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# Base-Promoted Oxidative Dearomatization of Pyrroles to 4-Pyrrolin-2-ones

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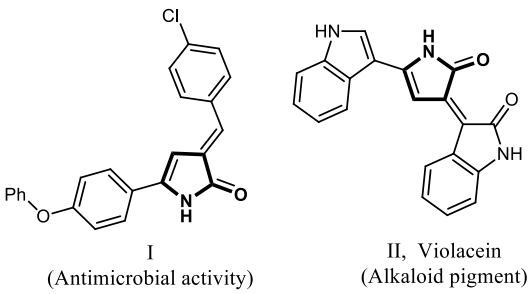
**Abstract.** A base-promoted oxidative dearomatization of substituted pyrroles for the synthesis of 3,3-disubstituted 4-pyrrolin-2-ones under mild reaction conditions is described. A cascade aerobic oxidation/semipinacol rearrangement reaction was involved, and the desired products bearing a quaternary carbon center were efficiently prepared using molecular oxygen ($O_2$) as an ideal oxidant.

**Keywords:** dearomatization; aerobic oxidation; semipinacol rearrangement; cascade reaction; 4-pyrrolin-2-one

4-Pyrrolin-2-ones (β,γ-unsaturated γ-lactams) constitute an important class of nitrogen heterocycles and are found as key structural motifs in many valuable biologically active molecules and natural products (as illustrated in Figure 1).[1] Moreover, 4-pyrrolin-2-ones are also versatile building blocks for the synthesis of pyrroles[2] and chiral auxiliaries.[3] Accordingly, a great deal of efforts has been devoted to the construction of these core structures.[4] However, reported approaches mainly rely on intramolecular cyclization or intermolecular annulation with prefunctionalized acyclic precursors. As such, there is still a need for more general methods to construct 4-pyrrolin-2-ones from readily available aromatic starting materials.

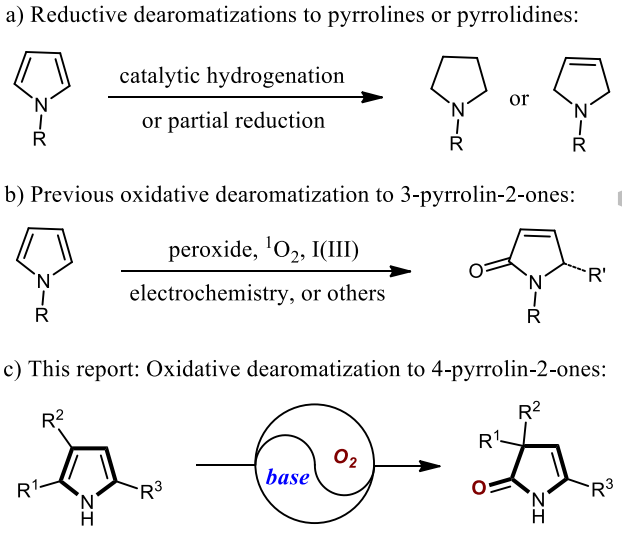



I
(Antimicrobial activity)

II, Violacein
(Alkaloid pigment)

**Figure 1**. Representative examples of 4-pyrrolin-2-ones.

Conceptually, heterocyclic dearomatization can be a powerful strategy for the preparation of carbo- and heterocyclic rings owing to the inherent reactivity of the cyclic system.[5] This can be exemplified by the ability of pyrrole, the stable and readily available nitrogen-containing five-membered aromatic heterocycle, to undergo partial reduction to pyrrolines or catalytic hydrogenation to pyrrolidines (Scheme 1a).[6] Recently, oxidative dearomatization of pyrrole has also been applied to yield 3-pyrrolin-2-one with the use of peroxide, singlet oxygen, hypervalent iodine reagents, or electrochemical approaches (Scheme 1b).[7] However, due to the reactive nature of this molecule it often undergoes decomposition or uncontrolled polymerization under oxidative conditions,[8] and oxidative dearomatization of pyrrole for the efficient synthesis of 4-pyrrolin-2-one under mild conditions is rarely reported.[9] In our continuing interest in base-mediated heterocyclic synthesis,[10] herein we report a base-promoted oxidative dearomatization of pyrroles to substituted 4-pyrrolin-2-ones (Scheme 1c). In this reaction, a base-promoted cascade aerobic oxidation/semipinacol



