A Novel Sodium Nitrite-Catalyzed Oxidative Coupling for Constructing Polymethoxyphenanthrene Rings

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Abstract: An efficient and green oxidative coupling for the direct construction of polymethoxyphenanthrene rings has been developed, which uses environment-friendly sodium nitrite as catalyst and oxygen as terminal oxidant. This methodology also provides an alternative possibility for forming biaryl products.

Keywords: biaryl products; oxidative coupling reaction; phenanthroindolizidines; polymethoxyphenanthrenes; sodium nitrite

Phenanthrene ring derivatives and biaryl linkages widely exist in natural products, pharmaceuticals, agrochemicals, dyes, organic materials, and many other important organic molecules.^[1] Among them polymethoxy-substituted phenanthroindolizidine and phenanthroquinolizidine alkaloids (Figure 1) exhibit many interesting and potent pharmacological activities.^[2] In the past decades, radical cyclization and transition metal-catalyzed coupling reactions were com-



als, and atom efficiency into consideration. Several direct oxidative coupling reagents have been developed, which include thallium(III) trifluoroacetate (TTFA),^[5] lead(IV) tetraacetate $[Pb(OAc)_4]$,^[6] vanadium oxytrifluoride (VOF₃) or vanadium oxytrichloride $(VOCl_3)$,^[7] hypervalent iodine,^[8] and 2,3-dichloro-5,6-dicyanobenzoquinone(DDQ).^[9] However, large excess amounts of oxidative reagents (at least stoichiometric equivalent), high toxicity, severe conditions, and/or low yields, also largely limit their applications. Recently, we applied the less toxic iron(III) chloride (3.5 equiv.) and catalytic iron(III) chloride (together with 1 equiv. of m-CPBA) for the construction of a phenanthrene ring and biaryls,^[10] which partly solved the problems. Nevertheless, the development of a more greener and efficient method for the construction of the phenanthrene ring is still in high demand. NO⁺ is a remarkable and diverse reagent, which is

monly used for constructing phenanthrene ring.^[3,4]

However, these reactions need prefunctionalized sub-

strates which, to a large extent, limited their applica-

tions. Direct oxidative coupling of two unfunctional-

lized arenes to form biaryls and a phenanthrene ring

would be much more attractive when taking the sim-

plicity of manual work, availability of starting materi-

commonly applied in nitrosation,^[11] nitration,^[12] oxygenation,^[13] and addition to alkenes to yield oximes, isooxazolines and imidazoles^[14]. NO⁺ is also a rather strong one-electron oxidant (1.5 V vs. SCE) and this had led to its use in the formation of cation radical intermediates.^[15] Using NO⁺ as catalyst, Neumann and co-workers reported the alkylation of arenes with alkenes,^[16] and Tanaka and colleagues reported the coupling of naphthalene derivatives^[17]. It is well known that NO⁺ could be easily produced by treatment of NaNO₂ with a Brønsted acid. Inspired by these reports, we envisioned that NaNO₂ could be applied to

Figure 1. Representatives of phenanthroindolizidine and phenanthroquinolizidine alkaloids.

the oxidative coupling reaction for constructing the phenanthrene ring.

Herein, we wish to report the first $NaNO_2$ -catalyzed oxidative coupling reaction for construction of the phenanthrene ring using O_2 as terminal oxidant.

Due to the importance of polymethoxyphenanthrene derivatives in the natural product field, especially in the synthesis phenanthroindolizidine and phenanthroquinolizidine alkaloids, methyl-(E)-2,3bis(3,4-dimethoxyphenyl)acrylate **1a** was selected to investigate suitable reaction conditions for the intramolecular oxidative coupling reaction. The results are summarized in Table 1.

The desired product 2a was obtained in 85% yield when 0.05 equivalents of NaNO₂ in TFA was used in the presence of air (Table 1, entry 5). With increasing amounts of NaNO₂, complex by-products increased drastically (entries 1–5). To make the reaction conditions much milder and to decrease the by-products, different solvents were screened (Table 1, entries 6–13). Among these solvents, only CH_2Cl_2 and CH_3CN could give the coupled product **2a**. Extensive investigation (entries 12–21) showed that a 99% yield of the desired product **2a** was obtained when the reaction was performed in TFA/CH₃CN (1:4), at 0°C and 20% NaNO₂ (entry 17). It is worth noting that when the reaction was carried at room temperature, no significant increase of the by-products was observed (entries 19 and 20). Entries 22–24 show that O₂ is the terminal oxidant in the reaction, and NaNO₂ is indispensable. The concentration effect on the coupling reaction is not very significant, and the corresponding data are summarized in the Supporting Information (Table 1).

