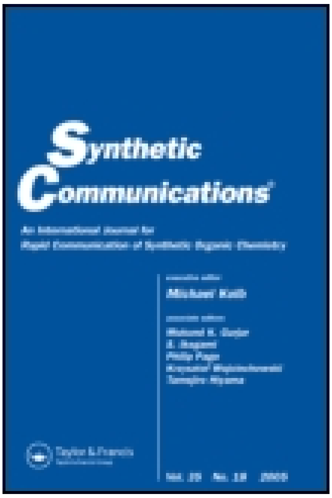

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Metal-Free-Catalyzed Oxidative Trimerization of Indoles Using $NaNO_2$ to Construct Quaternary Carbon Centers: Synthesis of 2-(1H-Indol-3-yl)-2,3′-biindolin-3-ones

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METAL-FREE–CATALYZED OXIDATIVE TRIMERIZATION OF INDOLES USING $NaNO_2$ TO CONSTRUCT QUATERNARY CARBON CENTERS: SYNTHESIS OF 2-(1*H*-INDOL-3-YL)-2,3′-BIINDOLIN-3-ONES

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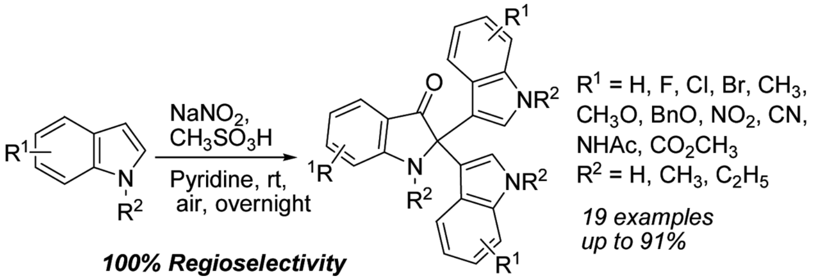
GRAPHICAL ABSTRACT



Abstract *A simple, convenient, and efficient synthesis of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives via a transition-metal-free-catalyzed oxidative trimeric reaction of indoles has been developed. This transformation may have occurred through a tandem oxidative homocoupling reaction by using $NaNO_2$ in pyridine as oxidant. This methodology provides an alternative approach for the direct generation of all-carbon quaternary centers at the C2 position of indoles.*

Keywords Indole; quaternary carbon; trimerization

INTRODUCTION

Indolin-3-ones with a chiral center at the 2-position are encountered in a large variety of natural products and can be used in the total synthesis of biologically active alkaloids.[1–3] For example, 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one **1** (Figure 1) was isolated as the product of indole oxidation by a strain of *Claviceps purpurea*.[3a] This compound has also been characterized from natural (bacterial) sources such as *Vibrio*

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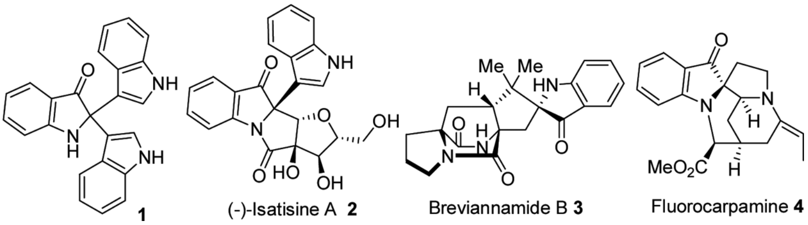


Figure 1. Representative natural products with a 2,2′-disubstituent indolin-3-one structural unit.

parahaemolyticus[2a] and *Haemophilus influenzae*.[3b] In addition, isatisine A **2**, an oxindole system having indole 2-substituents, is present in the roots and leaves of *Isatis indigotica* Fort. (Cruciferae). This biennial herbaceous plant is widely cultivated in China and eastern Asia for the prevention and treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis.[4] Therefore, developing convenient methods for the construction of 2,2-disubstituted indolin-3-ones are of considerable interest.[2d,4b,5] In 2008, Ganachaud and coworkers reported the biocatalytic synthesis of **1** by trimerization of indole.[6a] However, the chemical synthesis of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one **1** and its derivatives from indoles has been rarely reported.[6b,c]

Recently, we have developed a biomimetic synthetic method for the trimerization of indoles using 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) in air as oxidant with excellent regioselectivity under mild conditions.[7] However, extensive study in this group revealed several drawbacks: First, substrates with a strong electron-withdrawing group, such as NO_2 and CN, could not be applied. Second, the high loading of TEMPO is required (0.7 equiv). Third, a long reaction time of 3 days is needed. Thus, the development of new strategy for the oxidative trimerization of indoles continues to be of considerable interest.

