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Efficient Assembly of Polysubstituted Pyrroles via a (3 + 2) Cycloaddition/Skeletal Rearrangement/Redox Isomerization Cascade Reaction

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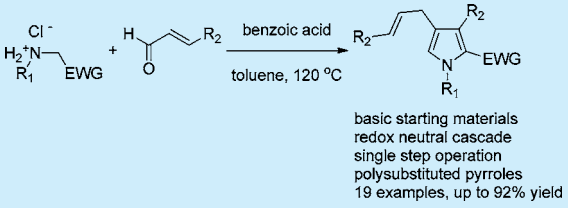
Supporting Information

ABSTRACT: An unprecedented cascade strategy, used in conjunction with a redox isomerization, for the synthesis of 3-allyl pyrroles is reported. In a single step, readily accessible simple starting materials are transformed into highly substituted pyrroles with high efficiency. The products obtained contain allyl substituents, which can be readily elaborated to other useful functional groups. The reaction proceeds through an unusual (3 + 2) cycloaddition/skeletal rearrangement/redox isomerization pathway.

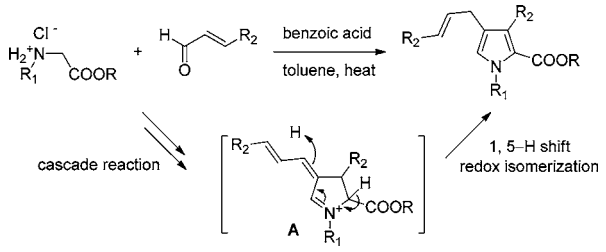


Pyrroles are ubiquitous as scaffolds of bioactive natural products, therapeutic agents, and functional materials.[1] Although numerous approaches for their preparation have been documented, including traditional "named reactions" and recently developed multicomponent coupling and metal promoted reactions,[2−4] some limitations still exist. Many established methods require preassembled precursors, elaborately designed substrates, or multiple synthetic operations. Additionally, only limited chemical diversity is typically accessible. Thus, the direct assembly of pyrroles, particularly polysubstituted pyrroles, from readily available starting materials in a single step operation remains an important research objective.

Within the contest of atom economy,[5] step economy,[6] and redox economy,[7] the assembly of valuable structures from simple materials is of high importance in modern synthetic chemistry and medicinal chemistry. Redox isomerization via hydride shift, which employs perfect atom economy and redox economy by avoiding additional steps of oxidation or reduction, has emerged as a powerful strategy for the synthesis of heterocycles and the direct functionalization of relatively unreactive C−H bonds.[8] Recently, the applications of redox isomerization in pyrrole synthesis have been accomplished by several research groups, representative examples including the redox amination reactions of carbonyls with pyrrolidines/pyrrolines[9] and the [4C+1N] cyclization of 4-acetylenic ketones with primary amines.[10] In addition, the development of cascade reactions, which allow for the formation of several bonds in a single step operation without isolating intermediates or adding additional reagents, has become a widely utilized complexity-generating strategy to achieve atom and step economy.[11] We envisioned that combining a redox isomerization and cascade reaction into a reaction sequence would represent an intriguing strategy to increase synthetic efficiency. Herein, we report an unprecedented cascade reaction, used in conjunction with redox isomerization, for the synthesis of polysubstituted pyrroles from readily accessible materials in a single step.

Our hypothesis for the synthesis of polysubstituted pyrroles is depicted in Scheme 1. We envisioned that the cascade reaction between an α,β-unsaturated aldehyde and a simple α-amino ester could furnish intermediate **A**, which could lead to the formation of a tetrasubstituted pyrrole through redox isomerization via a 1,5-hydride shift. Although the above design is conceptually viable and could allow for the generation of chemically diverse pyrroles from simple starting materials, we envisioned that controlling the reactivity of the highly reactive iminium species and directing those simple starting materials to the desired intermediate **A** would be of great importance.

