Pyrrole Synthesis

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Unusual Domino Michael/Aldol Condensation Reactions Employing Oximes as N-Selective Nucleophiles: Synthesis of *N*-Hydroxypyrroles**

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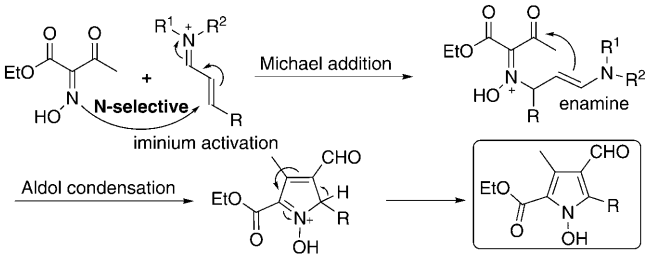
Dedicated to Professor Li-Xin Dai on the occasion of his 85th birthday

As one of the most important classes of heterocycles, pyrroles are not only important building blocks in the synthesis of natural products,[1] but also key structural units in compounds with interesting biological activities.[2] Pyrroles have also found broad application in materials chemistry.[3] Accordingly, substantial attention has been paid to develop efficient methods for their synthesis. One of the common approaches to pyrrole synthesis is the Paal–Knorr reaction, in which 1,4-dicarbonyl compounds are converted into pyrroles by acid-mediated dehydrative cyclization.[4] However, this approach is usually subject to significant limitations in terms of substituents introduced, substitution patterns, or regioselectivities.

Although several novel synthetic strategies have been described in recent years,[5,6] a general facile and regioselective approach to generate pyrroles with a wide functional-group tolerance from readily available precursors is still lacking. Over the past few years, organocatalytic domino reactions have emerged as a powerful synthetic paradigm to make diverse molecules.[7] The operational simplicity, readily available catalysts, and low toxicity associated with organocatalysis make it an attractive method in organic synthesis.

Herein, we report a catalytic synthesis of multisubstituted *N*-hydroxypyrroles by the domino reaction of α-carbonyl oxime compounds[8] and α,β-unsaturated aldehydes in the presence of secondary amine catalysts through the iminium activation strategy.[8a,9] This approach is differs from previously reported strategies, as oximes were employed as N-selective nucleophiles in the Michael addition step instead of the more commonly used O-selective nucleophiles in organocatalysis.[8a,b] To our knowledge, the formation of pyrrole derivatives through this simple and mild domino strategy has not been reported to date.

Amine catalysts perform efficient iminium activation by lowering the LUMO of α,β-unsaturated aldehydes.[7a,10] Thus, we set out to investigate the use of **IV** as a catalyst for a domino reaction involving sequential Michael addition and intramolecular aldol condensation (Scheme 1, Table 1). Initially, we used ethyl 2-(hydroxyimino)-3-oxobutanoate (**1a**) and (*E*)-hex-2-enal (**2a**) as reactants to test the reaction. Pleasingly, the reaction led smoothly to the formation of *N*-hydroxypyrrole in good yield. After optimizing the reaction conditions by changing the amount of the aldehyde and studying solvent effects, the yield was improved to 82% (Table 1, entry 4). With these encouraging results at hand, we explored other secondary amine catalysts (**I**–**VII**, Table 1).



Scheme 1. Proposed mechanism of the domino Michael addition/aldol condensation reaction by iminium activation in pyrrole synthesis.

The results were influenced by both amine catalysts and solvents. Surprisingly, no product was obtained when DMSO or DMF was used as solvent. Eventually, we decided to use diisopropylamine (**VII**) as a catalyst for this study, owing to its cheap price, ready availability, and higher catalytic efficiency in the reaction (Table 1, entry 7). After the optimal conditions have been established with catalyst **VII**, the generality of the domino process was investigated (Table 2). Good yields were achieved with many substrates (Table 2, entries 1–19) and several types of R^1 group, such as Me, MeO, EtO, *t*BuO, and BnO, did not significantly affect the reaction (Table 2, entries 1–9). If R^2 was changed from methyl to ethyl, the yields were almost the same even when different aldehydes were used (Table 2, entries 10–13). When a less reactive substrate was used, a higher catalytic loading and longer reaction time were required to obtain pyrrole **3u** in 58% yield (entry 21). To our delight, the above reaction proceeded well