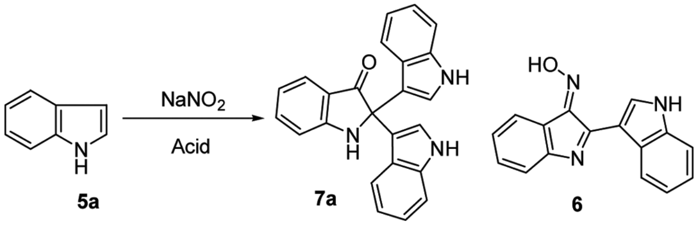
It is well known that $NaNO_2$ has been recently used as a transition-metal-free catalyst for aerobic transformations of organic compounds.[8] Inspired by these reports, we envisioned that $NaNO_2$ could be applied to the oxidative trimeric reaction of indoles. We report herein on the construction of all-carbon quaternary centers at the C2 position of indoles using sodium nitrite as the oxidant at room temperature.

RESULTS AND DISCUSSION

As a substrate for optimization studies we chose indole **5a**. Preliminary screening of Lewis acids and solvents allowed us to identify benzoic acid in CH_3CN as promising conditions for the trimeric reaction of indole at room temperature. However, dimer **6** was observed as major side product in the reaction mixture (Table 1, entry 1).[9] Changing benzoic acid to TsOH or carrying out the reaction in other solvents was also not encouraging (Table 1, entries 2–8). To our delight, when we treated **5a** with $NaNO_2$ and TsOH in the presence of pyridine at rt, a significant improvement was realized, because **7a** was the main product under the reaction conditions (Table 1, entry 9).

Based on these promising initial results we decided to optimize the reaction conditions further to increase the reaction yield, and the results are summarized in

Table 1. Optimization of the reaction conditions[a]



Entry	Acid (mmol)	Solvent	Yield (%)[b] **7a/6**
1	Benzoic acid (0.5)	CH_3CN	Trace/48
2	TsOH (0.5)	CH_3CN	25/40
3	TsOH (0.5)	THF	21/42
4	TsOH (0.5)	Xylene	Trace/29
5	TsOH (0.5)	1,4-Dioxane	17/36
6	TsOH (0.5)	$CHCl_3$	Trace/25
7	TsOH (0.5)	DMF	30/36
8	TsOH (0.5)	DMSO	32/31
9	TsOH (0.5)	Pyridine	65/10
10	TsOH (0.5)	Trimethylamine	16/45
11	TsOH (0.5)	Diisopropylamine	13/42
12	TsOH (0.5)	Aniline	36/34
13	TsOH (0.5)	*N*,*N*-Dimethyl aniline	35/27
14	TsOH (0.5)	Imidazole	29/46
15	Oxalic acid (0.5)	Pyridine	55/30
16	CF_3CO_2H (0.5)	Pyridine	63/23
17	HBF_4 (0.5)	Pyridine	65/27
18	CH_3SO_3H (0.5)	Pyridine	78/trace
19	CH_3SO_3H (0.3)	Pyridine	72/trace
20	CH_3SO_3H (0.7)	Pyridine	80/0
21	CH_3SO_3H (0.9)	Pyridine	84/0
22	CH_3SO_3H (1.0)	Pyridine	87/0
23	CH_3SO_3H (1.1)	Pyridine	82/0

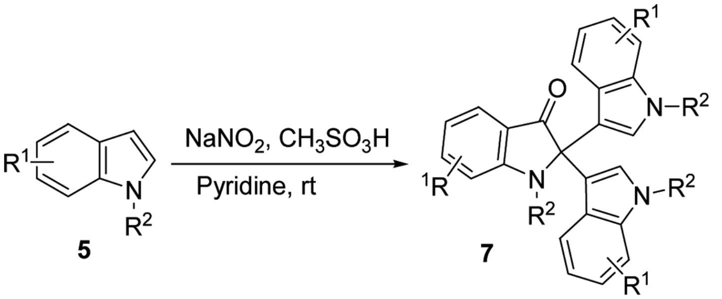
[a] Reaction conditions: indole (0.5 mmol), $NaNO_2$ (0.5 mmol), and solvent (0.6 mL) at rt for overnight.
[b] Isolated yield.

Table 1. The study revealed that the amine as solvent was crucial for this transformation. Pyridine gave the best outcome and other amines, such as trimethylamine, diisopropylamine, aniline, *N,N*-dimethyl aniline, and imidazole, resulted in poor yields (Table 1, entries 9–14). In addition, acid additive was critical to the trimeric reaction. Thus, different acid additives were screened to improve the yield. CH_3SO_3H was proven to be the best for the transformation of **5a**, because **7a** was obtained in 78% yield under the reaction conditions (Table 1, entry 18), whereas other acid additives such as oxalic acid, CF_3CO_2H, or HBF_4 under the similar reaction conditions resulted in the formation of **6** (Table 1, entries 15–17). With regards to the amount of CH_3SO_3H used, it was also established that 2 equivalents of CH_3SO_3H was indeed the preferred amount with more or less loading giving poor yields (Table **1**, entries 19–23). Our best conditions for the oxidative trimeric reaction of indole were, therefore, 100 mol% $NaNO_2$ and 200 mol% CH_3SO_3H in pyridine at rt (Table 1, entry 22).