Scheme 1. Pyrrole Synthesis via Cascade Reaction



A model reaction between cinnamaldehyde (**1a**) and *N*-methyl glycine methyl ester hydrochloride (**2a**)[12] was carried out first to identify the optimized reaction parameters (Table 1). To our delight, under acidic, neutral, and basic conditions, we observed the formation of the desired product **3a**, albeit in low yields (entries 1−4). The structure of **3a** was unambiguously confirmed by X-ray analysis. The use of benzoic acid alone without neutralization of the HCl salt led to the

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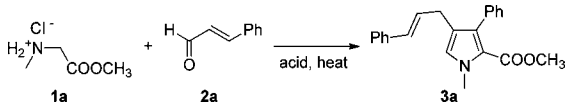
Table 1. Optimization of Reaction Conditions[a]



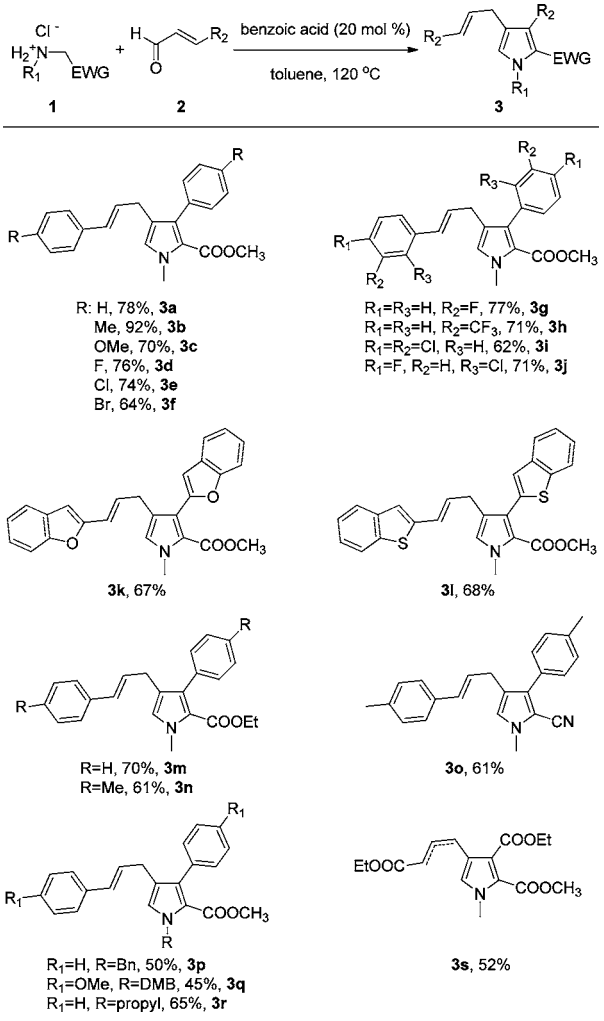
entry	additive	solvent	yield (%)[b]
1	none	toluene	35
2	0.5 equiv of K_2CO_3	toluene	53
3	1.0 equiv of K_2CO_3	toluene	40
4	0.5 equiv of K_2CO_3	toluene	44
	1.0 equiv of PhCOOH		
5	1.0 equiv of PhCOOH	toluene	70
6	1.0 equiv of PhCOOH	toluene	20[c]
7	1.0 equiv of AcOH	toluene	59
8	1.0 equiv of TFA	toluene	30
9	1.0 equiv of *p*-TsOH·H_2O	toluene	19
10	1.0 equiv of 4-NO_2-PhCOOH	toluene	34
11	1.0 equiv of 2-F-PhCOOH	toluene	43
12	1.0 equiv of $ZnCl_2$	toluene	trace
13	1.0 equiv of PhCOOH	DMF	31
14	1.0 equiv of PhCOOH	DMSO	trace
15	**0.2 equiv of PhCOOH**	**toluene**	78[d]

[a]Reaction conditions: A mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol) in 3.5 mL of solvent was heated to 110 °C in the presence of additive(s) for 24 h in a sealed pressure tube. [b]Isolated yield after silica gel chromatography. [c]Using the free amine instead of the HCl salt as the substrate. [d]The reaction was carried out at 120 °C.

formation of pyrrole with good yield (entry 5). In contrast, using the free amine instead of the HCl salt as the substrate gave a poor yield, presumably due to the decreased stability and enhanced reactivity of the amino ester (entry 6). It should be noted that the direct utilization of the commercially available and more stable HCl salt further simplifies the synthetic operation and renders the method more practical. Other Bronsted or Lewis acids produced inferior results (entries 7–12). Switching the solvent to DMF, DMSO, and many others failed to give synthetically useful yields of product (entries 13, 14). Ultimately, using less benzoic acid (20 mol %) as the additive at 120 °C further improved the reaction yield to 78% (entry 15). Attempts to decrease the molar ratio of **1a** and **2a** provided the product in lower yield (0.6:1, 61% yield). Thus, using an excess amount of **1a** is essential to drive the reaction to complete, and the yields are calculated based on the limiting reagent **2a**.