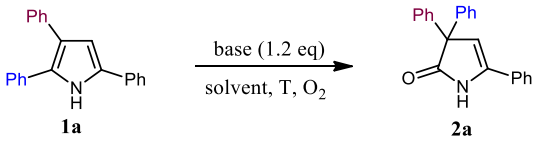

**Scheme 1.** Dearomatization reactions of pyrroles.

rearrangement reaction was involved, and molecular oxygen ($O_2$) was used as an ideal oxidant.[11]

Initially, 2,3,5-triphenyl-1H-pyrrole **1a**, which could be easily prepared from benzylamine and 1,3-diphenylprop-2-yn-1-one,[12] was selected as a model substrate to evaluate the feasibility of the proposed reaction in the presence of a base/$O_2$ system. To our delight, the reaction indeed proceeded smoothly in DMSO and the desired 4-pyrrolin-2-one **2a** was afforded in 72% yield (Table 1, entry 1). The structure of **2a** was confirmed by single crystal X-ray diffraction,[13] and only the substituent at C-2 was found to undergo rearrangement to provide the final product. Other DMSO-tailored heterogeneous base systems were subsequently investigated and the combination of NaO*t*Bu and DMSO turned out to be the most efficient for this transformation (Table 1, entries 2-7). DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), an organic base, was also tested but found to be less effective (Table 1, entry 8). Further solvent screening showed that DMSO was a more competent solvent than DMF, $CH_3CN$, toluene, and dioxane (Table 1, entries 9-12). Decreasing the reaction temperature resulted in increased yields (Table 1, entries 13-14). A 91% yield of the desired product was achieved when the reaction was carried out at room temperature (RT, 25 °C). Remarkably, a respectable 81% yield of **2a** was achieved when the reaction was carried out under air (Table 1, entry 15). However, under an atmosphere of $N_2$, no reaction occurred (Table 1, entry 16), indicating $O_2$ was crucial for this transformation. Finally, the standard reaction conditions for the base-promoted synthesis of the 4-pyrrolin-2-one derivatives were identified as follows: 1.2 equiv. of NaO*t*Bu as the additive and DMSO as the solvent under an atmosphere of $O_2$ for 4 hours (Table 1, entry 14).

With the established oxidative dearomatization conditions in hand, we then investigated the substrate scope of pyrroles in terms of functional group

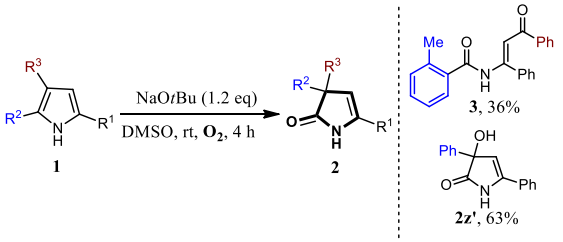
**Table 1.** Optimization of reaction conditions.[a]




| Entry | Solvent | Base | Temp (°C) | t (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | DMSO | KO*t*Bu | 60 | 2 | 72 |
| 2 | DMSO | NaO*t*Bu | 60 | 1 | 82 |
| 3 | DMSO | LiO*t*Bu | 60 | 2 | 71 |
| 4 | DMSO | KOH | 60 | 2 | 73 |
| 5 | DMSO | NaOH | 60 | 1 | 79 |
| 6 | DMSO | LiOH | 60 | 2 | 80 |
| 7 | DMSO | $Cs_2CO_3$ | 60 | 12 | 45 |
| 8 | DMSO | DBU | 60 | 12 | 18 |
| 9 | DMF | NaO*t*Bu | 60 | 12 | 16 |
| 10 | $CH_3CN$ | NaO*t*Bu | 60 | 12 | N.R. |
| 11 | Toluene | NaO*t*Bu | 60 | 12 | N.R. |
| 12 | dioxane | NaO*t*Bu | 60 | 12 | N.R. |
| 13 | DMSO | NaO*t*Bu | 40 | 3 | 83 |
| **14** | **DMSO** | **NaO*t*Bu** | **RT** | **4** | **87(91)** |
| 15[c] | DMSO | NaO*t*Bu | RT | 12 | 81 |
| 16[d] | DMSO | NaO*t*Bu | RT | 12 | 0 |

