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Bioinspired Construction of a Spirocyclohexadienone Moiety via Sodium Nitrite Catalyzed Aerobic Intramolecular Oxidative Phenol Coupling

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ABSTRACT

An efficient and green intramolecular oxidative phenol coupling for the direct construction of spirocyclohexadienones has been developed, which uses environment-friendly sodium nitrite as the catalyst and oxygen in the air as the terminal oxidant. Hydroxy-containing substituted phenanthrenes and dibenzoazepines could be easily obtained from the dienone–phenol rearrangement.

Intramolecular oxidative phenol coupling has long been recognized as the key step in the biosynthesis of phenolic alkaloids and other natural products (Scheme 1),[1] among which amaryllicaceae,[2] morphine and aporphine,[3] and phenanthroindolizidine alkaloids[4] were widely examined. The biogenesis of these natural products has inspired a number of elegant total syntheses[5] and led to extensive exploration of oxidizing reagents, mainly focusing on heavy metal reagents such as Tl(III),[6] Fe(III),[7] Pb(IV),[8] and V(V) salts.[9] In the past two decades, a nonmetal oxidizing reagent, a hypervalent iodine(III) reagent, has also been widely explored and applied in the oxidative coupling reactions.[10] However, large excess amounts of usage (at least stoichiometric equivalent), high toxicity, severe conditions, and/or low yield also largely limited their applications, especially

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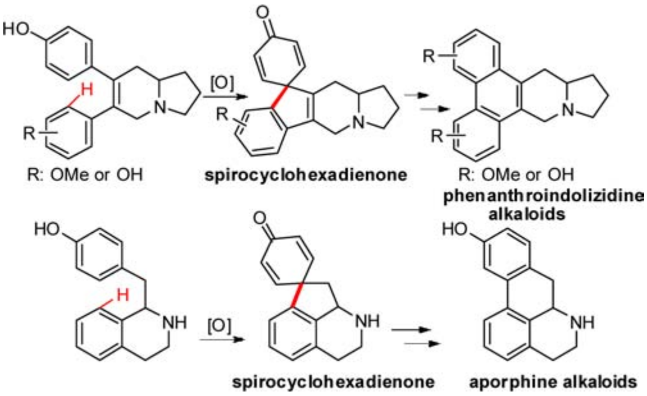
Scheme 1. Oxidative Phenol Coupling and Dienone−Phenol Rearrangement in the Biosynthesis of Phenanthroindolizidine and Aporphine Alkaloids

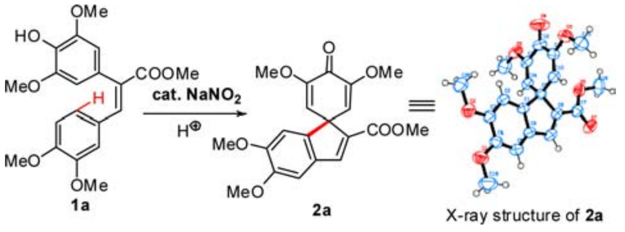


when the concepts of environmental friendliness and atom economy were taken into consideration. In addition, the nonenzymic analog of this reaction in the laboratory often results in large amounts of polymeric materials. In the past decade, great effort has been focused toward the catalytic version of hypervalent idion reagents, but auxiliary oxidants are also indispensable.[11] Therefore, a catalytic oxidative phenol coupling reaction is very appealing but is also very challenging.

Spirocyclohexadienone, containing a quaternary carbon center, is of high importance and ubiquitously presented in many bioactive molecules. Because it was also proposed to be a key intermediate in the biosynthesis of some natural occurring products, much attention has been given to the direct construction through oxidative phenol coupling reactions.[12] Recently, we reported a novel sodium nitrite catalyzed aerobic oxidative coupling of phenol ether derivatives, in which polymethoxyl-substituted phenanthrenes and biaryls could be synthesized efficiently.[13] As a continuation of our interest in developing efficient and environmentally benign catalytic oxidative coupling reactions, we report herein on the construction of a spirocyclohexadienone moiety using sodium nitrite as the catalyst and oxygen in the air as the terminal oxidant at room temperature.

