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COMMUNICATION

A facile and efficient synthesis of multisubstituted pyrroles from enaminoesters and nitroolefins†

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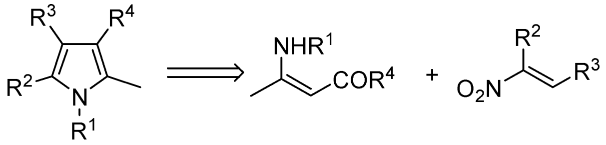
A facile and efficient method for the synthesis of substituted pyrroles from enaminoesters and nitroolefins is reported. This general procedure provides a wide variety of multisubstituted pyrroles in good to excellent yields under mild reaction conditions.

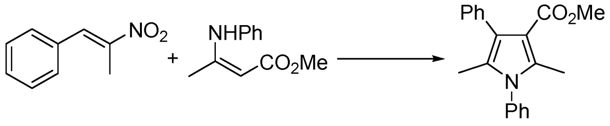
As one of the most important heterocycles, substituted pyrroles are not only found in many natural products[1] and pharmaceuticals[2] but are also widely used in material science,[3] bioorganic chemistry,[4] and supramolecular chemistry.[5] A variety of elegant methods for the synthesis of pyrroles have been developed in the past decades,[6,7] however, a facile and efficient procedure for the synthesis of multisubstituted pyrroles remains highly desirable.

Apart from the well-documented traditional methods, such as the Knorr,[8] Paal–Knorr,[9] and Hantzsch reactions,[10] the modern approaches to the synthesis of substituted pyrroles are mainly based on the transition-metal catalyzed cyclizations[11,12] and multicomponent coupling reactions.[13,14] However, the high catalyst loading in some of these processes results in not only high cost but also potential contamination of the products, particularly in the pharmaceutical industry.[15] Recently, a metal-free synthesis of substituted pyrroles by the domino reaction of cyclic enaminones with halogenated nitroolefins has emerged.[16] However, the procedure was not environmentally benign due to using halogenated nitroolefins. We envision that the Michael-type addition and cyclization of enaminones or enaminoesters to nitroolefins would be a direct approach to construct the pyrrole rings in accordance with the principles of green chemistry (Scheme 1). There is limited precedent for these transformations,[17] but the reaction is still limited in substrate scope and low yields.[18] In this communication, we have improved the synthetic method and developed an environmentally benign, facile and efficient synthetic method for the synthesis of multisubstituted pyrroles from readily available enaminoesters and nitroolefins.



Scheme 1 Addition and cyclization of enaminoesters to nitroolefins.

Table 1 Optimization of the reaction conditions[a]



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

Entry	Solvent	Additive	*t* (h)	Yield (%)
1	C_2H_5OH	—	14	57
2	H_2O	—	14	24
3	DMSO	—	14	42
4	CH_3CN	—	14	20
5	glycol	—	14	61
6	CH_3OH	—	14	75
7	CH_3OH	NaOAc	7	69
8	CH_3OH	pyridine	7	45
9	CH_3OH	CAN	8	62
10	CH_3OH	Zn powder	4	50

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), additive (0.6 mmol), in solvent (2 mL) at 120 °C.

To begin our study, 1-(2-nitroprop-1-enyl)benzene **1a** and methyl 3-(phenylamino)but-2-enoate **2a** were chosen as model substrates to optimize the reaction conditions. Screening of various solvents revealed that CH_3OH was the most efficient one for the transformation (Table 1, entries 1–6). Various additives, such as NaOAc, pyridine, CAN (ammonium cerium(IV) nitrate), and Zn powder were tested and failed to improve the efficiency of the transformation (Table 1, entries 7–10). Therefore, the combination of the nitroolefins **1a** (0.3 mmol) and enaminoesters **2a** (1.5 eq.) in CH_3OH at 120 °C gave the best result.