[a] Conditions: **1a** (0.2 mmol), base (0.24 mmol), solvent (1 mL), under an atmosphere of $O_2$.
[b] By GC, isolated yield in bracket.
[c] Under air.
[d] Under an atmosphere of $N_2$.

**Table 2.** Substrate scope.

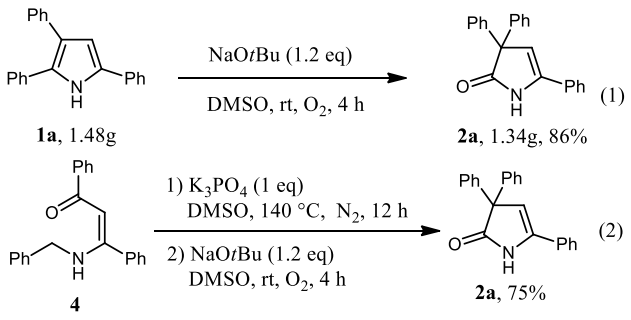



| Entry | $R^1$ | $R^2$ | $R^3$ | 2 | Yield (%) |
|---|---|---|---|---|---|
| 1 | Ph | Ph | Ph | **2a** | 91 |
| 2 | 4-$MeC_6H_4$- | Ph | Ph | **2b** | 93 |
| 3 | 3-$MeC_6H_4$- | Ph | Ph | **2c** | 95 |
| 4 | 2-$MeC_6H_4$- | Ph | Ph | **2d** | 93 |
| 5 | 4-$MeOC_6H_4$- | Ph | Ph | **2e** | 95 |
| 6 | 4-$FC_6H_4$- | Ph | Ph | **2f** | 91 |
| 7 | 4-$ClC_6H_4$- | Ph | Ph | **2g** | 88 |
| 8 | Thiophen-3- | Ph | Ph | **2h** | 85 |
| 9 | Ph | 4-$MeC_6H_4$- | Ph | **2i** | 89 |
| 10 | Ph | 4-$FC_6H_4$- | Ph | **2j** | 87 |
| 11 | Ph | 4-$ClC_6H_4$- | Ph | **2k** | 85 |
| 12 | Ph | 4-$MeOC_6H_4$- | Ph | **2l** | 88 |
| 13 | Ph | 4-*t*$BuC_6H_4$- | Ph | **2m** | 83 |
| 14 | Ph | 4-$CF_3C_6H_4$- | Ph | **2n** | 61 |
| 15 | Ph | 2-$MeC_6H_4$- | Ph | **2o** | 0 |
| 16 | Ph | Thiophen-2- | Ph | **2p** | 89 |
| 17 | Ph | Me | Ph | **2q** | 65 |
| 18 | Ph | Ph | 4-$MeC_6H_4$- | **2r** | 98 |
| 19 | Ph | Ph | 2-$MeC_6H_4$- | **2s** | 97 |
| 20 | Ph | Ph | 4-$FC_6H_4$- | **2t** | 95 |
| 21 | Ph | Ph | 4-$MeOC_6H_4$- | **2u** | 92 |
| 22 | Ph | Ph | 4-*t*$BuC_6H_4$- | **2v** | 86 |
| 23 | Ph | Ph | Naphthalen-2- | **2w** | 88 |
| 24 | Ph | Ph | Thiophen-2- | **2x** | 92 |
| 25 | Ph | Ph | Cyclohexyl- | **2y** | 89 |
| 26 | Ph | Ph | H | **2z** | 0 |

