (0.6 mmol) and *β*-nitroalkene (0.5 mmol) was suspended in 2 mL of water, and the reaction mixture was heated at 80 ℃ for 3 h. The reaction mixture was extracted with ethyl acetate (5 mL×3). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated to obtain crude product. Further purification was achieved by column chromatography using ethyl acetate/petroleum ether as eluent to furnish the products **3aa**—**3ma**.

General procedure for synthesis of 2-amino-2-chromene derivatives

A mixture of active methylene compounds (0.6 mmol) and (*E*)-2-(2-nitrovinyl)phenol (0.5 mmol) was suspended in 2 mL of water, and the reaction mixture was heated. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled, diluted with water (10 mL) and filtered. Further purification was achieved by column chromatography using ethyl acetate/petroleum ether as eluent to furnish the products **3na**—**3sb**.

Acknowledgement

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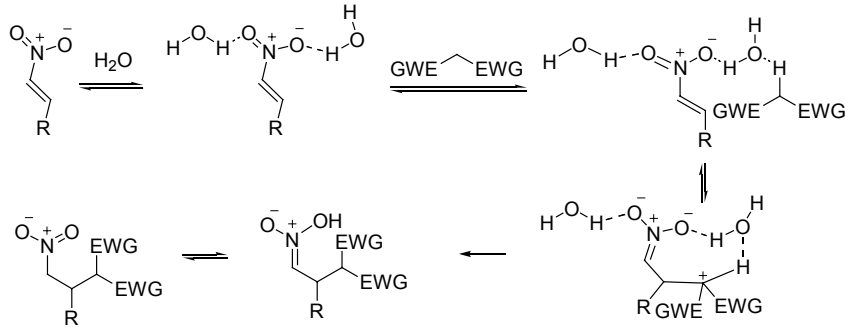
Scheme 1 Proposed mechanism of Michael addition of active methylene compounds with nitroalkenes



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