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Synthesis of 2,3,4,5-tetra-substituted pyrroles via a base-promoted double Michael reaction of oxime-enoates with nitroolefins

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ABSTRACT

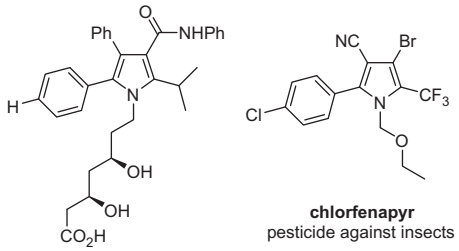
A new method of synthesizing 2,3,4,5-tetra-substituted pyrroles from oxime-enoates with nitroolefins is described. This reaction involves a base-promoted double Michael reaction, followed by dehydrative aromatization.

Pyrrole nuclei are important chemical cores found in natural products[1] and pharmaceuticals.[2] They are useful as reagents, catalysts, and substances in the context of organic synthesis.[3] The pyrrole scaffold has received much attention in material science because of its special optical and electronic properties.[4] Polysubstituted pyrroles play increasingly important roles as promising pharmacophores in medicinal chemistry (Fig. 1).[5] The broad applicability of substituted pyrroles has inspired significant efforts toward investigating their synthesis.[6,7] Classical methods, such as the Knorr, Hantzsch, and Parr–Knorr syntheses, are widely recognized as relevant for the preparation of pyrroles; however, a facile and efficient procedure for the synthesis of multi-substituted pyrroles remains highly desirable.

Recently, Zhong and co-workers reported the preparation of poly-substituted *N*-hydroxypyrroles by means of an amine-catalyzed reaction of 1,3-diketo-2-oximes with α,β-unsaturated aldehydes.[8] The reaction was assumed to begin with a Michael addition of the nitrogen atom of the oximes to the β-position of the unsaturated iminiums that were generated in situ from the aldehydes with an amine catalyst. An intramolecular aldol condensation, followed by aromatization, furnished the *N*-hydroxypyrroles in good yields (Scheme 1a). These compounds could be successfully reduced into the corresponding pyrroles. Inspired by this brilliant work, we envisaged that the reaction of the oxime-enoate with α,β-unsaturated carbonyl compounds could afford highly substituted pyrroles by means of a double Michael sequence[9] (Scheme 1b).

The substrates were prepared from the corresponding 4-oxobutenoates via condensation with a hydroxylamine HCl salt (Scheme 2). The oxime-dienoate **1**, which possessed no geometrical isomers around the C=N bond, was obtained from diethyl (*E*,*E*)-4-oxo-2,5-heptadienedioate in 96% yield. The oxime ether **2** was also prepared from methoxyamine hydrochloride in 50% yield. The asymmetrical oxime **3** was prepared from the commercially available ethyl (*E*)-4-oxo-4-phenylbutenoate[10] in 72% yield as an inseparable mixture of isomers (*syn*/*anti* = 29:71).

When oxime **1** was treated with β-nitrostyrene (**4a**) in the presence of KOH (1.1 equiv) in EtOH, **1** was fully consumed within 30 min at 0 °C to give the desired tetra-substituted pyrrole **5a** in 56% yield (Table 1, entry 1). The structure of **5a** was elucidated



atorvastatin (Lipitor)
HMG-CoA reductase inhibitor

chlorfenapyr
pesticide against insects

Figure 1. Biologically active tetra-substituted pyrroles.