Under the optimized reaction conditions, we have explored the substrate scope. The reaction results of enaminoester **2a** with various nitroolefins[19] **1a–1j** are summarized in Table 2. These

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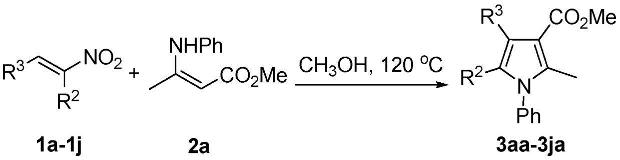
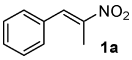
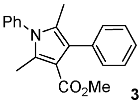
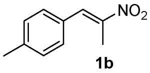
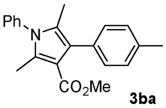
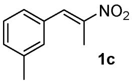
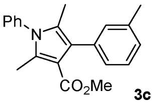
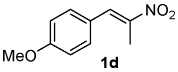
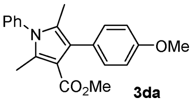
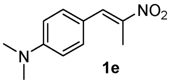
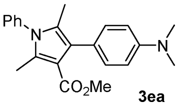
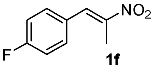
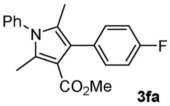
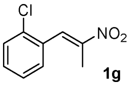
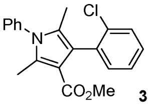
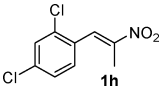
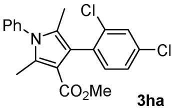
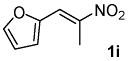
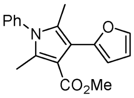
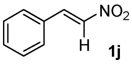
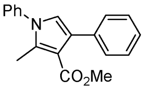
† Electronic supplementary information (ESI) available: Experimental procedure, ^1H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/c1gc15278e

Table 2 Reactions of enaminoester **2a** with various nitroolefins **1**[a]

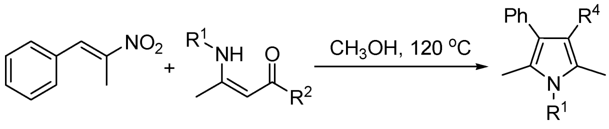


Entry	Nitroolefin **1**	Pyrrole **3**	*t* (h)	Yield (%)
1	 **1a**	 **3aa**	14	75
2	 **1b**	 **3ba**	22	83
3	 **1c**	 **3ca**	22	80
4	 **1d**	 **3da**	23	78
5	 **1e**	 **3ea**	35	79
6	 **1f**	 **3fa**	24	74
7	 **1g**	 **3ga**	24	65
8	 **1h**	 **3ha**	30	67
9	 **1i**	 **3ia**	35	79
10	 **1j**	 **3ja**	12	78

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), in CH_3OH (2 mL) at 120 °C.

transformations displayed high functional group tolerance. Nitroolefins with methyl, methoxyl, amino, fluoro and chloro groups on the arene all gave the corresponding pyrroles in good yields (Table 2, entries 2–8). For the electronic effects of the transformation, we found that electron-rich nitroolefins showed better reactivity and gave higher yields than electron-deficient ones (Table 2, entries 2–8). In addition, the nitroolefin possessing a furanyl group also underwent the desired reaction to give the corresponding pyrrole product **3ia** in good yield (Table 2, entry 9). An extensive investigation of the reaction shows that the

Table 3 Reactions of various enaminoesters **2** with nitroolefin **1a**[a]