Initially, substrate **1a** was selected to investigate suitable reaction conditions, and the results are summarized in Table 1. It was found that spirocyclohexadienone **2a** (confirmed by single crystal X-ray diffraction analysis) was obtained in 86% yield when 0.2 equiv of $NaNO_2$ in TFA was used in the presence of air, while no desired product was detected when AcOH was used (entries 1 and 2). To make the reaction conditions much milder and to decrease byproducts, different solvents were screened, among which CH_2Cl_2 showed the best result (entries 3−7). The concentration effect of the trifluoacetic acid on the oxidative coupling reaction was not very significant (entries 8 and 9); 49% desired product **2a** could also be obtained when only 5 equiv of trifluoacetic acid was used (entry 10). When the usage of $NaNO_2$ was reduced to 0.1 equiv, a relatively long reaction time was needed (entry 11). But if the reaction was run under an atmosphere of oxygen, 0.02 equiv of $NaNO_2$ is sufficient (entry 12), which demonstrates the fact that the concentration of oxygen is of high importance for both the rate and efficiency of the reaction. Byproducts increased when the reaction was run at a lower temperature (entry 13), and only trace amounts of the desired product were obtained (entry 14) when the much stronger acid TfOH was used.

Table 1. Optimization of Conditions^{a}



entry	$NaNO_2$ (equiv)	solvents (6 mL)	time (min)	conv^{b} (%)	yield^{b} (%)
1	0.2	TFA	20	100	86
2	0.2	AcOH	20	100	0
3	0.2	DMF/TFA 5:1	20	100	2
4	0.2	EtOAc/TFA 5:1	20	100	33
5	0.2	toluene/TFA 5:1	20	100	89
6	0.2	MeCN/TFA 5:1	20	100	90
7	0.2	DCM/TFA 5:1	20	100	96
8	0.2	DCM/TFA 1:1	20	100	95
9	0.2	DCM/TFA 23:1	35	100	93
10	0.2	DCM/TFA 79:1	35	70	49
11	0.1	DCM/TFA 5:1	35	100	90
12^{c}	0.02	DCM/TFA 5:1	10	100	97
13^{d}	0.2	DCM/TFA 5:1	20	100	79
14	0.2	DCM/TfOH 5:1	20	100	5

^{a} General reaction conditions: **1a** (187 mg, 0.5 mmol), solvents (6 mL), at room temperature and under an atmosphere of air unless noted. ^{b} Conversion and yield were determined by HPLC. ^{c} Reaction was carried out under an atmosphere of O_2. ^{d} Reaction was carried out at 0 °C.

With the optimized reaction conditions in hand, the substrate scope was briefly investigated first (Scheme 2). Substrates **1a**−**1f**, which have two methoxyl groups on the phenol, were found to react smoothly and give the corresponding spirocyclohexadienones **2a**−**2f** in good to excellent yields. With only one methoxyl group on the phenol, substrates **1g**−**1j** also gave the desired products **2g**−**2j** efficiently, but substrate **1k**, of which the lower aryl is less nucleophilic, only gave the desired coupled product in 22%