With the optimal reaction conditions in hand, we started to study the substrate scope. Firstly, we investigated the effects of the substitutes at the double

Table 1. Optimization study of the NaNO₂-catalyzed intramolecular coupling reaction.^[a]



Entry	NaNO ₂ (equiv.)	Solvent (10 mL)	Temperature [°C]	Time [min]	Conversion ^[b] [%]	Yield ^[b] [%]
1	1	TFA	0	15	98	24
2	0.5	TFA	0	15	100	34
3	0.2	TFA	0	15	100	31
4	0.1	TFA	0	15	100	69
5	0.05	TFA	0	15	99	85
6	0.2	TFA/THF (1:1)	0	30	12	0
7	0.2	TFA/AcOEt (1:1)	0	30	8	0
8	0.2	TFA/dioxane (1:1)	0	30	0	0
9	0.2	TFA/acetone (1:1)	0	30	0	0
10	0.2	TFA/EtOH (1:1)	0	30	0	0
11	0.2	TFA/DMSO (1:1)	0	30	0	0
12	0.2	TFA/CH_2Cl_2 (1:1)	0	30	100	66
13	0.2	TFA/CH_3CN (1:1)	0	15	100	68
14	0.1	TFA/CH_2Cl_2 (1:4)	0	15	100	87
15	0.1	TFA/CH_2Cl_2 (1:9)	0	15	93	93
16	0.2	TFA/CH ₃ CN (1:4)	0	15	84	82
17	0.2	$TFA/CH_{3}CN(1:4)$	0	30	100	99
18	0.2	TFA/CH ₃ CN (1:9)	0	60	12	12
19	0.2	$TFA/CH_3CN(1:4)$	r.t.	15	100	96
20	0.1	TFA/CH ₃ CN (1:4)	r.t.	15	100	94
21	0.05	$TFA/CH_3CN(1:4)$	r.t.	15	63	58
22 ^[c]	0.2	$TFA/CH_{3}CN(1:4)$	0	15	100	99
23 ^[c]	0	TFA/CH_3CN (1:4)	0	15	0	0
24 ^[d]	0.2	$TFA/CH_{3}CN(1:4)$	0	15	39	39

^[a] General reaction conditions: **1a** (180 mg, 0.5 mmol); under an atmosphere of air unless noted.

^[b] Conversion and yield were determined by HPLC.

^[c] Reaction was carried out under an atmosphere of O₂.

^[d] Reaction was carried out under an atmosphere of Ar.

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Table 2. Effects of substituents at the double bond on the re-

Entry	Substrate	Product	Time	Yield ^[b]
1	1a: R = COOMe	2a	15 min	99%
2	1b: R = COOH	2b	30 min	91%
3	1c: $R = COCH_3$	2c	20 min	95%
4	1d: R = CO- <i>n</i> -Bu	2d	20 min	92%
5	(<i>Z</i>)- 1b: R = COOH	2b	30 min	99%
6	(Z)-1e: R = CN	2e	60 min	73%
7 ^[c]	1f: $R = CH_2OCH_3$	2f	10 min	84%
8 ^[c]	1g: $R = CH_3$	2g	30 min	29%

^[a] Unless otherwise noted, the reaction was carried out with **1** (0.5 mmol) and the solvent (10 mL).

^[b] The yield refers to isolated product.

^[c] The reaction was performed in TFA/CH₃CN (1:19).

bond (Table 2). Substrates 1a-d (entries 1–4), which have an electron-withdrawing group at the double bond, were found to react smoothly and form the corresponding coupled products 2a-d in excellent yields. (Z)-1b and (Z)-1e (entries 5 and 6) also gave the coupled products, which suggests that the configuration of the double bond has no effect on the reaction. It is noteworthy that when R is a strong electron-donating group (entry 7), the desired coupled product could also be obtained, while other reported oxidative re-

Table 3. Effects of oxy substituents on the phenyls.^[a]

agents (such as FeCl₃, MnO_2 , *m*-CPBA and so on) could not give the coupled product. When R is a poor electron-donating group (entry 8), only 29% of the coupled product was obtained and the other part of the substrate converted to unindentifiable compounds, which is believed to be due to the small difference in reactivity and low selectivity between the two aryls.

Different polyoxy-substituted substrates were tested due to the common presence and importance of oxy substituents in alkaloids (Table 3). Entries 1-5 illustrate that electron-donating substituents on both aryls are extremely important. Substrate 1k (entry 4) with only two methoxy groups on the phenyl did not react due to the drastically decreased reactivity. It is interesting that when substrate 11 (entry 5) was tested for the coupling reaction, besides 51% of coupled product, 29% of further intermolecular coupled product 211^[18] was also obtained, which was because of the increased reactivity. And it should be noted that substrates which contain other electron-rich groups such as thiols and amines on the phenyls were not suitable for the coupling reaction. Because thiol groups are easily oxidized and amine groups would be protonated under the acidic coupling reaction conditions, this would make the aryls become electron-deficient.