1a **2b-2q** **3ab-3aq**

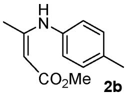
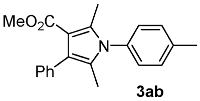
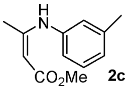
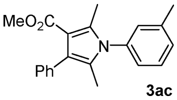
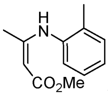
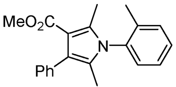
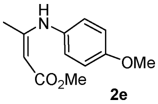
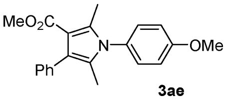
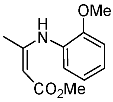
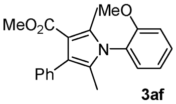
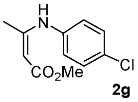
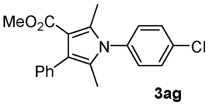
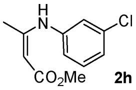
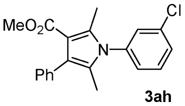
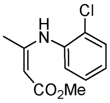
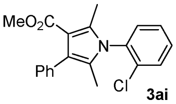
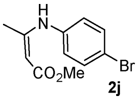
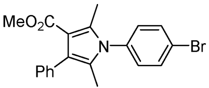
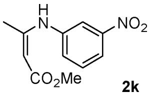
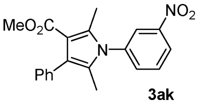
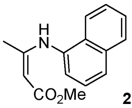
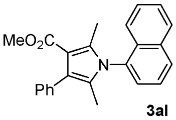
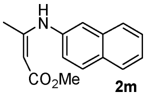
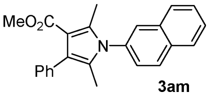
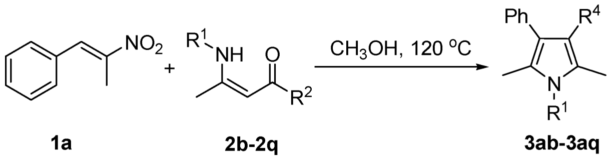
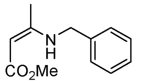
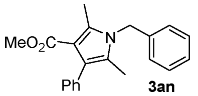
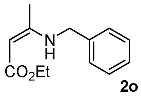
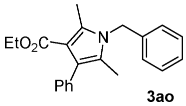
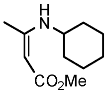
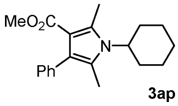
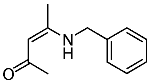
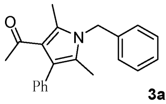
Entry	Enaminoester **2**	Pyrrole **3**	*t* (h)	Yield (%)
1	 **2b**	 **3ab**	12	81
2	 **2c**	 **3ac**	13	77
3	 **2d**	 **3ad**	24	79
4	 **2e**	 **3ae**	13	83
5	 **2f**	 **3af**	24	82
6	 **2g**	 **3ag**	24	73
7	 **2h**	 **3ah**	24	63
8	 **2i**	 **3ai**	25	50
9	 **2j**	 **3aj**	30	75
10	 **2k**	 **3ak**	24	30(54)[b]
11	 **2l**	 **3al**	29	60(68)[b]
12	 **2m**	 **3am**	27	82

Table 3 *(Contd.)*



Entry	Enaminoester **2**	Pyrrole **3**	*t* (h)	Yield (%)
13	 **2n**	 **3an**	7	92
14	 **2o**	 **3ao**	6	89
15	 **2p**	 **3ap**	12	86
16	 **2q**	 **3aq**	24	58

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol), in CH$_3$OH (2 mL) at 120 °C. [b] NaOAc (0.6 mmol) was added.

nitroolefin **1j** also worked well, and a 78% yield of the desired pyrrole **3ja** was obtained (Table 2, entry 10).

For extending the substrate scope, we have investigated the reactions of various enaminoesters[20] **2b–2q** with nitroolefin **1a** as well, and the results are illustrated in Table 3. Satisfactorily, the reactions displayed high functional group tolerance and afforded the corresponding pyrroles with great efficiency. In general, the electron-rich enaminoesters show better reactivity and gave higher yields than electron-deficient ones, and the reactions were insensitive to the steric hindrance of the substitutes on the aromatic rings (Table 3, entries 1–9). Pyrrole **3ak** was only obtained in low yield because NO$_2$ substituted enaminoester **2k** was partially decomposed in the reaction. This issue has been resolved by using NaOAc as an additive (Table 3, entry 10). The reaction of enaminoesters **2l** and **2m**, which derived from naphthalen-1-amine and naphthalen-2-amine respectively, also gave the corresponding pyrrole products **3al** and **3am** in good yields (Table 3, entries 11–12). It is worth noting that *N*-benzyl substituted pyrroles were obtained in excellent yields in the transformations (Table 3, entries 13–14). Similarly, *N*-cyclohexanyl substituted pyrrole **3ap** was achieved in 86% yield (Table 3, entries 15). Moreover, the reaction of nitroolefin **1a** with enaminone **2q** also gave the pyrrole product **3aq** in good yield (Table 3, entry 16).

In conclusion, we have demonstrated a facile and efficient procedure for the synthesis of multisubstituted pyrroles. This general protocol employs readily available starting materials and shows good functional group tolerance. Under the transition metal-free and non-halogenation conditions, a wide variety of multisubstituted pyrroles were synthesized in good to excellent yields in an environmentally benign manner.

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