diversity and substitution pattern. As illustrated in Scheme 2, when $R^1$ was an aryl substituent, the reaction proved to be tolerant of different substituents on the aromatic core. Aryl substituents bearing either electron-rich or electron-deficient groups were tolerated, and afforded the desired products in excellent yields (**2a**-**2h**, 85–95%). Pyrroles substituted with halogens (F and Cl) afforded the corresponding 4-pyrrolin-2-ones in good yields (**2f** and **2g**, 88-91% yields), which could be applied in further functionalization. When $R^1$ is a heteroaryl group, such as 3-thienyl, the reaction still could proceed smoothly and gave the heterocycle product **2h** in 85% yield. Unfortunately, when $R^1$ was an alkyl group or H, the substrates decomposed and no product could be obtained.

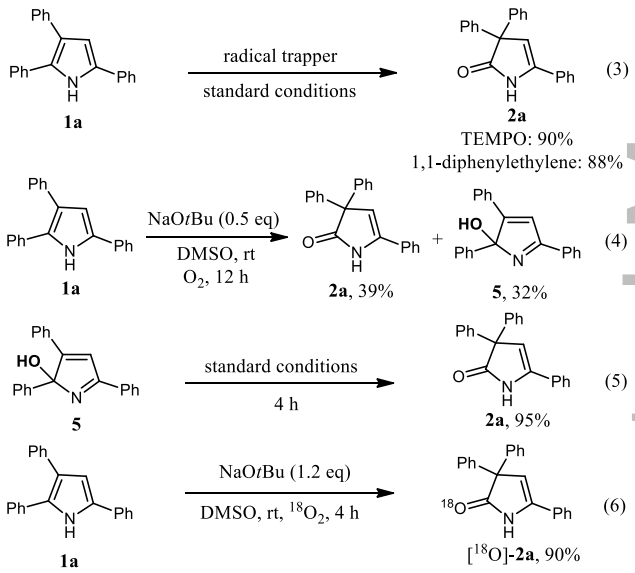
When $R^2$ and $R^3$ were aryls, pyrroles **1** with both electron-withdrawing and electron-donating groups, such as methyl, methoxy, *tert*-butyl, and fluoro,trifluoromethyl, afforded the corresponding 4-pyrrol-in-2-ones in appreciable yields (**2i**–**2n** and **2r**–**2v**, 61–98%). Halogens were also tolerated, leading to the halogenated products in excellent yields (**2j**–2**k**, **2t**, 85–95%). When fused aryl and heteroaryl substituted pyrroles were used, the corresponding 4-pyrrolin-2-ones were furnished efficiently (**2p**, **2w**–**2x**, 88–92% yields). It is worth mentioning that when $R^3$ was *o*-methylphenyl and $R^2$ was phenyl, the reaction proceeded smoothly and provided the desired product **2s** in 97% yield. In contrast, when $R^2$ was *o*-methylphenyl and $R^3$ was phenyl, the same product **2o** was not observed, only *N*-acyl enaminone **3** from Witkop-type oxidation[14] was obtained in 36% yield. Moreover, when $R^2$ or $R^3$ was an alkyl group, the reaction could still process well and provide the corresponding products **2q** and **2y** in 65% and 89% yield, respectively. Notably, when 2,5-diphenyl-1H-pyrrole was employed as a substrate ($R^3$ = H), a 3-hydroxy-4-pyrrolin-2-one product **2z'** was obtained by the further aerobic oxidation of designed 4-pyrrolin-2-one **2z**.[15] When $R^2$ was H, the substrate decomposed.

To prove the practicality of this base-promoted cascade reaction, a gram-scale synthesis of 4-pyrrolin-2-one **2a** was carried out. When 1.48 g of 2,3,5-triphenyl pyrrole **1a** (5 mmol) was loaded, 1.34 g of the **2a** could be obtained in 86% yield (Scheme 2, eq 1).Since the pyrroles can be easily prepared from *N*-benzyl enaminones,[12] the "one-pot" strategy to synthesize **2a** direct from enaminone **4** was explored to further make this reaction more attractive. Upon addition of NaO*t*Bu to the crude mixture derived from the reaction of enaminone **4**, 4-pyrrolin-2-one **2a** could be isolated in a 75% overall yield (Scheme 2, eq 2).