The generality and scope of the cascade process was next investigated (Scheme 2). Under optimized reaction conditions, a variety of α,β-unsaturated aldehydes proved to be efficient substrates, generating tetrasubstituted pyrroles in good yields. Various aryl substitution patterns (2,3,4-substituted phenyl) and electronic properties (both electron-donating and -withdrawing substituents) were well tolerated. Heterocycles containing α,β-unsaturated aldehydes were suitable substrates as well, and the one-step cascade process could incorporate three heterocycles into the products. The corresponding amino ethyl ester and amino nitrile could also participate in the cascade reaction with good yields. Substituents on nitrogen could be varied by the incorporation of longer chain and protecting groups (i.e., **3p**, **3q**, **3r**). It should be mentioned that the introduction of a benzyl or 2,4-dimethoxy benzyl protecting group could potentially allow further functionalization on the nitrogen. The reaction with alkyl α,β-unsaturated aldehydes generally did not proceed well, but a carboxylic ester could be

Scheme 2. Generality and Scope of the Cascade Reaction



introduced into the product, albeit with a mixture of two isomers (**3s**, 1,5-H shift vs 1,7-H shift).[13] In general, the one-step cascade processes allow for the successful transformation of simple materials into polysubstituted pyrroles, which are not easily accessed by known methods.

A plausible reaction mechanism for the synthesis of polysubstituted pyrroles is depicted in Scheme 3. The condensation of the α,β-unsaturated aldehyde and secondary amine results in the formation of the iminium **B** (*E* or *Z* isomer or equilibrium between them), which could enter two different pathways. In pathway 1, the iminium **B** undergoes electrocyclization to generate enamine **C**.[14] Subsequent 1,2-addition and dehydration leads to the formation of intermediate **A**. Alternatively, in pathway 2, the iminium **B** participates in a (3 + 2) cycloaddition[15] with a second equivalent of α,β-unsaturated aldehyde to generate intermediate **D**, which could undergo a skeletal rearrangement through elimination and iminium formation to furnish the same intermediate **A**. Ultimately, tetrasubstituted pyrrole could be accessed from **A** through a redox isomerization via a 1,5-hydride shift.

To differentiate these two reaction pathways, control experiments were designed and carried out (Scheme 4). We discovered that the (3 + 2) cycloaddition between *N*-methyl glycine methyl ester and an α,β-unsaturated aldehyde could be catalyzed by zinc chloride and produced compound **4** as a major isomer. While the (3 + 2) cycloaddition between

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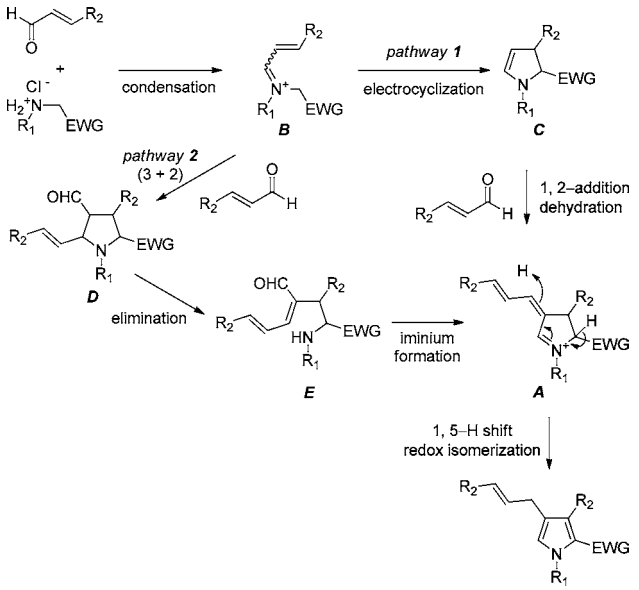
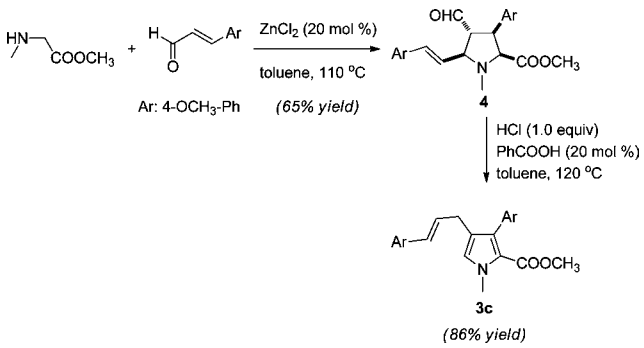
Scheme 3. Proposed Reaction Mechanism