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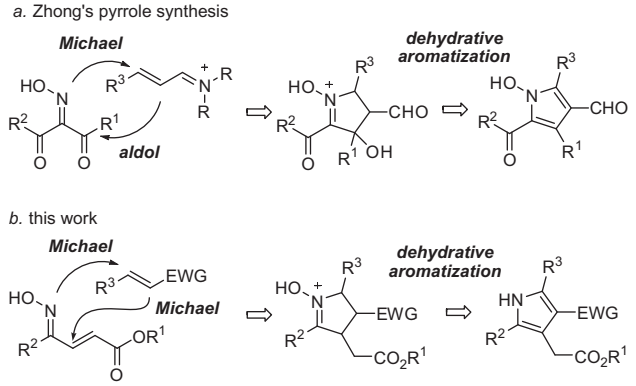
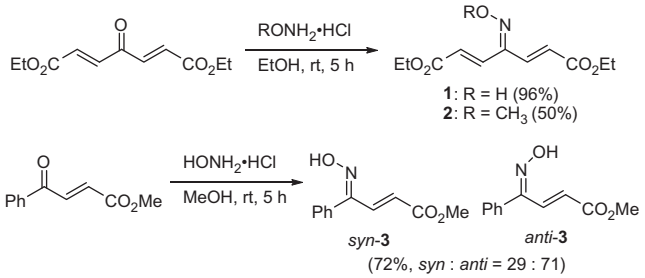
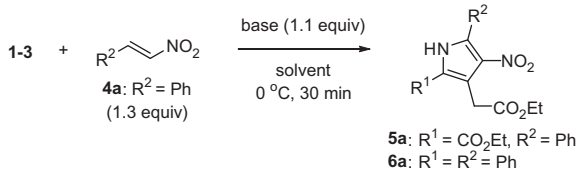


Scheme 1. Pyrrole synthesis from oximes: (a) Zhong's Michael/aldol strategy, and (b) our double Michael strategy.



Scheme 2. Synthesis of the substrates **1**–**3**.

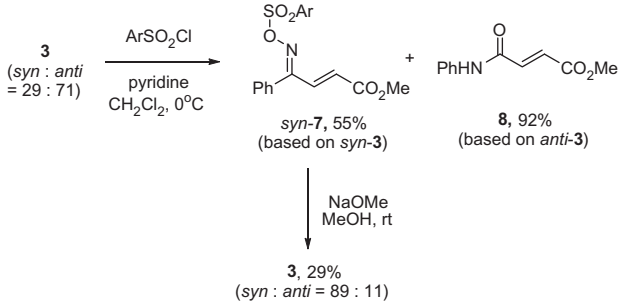
Table 1
Synthesis of the pyrroles via a double Michael addition[a]



Entry	Substrate	Base	Solvent	Product	Yield (%)
1	**1**	KOH	EtOH	**5a**	56
2	**1**	NaOH	EtOH	**5a**	73
3	**1**	NaOEt	EtOH	**5a**	74
4	**1**	Na_2CO_3	EtOH	**5a**	0
5	**1**	DBU	EtOH	**5a**	0
6	**2**	NaOH	EtOH	**5a**	0
7[b]	**3**[c]	NaOMe	MeOH	**6a**	18

[a] Conditions: **1**–**3** (0.2 mmol), **4a** (1.3 equiv), base (1.1 equiv), solvent (1.0 mL), 0 °C, 30 min.
[b] 2.0 equiv of **4a** was used.
[c] A mixture of the isomers (*syn*:*anti* = 29:71) was used.

by ^{1}H and ^{13}C NMR spectroscopy, and the regiochemistries of the substituents were fully assigned according to HMBC. The NaOH base afforded **5a** in 73% yield (entry 2). The use of NaOEt as a base suppressed the decomposition of **1** and **4a**, and the yield of **5a** was improved to 74% (entry 3).[11] Alcohols were clearly crucial as the solvents. No desired product was obtained in DMSO or acetonitrile. In the presence of the weaker bases, such as Na_2CO_3 or DBU, the reaction did not proceed, even when the reaction time was elongated (entries 4 and 5). Interestingly, no reaction occurred from oxime ether **2** (entry 6). These results indicated that deprotonation of the hydroxyl group of **1** drove the promotion of the first Michael addition to nitrostyrene **4a**. Thus, the nucleophilicity of the nitrogen atom of **1** was enhanced under the strongly basic conditions. The reaction of the asymmetrical oxime **3** (*syn*:*anti* = 29:71) with **4a** was carried out in the presence of NaOMe in MeOH to yield pyrrole **6a** in 18% yield (entry 7). In the reaction, *anti*-**3** was recovered (17%) but no *syn*-isomer was detected.



Scheme 3. Preparation of *syn*-3. Ar = 3,5-$(CF_3)_2C_6H_3$.