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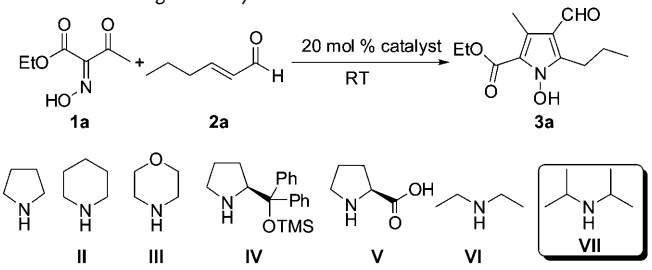
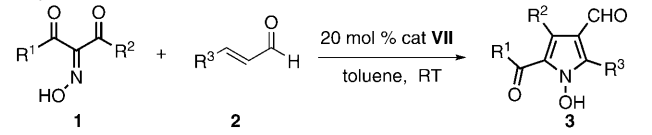
Table 1: Screening of catalysts and solvents for the domino reaction[a]



Entry	Catalyst	Solvent	Time [h]	Yield [%][b]
1	**I**	toluene	10	58
2	**II**	toluene	12	61
3	**III**	toluene	12	63
4	**IV**	toluene	10	82
5	**V**	toluene	18	66
6	**VI**	toluene	18	67
7	**VII**	toluene	18	83
8	**VII**	CH_2Cl_2	24	79
9	**VII**	Et_2O	24	33
10	**VII**	DMSO	24	0

[a] Reactions were carried out using **1a** (0.2 mmol, 1.0 equivalents) and **2a** (0.5 mmol, 2.5 equivalents) with catalyst (20 mol%) in solvent (1.0 mL) at room temperature. [b] Yield of isolated product.

Table 2: Synthesis of *N*-hydroxypyrroles by the domino Michael addition/aldol condensation reaction.[a]

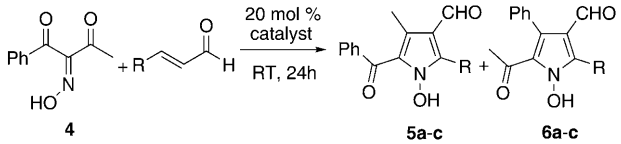


Entry	Oxime **1** R^1	R^2	Enal **2** R^3	Time [h]	Yield of **3** [%][b]
1	EtO	Me	*n*Pr	18	**3a**, 83
2	EtO	Me	Me	18	**3b**, 83
3	EtO	Me	Et	18	**3c**, 81
4	EtO	Me	$Me(CH_2)_4$	18	**3d**, 76
5	EtO	Me	$PhCH_2CH_2$	24	**3e**, 82
6	EtO	Me	$BnOCH_2CH_2CH_2$	24	**3f**, 78
7	MeO	Me	Me	18	**3g**, 73
8	*t*BuO	Me	Me	24	**3h**, 72
9	BnO	Me	Me	18	**3i**, 75
10	MeO	Et	Me	24	**3j**, 77
11	MeO	Et	*n*Pr	24	**3k**, 67
12	MeO	Et	Et	24	**3l**, 79
13	MeO	Et	$Me(CH_2)_4$	24	**3m**, 66
14	Me	Me	Me	18	**3n**, 79
15	Me	Me	*n*Pr	18	**3o**, 81
16	Me	Me	Et	18	**3p**, 83
17	Me	Me	$Me(CH_2)_4$	18	**3q**, 77
18	Me	Me	$PhCH_2CH_2$	18	**3r**, 82
19	Me	Me	$BnOCH_2CH_2CH_2$	18	**3s**, 73
20	Me	Me	$BocNHCH_2CH_2$	24	**3t**, 61
21[c]	Ph	Ph	Me	48	**3u**, 58

[a] Unless otherwise specified, reactions were carried out using **1** (0.2 mmol, 1.0 equivalents) and **2** (0.5 mmol, 2.5 equivalents) in the presence of **VII** (20 mol%) in toluene (1.0 mL) at room temperature. [b] Yield of isolated product. [c] 30 mol% catalyst was used. Boc = *tert*-butoxycarbonyl.

with a variety of different functional groups R^3, such as phenylethyl, benzoxypropyl, and 2-(*tert*-butoxycarbonylamino)ethyl, attached to the α,β-unsaturated aldehydes (Table 2, entries 5, 6, 18–20). However, the reaction did not proceed when the α,β-unsaturated aldehydes possessed beta aromatic substituents, such as phenyl. We believe that this domino reaction could find potential use in synthetic chemistry laboratories and in industry, despite its limitations, since R^3 bearing many different functionalities could be tolerated.

When oxime compound **4** was subjected to the above reaction conditions, the two theoretically predicted pyrroles (**5** and **6**, Scheme 2) were isolated (Table 3, entries 2 and 3). Interestingly, the use of different substituted aldehydes could



Scheme 2. Regioselectivity of the domino reaction.

