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Methylsulfonic Acid Adsorbed on Silica Gel as a Solid Acid for Dimerization of Indoles: A Convenient Synthesis of 2,3'-Bi(3H-indol)-3-one Oximes

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METHYLSULFONIC ACID ADSORBED ON SILICA GEL AS A SOLID ACID FOR DIMERIZATION OF INDOLES: A CONVENIENT SYNTHESIS OF 2,3'-BI(3*H*-INDOL)-3-ONE OXIMES

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GRAPHICAL ABSTRACT



Abstract A simple, convenient, and efficient approach for the synthesis of (E)-2,3'-bi(3Hindol)-3-one oxime derivatives has been developed. The methodology is based on a three-component coupling reaction of indoles and sodium nitrite using a silica-supported methylsulfonic acid as solid acid. The practical utility of this three-component coupling reaction has been demonstrated in the gram-scale dimerization of indole.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource: Full experimental and spectral details.]

Keywords Biindoles; CH₃SO₃H-SiO₂; indoles; tandem reaction; three-component coupling reaction

INTRODUCTION

Indole derivatives are important compounds that are widespread in nature and exhibit significant biological activity.^[1] For example, the bis-indole alkaloid indirubin **1** and its analogs (collectively referred to as indirubins) were among the early cyclin-dependent kinase (CDK) inhibitors to be discovered.^[2] Indirubins can be found in various indigo dye-producing plants (more than 200 species) (Fig. 1).^[3]

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Figure 1. Structure of some bisindole alkaloids.

Moreover, indirubin is the active ingredient of a traditional Chinese medicine recipe, "Danggui Longhui Wan," used to treat various diseases including chronic myelocytic leukemia.^[3] Bisindole alkaloids **2a–c** were isolated from field-collected fruiting bodies of the myxomycete *Perichaena chrysosperma*, and compound **2a** was shown to have hedgehog signal inhibitory activity (Figure 1).^[4] In addition, isatisine A **3** (Figure 1), 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 East Asia for the prevention and treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis.^[5]

Thus, the development of new methods for accessing unique biindole derivatives for new leads in drug and material discovery is still highly desirable. Various attempts have been made to construct biindolyl scaffolds.^[6–9] Among various methods, the oxidative dimerization of indoles has been well investigated.^[6] Recently, some progress on construction of the 2,3'-linked and 3,3'-linked biindolyl scaffolds was made, including the palladium- or copper-catalyzed intermolecular coupling reaction^[7] and iodine-induced dimerization of indoles.^[8] For example, Shi and coworkers reported the oxidative homo dimerization of *N*-protected and free indole derivatives toward 3,3'-linked biindolyl scaffolds via Pd-catalyzed direct C-H transformations.^[7d] However, most of these procedures require expensive metal catalysts and high loading of metal oxidants.^[8]

With the demand for green chemistry, solid-supported reagents have gained much prominence because of their environmental benefits and easy separation of the products.^[10] In the past several years, some Brønsted acids, such as HBF_4 ,^[11] $HClO_4$,^[12] and $TfOH^{[13]}$ have been successfully supported on silica gel and applied as solid acids in various catalytic reactions. However, the study of methylsulfonic acid supported on silica gel is still very rare.^[14]

RESULTS AND DISCUSSION

Recently, we reported the highly regioselective preparation of 2-(1H-indol-3-yl)-2,3'-biindolin-3-one derivatives starting from indoles by using 2,2,6,6-tetramethylpiperidine N-oxyl radical (TEMPO) in air as an environmentally benign oxidant.^[15]

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As a part of our ongoing project aimed at developing environmentally benign chemical transformations, herein we report the successful one-pot, three-component coupling of indoles with sodium nitrite for the construction of various (E)-2,3'-bi(3H-indol)-3-one oximes by using a silica-supported methylsulfonic acid as solid acid.