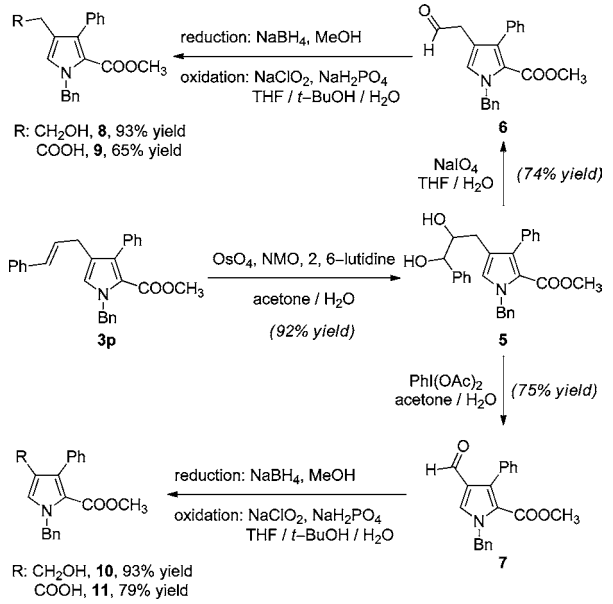
Scheme 4. Control Experiments for Mechanism Validation



azomethine ylides and alkenes is a well-known process, to our surprise, this particular coupling described here has not been described before. Under our standard conditions employing HCl and benzoic acid as additives, **4** was smoothly converted to the polysubstituted pyrrole **3c** in high yield. As we failed to prepare a substrate resembling intermediate **C** (Scheme 3) due to the stability issues, we cannot completely rule out the electrocyclization pathway. However, at this stage we prefer reaction pathway 2 as shown in Scheme 3.

These one-step cascade reactions also allow for the incorporation of different substituents onto the pyrrole ring system, including an allyl group that serves as a versatile handle for the introduction of other functional groups. To demonstrate the synthetic potential and lay the foundation for the construction of pyrrole-based small molecule libraries through diversity oriented synthesis, several synthetic transformations were investigated to convert the allyl group into other functional groups using **3p** (Scheme 5). For example, **5** was obtained by dihydroxylation reaction of **3p** in the presence of a catalytic amount of OsO_4 and NMO. From diol **5**, using different oxidative cleavage conditions, aldehyde **6** and **7** were prepared in good yields. The generation of **7** is quite unusual and presumably involves a benzylic oxidation followed by oxidative cleavage. From **6** and **7**, the aldehydes were successfully converted into other important functional groups, such as alcohols (i.e., **8** and **10**) and carboxylic acids (i.e., **9** and

Scheme 5. Transformation of Allyl Group into Other Functional Groups



11). The versatile reactivities of these groups, coupled with the well-established cross-coupling strategies for the elaboration of pyrroles,[16] potentially enables the generation of chemically diverse pyrroles in a controlled manner.

In conclusion, we have developed a cascade reaction for the synthesis of polysubstituted pyrroles. This one-step operation allows for the efficient assembly of highly substituted pyrrole ring systems from simple starting materials. The reaction proceeds through an unprecedented (3 + 2) cycloaddition/skeletal rearrangement/redox isomerization pathway. The significance of pyrrole scaffolds as structural elements in natural products chemistry and drug discoveries should render this strategy attractive for both synthetic and medicinal chemistry. We expect this new transformation will lay the foundation for the efficient chemical synthesis of pyrrole containing natural products and small molecule libraries, while also demonstrating the virtues of redox cascade processes.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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