After the establishment of optimized reaction conditions, we extended this new protocol to substituted indoles. A variety of representative indole derivatives were subjected to the optimized conditions, as depicted in Table 2. Thus, a trimeric reaction of substituted indoles proceeded smoothly to provide corresponding 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives in moderate to excellent yields. The reaction can tolerate a variety of functional groups at the 1, 4, 5, 6, and 7 positions of indoles, such as F, Cl, Br, CH_3, CH_2CH_3, CH_3O, BnO, NHAc, CO_2CH_3, and NO_2, providing opportunities for further synthetic elaboration.

It was found that the electronic nature of the substituents on the indole ring did not play a key role. Both electron-donating and electron-withdrawing indoles were readily converted to the corresponding products in moderate to excellent yields. We were delighted to note that the substrates with a strongly electron-withdrawing group, such as NO_2, smoothly underwent the reaction to afford corresponding

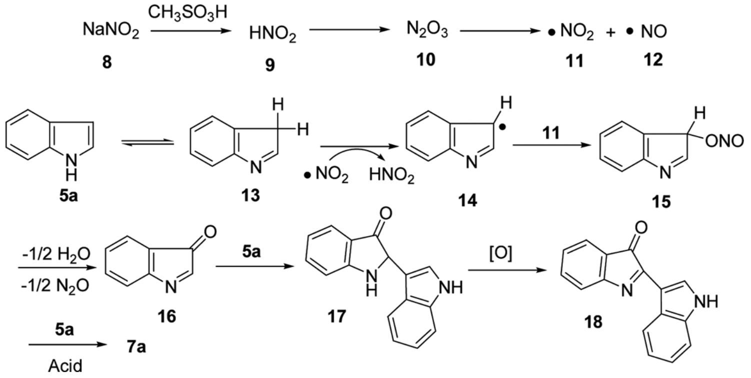
Table 2. Trimeric reaction of indoles by using $NaNO_2$ in air as oxidant[a]



Entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	**7a**	87
2	5-Br	H	**7b**	80
3	5-F	H	**7c**	73
4	5-CH_3	H	**7d**	77
5	**5**-OCH_3	H	**7e**	63
6	5-OBn	H	**7f**	66
7	5-NHAc	H	**7g**	91
8	5-CO_2CH_3	H	**7h**	78
9	5-NO_2	H	**7i**	56
10	5-CN	H	**7j**	49
11	6-CI	H	**7k**	61
12	6-F	H	**71**	78
13	6-CO_2CH_3	H	**7m**	71
14	**7**-CH_3	H	**7n**	63
15	**7**-OCH_3	H	**7o**	68
16	7-NO_2	H	**7p**	43
17	**4**-OCH_3	H	**7q**	67
18	H	CH_3	**7r**	60
19	H	CH_2CH_3	**7s**	51

[a] Reaction conditions: indole (0.5 mmol), $NaNO_2$ (0.5 mmol), CH_3SO_3H (1.0 mmol), pyridine (0.6 mL), rt.

[b] Isolated yield.



Scheme 1. Plausible pathway for the formation of **7a**.

products in moderate yields. For example, 5-nitro-1*H*-indole was transformed into trimer **7i** in 56% yield (Table 2, entry 9). In our previous work on oxidative trimeric reaction of indoles,[7] the efficiency of this transformation is highly dependent upon the electronic properties of R^1 groups. Electron-rich groups showed better results than electron-withdrawing groups in this trimerization. In contrast, the strongly electron-withdrawing group, NO_2, totally inhibited the process.

Based on these preliminary results and previous study,[10] a tentative pathway for the formation of **7a** is proposed in Scheme 1. The first step is indolenine tautomer **13** reacts with $\cdot NO_2$ generated from HNO_2, leading to the formation of radical intermediate **14**. A coupling reaction between **14** and nitrogen dioxide (through its oxygen atom) would lead to indol-3-one **16**. Subsequently, the highly reactive species **16** is trapped by second indole molecule to give dimer **17**, which is further oxidized (likely by $NaNO_2$) to result in the formation of dimer **18**. Finally, a CH_3SO_3H-catalyzed nucleophilic addition of third indole molecule to dimer **18** affords compound **7a**.

CONCLUSIONS

In summary, we have developed an operationally simple and efficient method to construct all-carbon quaternary centers at the C2 position of indoles via a transition-metal-free-catalyzed oxidative trimeric reaction of indoles. It is noteworthy that the substrates with strongly electron-withdrawing group, such as NO_2, smoothly underwent the reaction to afford corresponding products in moderate yields. Moreover, it is highly regioselective (2,3′-linkage). Importantly, the broad group tolerance made this method useful to construct such unique scaffolds from commercially available indole and its derivatives.

EXPERIMENTAL

General Procedure for the Preparation of 2-(1*H*-Indol-3-yl)-2,3′-biindolin-3-ones

CH_3SO_3H (1.0 mmol) was added to a solution of indole (0.5 mmol) and $NaNO_2$ (0.5 mmol) in pyridine (0.6 mL) in air and the mixture was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:2) to yield the corresponding product.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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