Table 3: Regioselectivity in the domino reaction of diketone oximes **4** and α,β-unsaturated aldehydes.[a]

Entry	R	Cat	Solvent	Yield of **5** [%][b]	Yield of **6** [%][b]
1	Me	**VII**	toluene	**5a**, 76	**6a**, trace[c]
2	*n*Pr	**VII**	toluene	**5b** (62)	**6b**, 13
3	$Me(CH_2)_4$	**VII**	toluene	**5c**, 60	**6c**, 16
4	$Me(CH_2)_4$	**VII**	CH_2Cl_2	**5c**, 64	**6c**, 13
5	$Me(CH_2)_4$	**IV**	toluene	**5c**, 71	**6c**, trace
6	$Me(CH_2)_4$	**V**	toluene	**5c**, 61	**6c**, trace
7	*n*Pr	**IV**	toluene	**5b**, 78	**6b**, trace

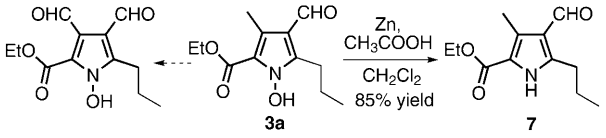
[a] Reactions were carried out using **4** (0.3 mmol, 1.0 equivalents) and aldehyde (0.6 mmol, 2.0 equivalents) in the presence of catalyst (20 mol%) in solvent (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Almost undetectable.

influence the results significantly. For example, when R^3 was a methyl group, only one product (**5a**) was isolated, prompting us to investigate the reaction further by changing other conditions in order to achieve higher regioselectivity. Although changing the solvent did not improve the results, changing the catalyst to **IV** or **V** (Table 3, 5–7) surprisingly led to the formation of only one major product. The excellent regioselectivity may be attributed to the bulky group in catalyst **IV** and hydrogen bonding in catalyst **V**.

Transforming product **3a** into 1*H*-pyrrole under mild conditions with good yield illustrated the synthetic usefulness of these polyfunctionalized *N*-hydroxypyrroles. Furthermore, the methyl group can be facilely converted into an aldehyde (Scheme 3).[11]

X-ray crystallographic analysis (Figure 1)[12] of the domino product **3r** further confirmed the structure of the product established by NMR spectroscopy.

One-pot multicomponent reactions have recently gained considerable and steadily increasing academic, economic, and ecological attention owing to their improved efficiency, reduced waste, and rapid access of structural diversity.[10]



Scheme 3. Transformation into 1*H*-pyrrole **7**.

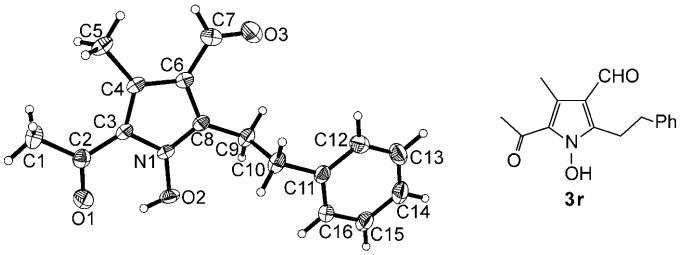
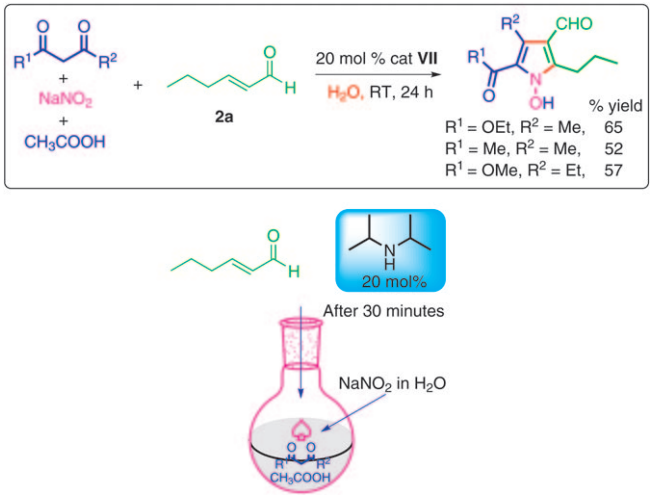


Figure 1. Molecular structure of **3r** determined by X-ray diffraction crystallography.