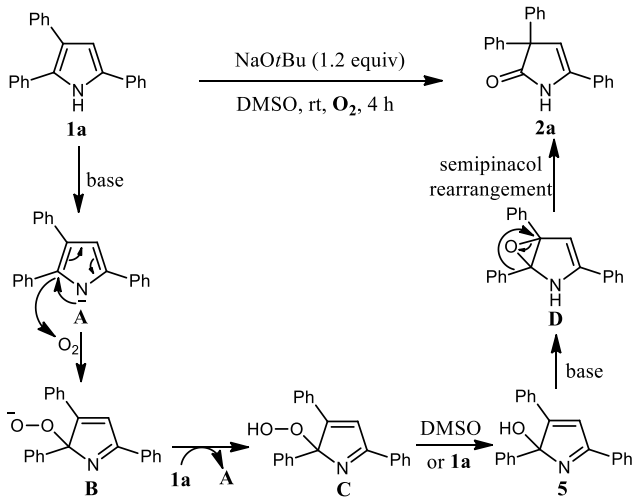

**Scheme 2.** Large-scale and "one-pot" synthesis of **2a**.

To better understand this base-promoted cascade aerobic oxidation/semipinacol rearrangement reaction, we conducted control experiments. As shown in Scheme 3, the radical scavengers, TEMPO (2,2,6,6-tetramethylpiperidinooxy) and 1,1-diphenylethylene, did not influence this reaction (Scheme 3, eq 3), which indicated that a radical pathway might not be involved in this reaction.[9b, 16] When 0.5 equiv. of NaOtBu was used as an additive, a 2H-pyrrol-2-ol intermediate **5** could be isolated in 32% yield (Scheme 3, eq 4). The structure of **5** was confirmed by X-ray single-crystal diffraction [13]. The reaction of **5** under the standard conditions gave the desired 4-pyrrolin-2-one product **2a** in 95% yield, suggesting the crucial intermediate **5** was generated *in-situ* and involved in this cascade reaction (Scheme 3, eq 5). Finally, the $^{18}O$ labeling experiment proved that the oxygen atom in the final product originated from molecular oxygen (Scheme 3, eq 6).




**Scheme 3.** Control experiments.

On the basis of the aforementioned observations and previous reports,[17-18] a tentative mechanism for this oxidative dearomatization of pyrrole was proposed, as depicted in Scheme 4. Initially, pyrrole **1a** undergoes a base-initiated deprotonation to produce anion **A**. **A** reacts through C-2 with oxygen and then extracts a proton from **1a** to generate the hydroperoxide **C**. Reduction of **C** by DMSO or substrate **1a** give the intermediate **5**.[17] Base-promoted 1,4-addition of **5** produce epoxy intermediate **D**, and the final 4-pyrrolin-2-one **2a** was formed by a semipinacol type rearrangement.[18]




**Scheme 4**. Proposed mechanism.

In conclusion, an efficient base-promoted cascade approach to substituted 4-pyrrolin-2-ones from readily available pyrroles under metal-free conditions has been developed. A novel cascade aerobic oxidation/semipinacol rearrangement was involved in this transformation. This protocol employed 1 atm of molecular oxygen as the ideal oxidant and could proceed well at room temperature, making this method sustainable and environmentally friendly.

## Experimental Section

A mixture of pyrroles **1** (0.5 mmol) and NaO*t*Bu (0.6 mmol, 1.2 equiv.) in DMSO (2 mL) was stirred in room temperature (25 °C) under an atmosphere of $O_2$ for 4 h (monitored by TLC). Then $H_2O$ was added and the resultant was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were dried over $Na_2SO_4$ and concentrated. Then solvent was evaporated and the residue was purified by silica gel flash chromatography (EtOAc/PE: 1/8) to give 4-pyrrolin-2-ones **2**.

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# Base-Promoted Oxidative Dearomatization of Pyrroles to 4-Pyrrolin-2-ones

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