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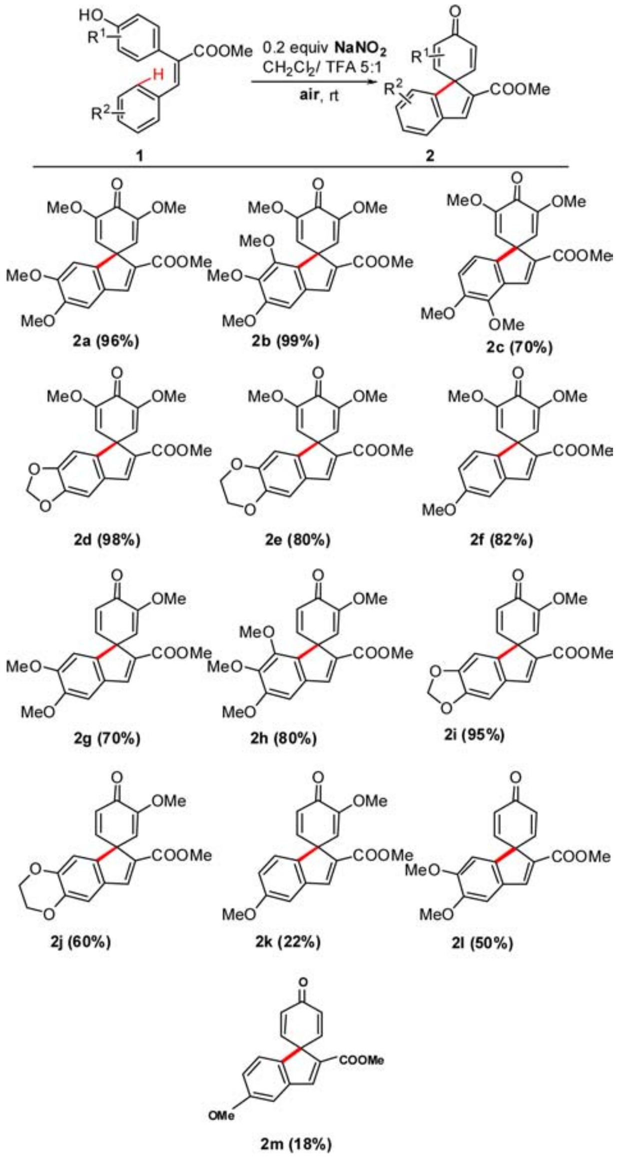
yield. Similar results were also observed for substrate **1l** and **1m**. As can be seen from the results above, the electron-donating substituents on both the phenol and the lower aryl are highly important for the reaction, and the influence of the oxy substituents on the phenol was crucial for the formation of the desired spirocyclohexadienones.

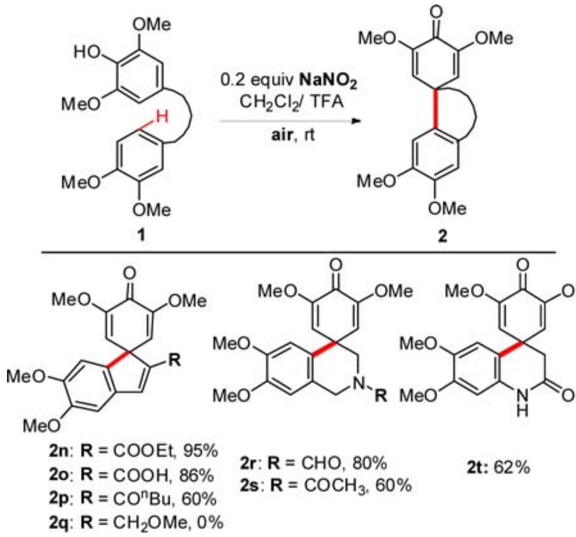
Scheme 2. Effects of Oxy Substituents on the Aryls[a]



[a] Unless otherwise noted, the reaction was carried out with **1** (0.5 mmol) and solvents (6 mL), and yields in the parentheses referred to isolated yields.

Furthermore, the influence of the tether between the phenol and the lower aryl on the reaction was also investigated (Scheme 3). It was found that when the tether is ethylene, an electron-withdrawing group at the double bond is necessary. Substrates **1n**–**1p** worked well to give the spirocyclohexadienones **2n**–**2p** respectively in good yields, while substrate **1q** gave complex unidentified byproducts. It is worth noting that ***Z*-1a** could also give the desired spirocyclohexadienone **2a** in 50% yield (not shown, see Supporting Information), which suggests the configuration of the alkene has little effect on the reaction. The reaction of substrates **1r**–**1t**, which contain a nitrogen in the tether, also proceeded smoothly and offered valuable nitrogen-containing spirocyclohexadienones **2r**–**2t** respectively in good yields.