Such reactions carried out in water[13] would be ideal reactions from a green chemistry perspective. Considering these advantages, we carried out these reactions in water, leading to *N*-hydroxypyrroles isolated as major products in moderate yields (Scheme 4). Notably, lower yields were obtained from



Scheme 4. One-pot synthesis of *N*-hydroxypyrrole in water.

the one-pot synthesis of pyrrole when compared with that from two separate steps with carbonyl compounds, possibly as a result of the significant influence of solvent in these reactions.

A possible explanation as to why the unusual N-selective Michael products were obtained from the above reaction protocol is attributed to the different substrate structures. The ability of the dicarbonyl oxime to form an intramolecular hydrogen bond (Figure 2). The intramolecular hydrogen bond could decrease the nucleophilicity of the oxime oxygen, thus increasing the nucleophilicity of the oxime nitrogen and resulting in N-selectivity. Based on the above deduction, we carried out some control experiments. (*E*)-Oxime **8** afforded

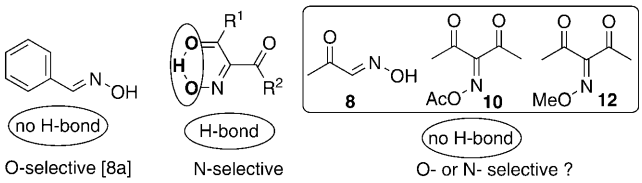
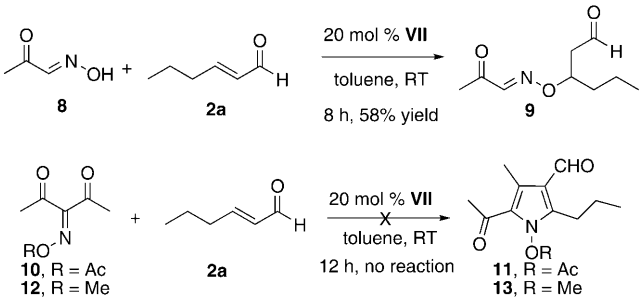


Figure 2. Preliminary conjecture of mechanism: the effect of intramolecular hydrogen bonding (see Scheme 5).

exclusively the O-selective Michael adduct, which supported our hypothesis as **8** was unable to form intramolecular hydrogen bonds. Furthermore, when acetyl or methyl-protected oxime **11** or **13** was used in this reaction, the reaction did not proceed at all (Scheme 5), further strengthening our conjecture that the intramolecular hydrogen bond is the main driving force for producing N-selective products.



Scheme 5. Control reactions for investigation of O/N-selectivity.

In summary, a facile and efficient one-pot synthesis of polyfunctionalized *N*-hydroxypyrroles has been developed, using readily available carbonyl oximes and α,β-unsaturated aldehydes. This synthesis involves sequential Michael addition, intramolecular aldol condensation, and aromatization reactions through iminium activation of α,β-unsaturated aldehydes by diisopropylamine. In the domino synthesis, carbonyl oximes acted as unusual N-selective nucleophiles in the Michael addition reaction. This method employed readily available starting materials and mild conditions, and proceeded in good yields with wide substrate scope, high regioselectivity, and flexible substitution patterns, affording products with great synthetic potential. Our future studies will entail expansion of the scope and applications of these powerful domino processes.

Experimental Section

Typical Procedure for *N*-Hydroxypyrrole Synthesis (Table 2, entry 1): Catalyst **VII** (0.04 mmol, 0.2 equivalents)was added to a solution of oxime **1a** (0.2 mmol, 1.0 equivalents) and (*E*)-hex-2-enal **2a** (0.5 mmol, 2.5 equivalents) in toluene (1.0 mL) at room temperature. The resulting mixture was stirred vigorously. After the reaction was completed (monitored by thin-layer chromatography), the mixture was quenched with saturated ammonium chloride, extracted with dichloromethane (8 mL) three times, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography on silica gel (gradient elution, EtOAc/Hexane = 1:15–1:10)

afforded the pure product **3a** in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.37$ (s, 1H), 9.96 (s, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 2.96 (t, $J = 7.6$ Hz, 2H), 2.57 (s, 3H), 1.74–1.66 (m, 2H), 1.44 (t, $J = 7.6$ Hz, 3H), 0.99 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 184.8, 165.5, 137.9, 127.8, 115.1, 112.4, 61.6, 24.7, 21.7, 14.3, 13.7, 10.6 ppm. HRMS (ESI) $[M+H]^+$ calcd for $C_{12}H_{18}NO_4$: 240.1236; found: 240.1238 (see the Supporting Information for full experimental details).

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[12] CCDC 703858 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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