Table 2
Reaction of **1** with a variety of nitroolefins **4b**–**g** to give the highly substituted pyrroles[a]

Entry	Nitroolefin **4** (R^2)	Product	Yield (%)
1	**4b** (^{p}BrC$_6$H$_4$)	**5b**	60
2	**4c** (^{p}CF$_3$C$_6$H$_4$)	**5c**	55
3	**4d** (^{p}MeOC$_6$H$_4$)	**5d**	61
4	**4e** (^{o}MeC$_6$H$_4$)	**5e**	58
5	**4f** (Cyclohexyl)	**5f**	59
6	**4g** (Pentyl)	**5g**	66

[a] Conditions: **1** (0.2 mmol), **4** (1.3 equiv), NaOMe (1.1 equiv), MeOH (1.0 mL), 0 °C, 30 min.

The above results (Table 1, entry 7) indicated an interesting stereochemical outcome in the reactions of the *syn*/*anti*-oximes; that is, the geometry around the nitrogen lone pair of **3** was important for the formation of the pyrrole. This result is consistent with the proposed mechanism that the oximes can act as *N*-selective nucleophiles in a double Michael reaction. The mixture of geometrical isomers of **3** was difficult to separate; therefore, the preparation of each isomer was assessed through chemical transformations (Scheme 3). Sulfonylation of a mixture of **3** was carried out using 3,5-bis(trifluoromethyl)benzenesulfonyl chloride at 0 °C to yield the oxime sulfonate *syn*-**7** as a pure geometrical isomer, along with amide **8**. In the process, only *anti*-**3** spontaneously underwent a Beckman rearrangement after sulfonylation at this temperature due to the higher electron-donating properties of the phenyl group of the *anti*-**7** relative to the enoate moiety of the *syn*-**7**. The *syn*-**3** was obtained by treatment of *syn*-**7** with NaOMe, although the overall yield was unsatisfactory. Unfortunately, a small amount of *syn*-**3** was isomerized into *anti*-**3** during silica gel chromatography purification. No isomerization was observed under the conditions used for the pyrrole synthesis (NaOMe in MeOH at 0 °C).

Anti-**3**, which was obtained in the above reaction (Table 1, entry 7) as a pure stereoisomer, did not react under the conditions described above, and *anti*-**3** was recovered in 61% yield. By contrast, the *syn*-enriched **3** (*anti*:*syn* = 89:11) afforded pyrrole **6a** in 53% yield. The results clearly indicated that the geometry of the nitrogen lone pair of **3** was important for the formation of the pyrrole. These results were consistent with the proposed mechanism, in which the oximes acted as *N*-selective nucleophiles[8] in a double Michael reaction.

Finally, we examined the pyrrole synthesis of oxime **1** via reaction with various nitroolefins (Table 2). The nitoroolefins **4b**–**e**, which featured an electron-withdrawing or -donating aryl group, were good substrates and afforded the pyrroles **5b**–**e**, respectively,

in a reaction with **1** (entries 1–4). Good yields were achieved with the nitroolefins **4f** and **4g**, which included alkyl group substituents at the β positions (entries 5 and 6). By contrast, no formation of the desired pyrrole was observed in the reaction with α,β-unsaturated esters or nitriles instead of nitroolefins.

In summary, we describe a facile synthesis of the tetra-substituted pyrroles from oxime-enoates and nitroolefins in the presence of a strong base. The reaction sequence involved a double Michael addition and a dehydrative aromatization. The oxime-enoates, in particular, acted as *N*-selective nucleophiles in the initial Michael addition. The new strategy should have broad applications to the synthesis of biologically important heterocyclic compounds and organic materials.

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.2013.05.100.

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11. General procedure for the preparation of pyrrole: To a stirred solution of **1** (0.20 mmol) and **4** (0.26 mmol) in EtOH (1.0 mL) was added NaOEt (0.22 mmol) at 0 °C. After stirring for 30 min, the resulting mixture was diluted with $CHCl_3$ and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with $CHCl_3$ three times. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 4:1) to afford the desired product **5**.