Encouraged by this exciting result, we applied this oxidative coupling reaction to the construction of polymethoxybiaryls (Table 4). The results showed that aryls with two or more methoxy groups could give the coupled products in moderate to good yields. Less reactive substrates could also furnish the coupled products (**2o** and **2p**) when a much stronger acid (CF_3SO_3H) was used. It is worth noting that some other substrates such as methoxybenzene, toluene, benzene and chlorobenzene, which are much less re-

COOMe

	1	2		
Entry	Substrate	Product	Time	Yield ^[b]
1	1h: $R^1 = R^2 = OCH_2CH_2O; R^3 = H; R^4 = R^5 = OMe$	2h	20 min	93%
2	1i: R^{1} , $R^{2} = OCH_{2}O$; $R^{3} = H$; $R^{4} = R^{3} = OCH_{2}O$	2i	30 min	92%
3	1j: R^{1} , $R^{2} = OCH_{2}CH_{2}O$; $R^{3} = H$; R^{4} , $R^{3} = OCH_{2}CH_{2}O$	2j	30 min	73%
4	1k: $R^{1} = R^{2} = OMe; R^{3} = R^{4} = R^{3} = H$	2k	60 min	0%
5	11: $R^{1} = R^{2} = R^{3} = R^{4} = R^{3} = OMe$	21	60 min	51%

20% NaNO₂, air TFA/CH₃CN (1:1) r.t.

^[a] Unless otherwise noted, the reactions were carried out with $\mathbf{1}$ (0.5 mmol) and the solvent (10 mL).

COOMe

^[b] The yield refers to isolated product.



 Table 4. NaNO₂-catalyzed intermolecular oxidative coupling reaction.^[a]

^[a] Unless otherwise noted, the reactions were carried out with 1 (1 mmol), 2 equiv. CF₃SO₃H, CH₃CN (10 mL) as solvent, and the yield refers to isolated product.

^[b] The reaction was performed in TFA/CH₃CN (1:9).

active, did not give coupled products under the present conditions due to their low reactivity.

On the basis of these preliminary studies, the reaction mechanism for the present oxidative coupling was proposed as shown in Scheme 1. The reaction proceeds with a typical radical mechanism^[10b] via the one-electron transfer from substrate 1 to the NO⁺ cation, giving radical cationic species 3 and NO radical. The newly formed radical cationic species 3 undergoes electrophilic attack to another phenyl ring and then deprotonation. The oxidation of the NO



Scheme 1. Plausible mechanism for the $NaNO_2$ -catalyzed oxidative coupling/deprotonation step to form radical 4, which gave the aryl-aryl coupled product 2 after reoxidation.

radical with O_2 forms the NO_2 radical after electron transfer of the NO^+ cation with the aryl, and the NO^+ cation can be regenerated through equilibrium as illustrated in Scheme 1.

In conclusion, we have developed an NaNO2-catalyzed oxidative coupling for the direct construction of the the phenanthrene ring using O_2 in the air as terminal oxidant at room temperature in good to excellent yields. Compared with previous methods, the present system has the following significant advantages: (i) the use of much more cheaper and less toxic $NaNO_2$ as catalyst; (ii) the oxidant (O_2 in the air) is really green and environment-friendly; (iii) the product is much easier to be separated from the reaction mixture and less contaminated by heavy metal and/or organic oxidant; (iv) this is the first truely catalytic oxidative coupling for the construction of phenanthrene. Further applications of the methodology in organic synthesis are currently being studied in our laboratory.

Experimental Section

General Procedure for the NaNO₂-Catalyzed Intramolecular Coupling Reaction (1a as an Example)

To the solution of **1a** (0.5 mmol, 179 mg) in TFA/CH₃CN (1:4) (10 mL) was added NaNO₂ (0.1 mmol, 6.9 mg) under an atmosphere of air. The mixture was stirred at room temperature for 15 min, and then aqueous saturated Na₂CO₃ was added until pH7 was achieved. Water (10 mL) was added to the mixture which was then extracted with dichloromethane (10 mL×3). The combined organic phase was washed with water, brine, and then concentrated under vacuum. The product was further purified by flash chromatography on silica gel to give **2a** as a white solid; yield: 176 mg (99%); mp 201–203 °C. ¹H NMR (CDCl₃, 400 MHz): δ =8.65 (s, 1H), 8.43 (s, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.27 (s, 1H), 4.14 (s, 3H), 4.13 (s, 3H), 4.08 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H).

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- [18] We proposed **2l** was formed through intramolecular coupling, then **2l** was converted to **2ll** by further intermolecular oxidative coupling.