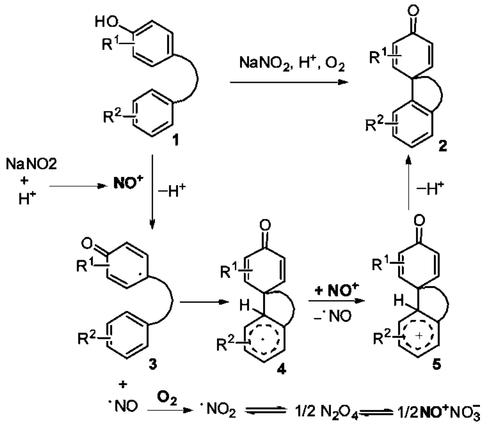
Scheme 3. Effects of Tether between Aryls[a]



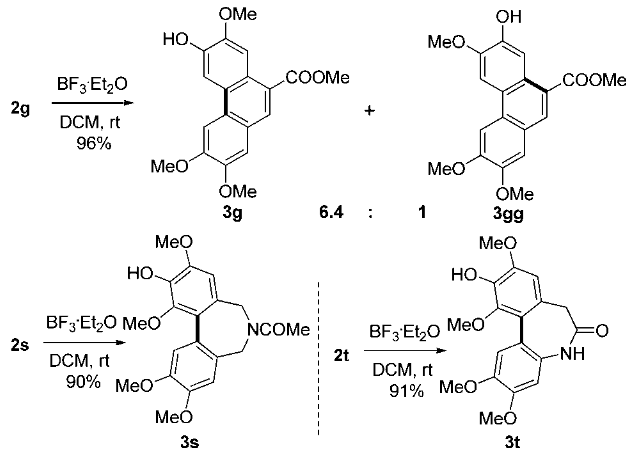
[a] Unless otherwise noted, the reaction was carried out with **1** (0.5 mmol) and solvents (6 mL), and yields in the parentheses referred to isolated yields.

On the basis of the preliminary studies, a plausible mechanism for the present oxidative coupling was proposed in Scheme 4. The reaction proceeds with a typical radical mechanism via the one-electron transfer from substrate **1** to the NO^+ cation and subsequent deprotonation, giving hexadienone radical **3** and a NO radical. Radical intermediate **4**, which results from intramolecular radical attack of species **3**, was further oxidized and deprotonated to give spirocyclohexadienone **2**.

Scheme 4. Plausible Mechanism for the Oxidative Phenol Coupling Reaction



Scheme 5. Spirocyclohexadienone−Phenol Rearrangement



Spirocyclohexadienone−phenol rearrangement has also been a well-known biogenetic process (Scheme 1) and contributes greatly to the structural diversity of natural products.[1−4] Spirocyclohexadienone **2g** was selected to investigate the rearrangement (Scheme 5). Among the Lewis acids and Brønsted acids screened for promoting the reaction, $BF_3 \cdot Et_2O$ was found to be the best choice, resulting in 3-hydroxyphenanthryl ester **3g** (formed via aryl migration) and 4-hydroxyphenanthryl ester **3gg** (formed through alkenyl migration) in 96% combined yield. **2s** and **2t**, when subjected to the same conditions, gave two valuable dibenzoazepines **3s** and **3t** in excellent yield respectively. It is noteworthy that the construction of seven-membered dibenzoazepines usually required multiple steps, often involving palladium catalyzed biaryl coupling as one of the key steps.[14]

In summary, the bioinspired sodium nitrite catalyzed oxidative phenol coupling for the direct construction of the spirocyclohexadienone moiety was developed using O_2 in the air as the terminal oxidant at room temperature. The resulting spirocyclohexadienones could lead to diverse valuable scaffolds via Lewis acid catalyzed hexadienone−phenol rearrangement.

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Supporting Information Available. Detailed experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for compounds **1a**−**1t**, **2a**−**2t**, **3g**, **3gg**, **3s**, and **3t**; crystal structure data and cif file for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.