Initially, the reaction of indole with sodium nitrite in the presence of HBF₄ was screened to obtain the optimized reaction conditions. A mixture of indole (0.5 mmol), HBF₄ (0.5 mmol), and sodium nitrite (0.6 mmol) in CH₃CN was stirred at room temperature for 10 h. As expected, the desired coupling product **5a** was obtained in 37% isolated yield (Scheme 1), and the major by-product of this reaction came from the dimer **6** and trimer **7**.

To improve the reaction yield and limit the formation of by-products, different protic acids were screened, and the results are summarized in Table 1. As depicted in Table 1, methylsulfonic acid was optimal, with which the highest yield of 73% was obtained (Table 1, entry 4). Interestingly, phenylsulfonic acid afforded the product in poor yield (Table 1, entry 7), whereas TsOH afforded the product in moderate yield (Table 1, entry 2).

With the demand for green chemistry, solid supporters such as silica gel have attracted lots of attention in recent decades, because the heterogeneous reaction provides for easy separation of the products without tedious experimental workup. In view of the corrosive and fuming problems of CH_3SO_3H , we prepared the silica gel-supported CH_3SO_3H . To our surprise and pleasure, an important improvement was observed when CH_3SO_3H -SiO₂ was used as a solid acid, because **5a** was obtained in 85% yield (Table 1, entry 5). Finally, the influence of the amount of CH_3SO_3H -SiO₂ was also evaluated. As shown in Table 1 (entries 10–14), the amount of CH_3SO_3H -SiO₂ used in the reaction was 1.1 equiv CH_3SO_3H -SiO₂ (Table 1, entry 12).

In addition, the choices of solvent are also critical to the three-component coupling reaction. Pyridine was proved to be the best for the formation of 5a, with which the greatest yield of 89% was obtained (Table 1, entry 12). When CHCl₃ or CCl₄ was employed as the reaction solvent, the desired 5a was obtained in a lower yield of 33% and 21%, respectively (Table 1, entries 18 and 19). However, when the reaction solvent was changed from pyridine to dicyclohexylamine (DCHA) or dibenzylamine, no product was observed (Table 1, entries 20–21).



Scheme 1. Reaction of indole with sodium nitrite in the presence of HBF₄.

Table 1. Optimization of the reaction conditions^a



Entry	Acid (equiv)	Solvent	Yield (%) ^b
1	HBF ₄ (1)	Pyridine	62
2	TsOH (1)	Pyridine	48
3	$CF_3CO_2H(1)$	Pyridine	65
4	$CH_3SO_3H(1)$	Pyridine	73
5	CH_3SO_3H -SiO ₂ (1) ^c	Pyridine	85
6	HOAc (1)	Pyridine	Trace
7	$PhSO_3H(1)$	Pyridine	10
8	$PhCO_2H(1)$	Pyridine	0
9	SiO_2 (10)	Pyridine	0
10	CH ₃ SO ₃ H-SiO ₂ (0.5)	Pyridine	45
11	CH_3SO_3H -SiO ₂ (0.8)	Pyridine	76
12	CH ₃ SO ₃ H-SiO ₂ (1.1)	Pyridine	89
13	CH_3SO_3H -SiO ₂ (1.2)	Pyridine	86
14	CH_3SO_3H -SiO ₂ (1.3)	Pyridine	81
15	CH_3SO_3H -Si O_2 (1.1)	CH ₃ CN	41
16	CH_3SO_3H -SiO ₂ (1.1)	THF	6
17	CH_3SO_3H -Si O_2 (1.1)	EtOH	5
18	CH_3SO_3H -SiO ₂ (1.1)	CHCl ₃	33
19	CH_3SO_3H -Si O_2 (1.1)	CCl ₄	21
20	CH_3SO_3H -SiO ₂ (1.1)	DCHA ^d	0
21	CH_3SO_3H - SiO_2 (1.1)	Dibenzylamine	0

^aReaction conditions: indole (0.50 mmol), NaNO₂ (0.60 mmol), rt.

^bIsolated yield.

^cCH₃SO₃H adsorbed on silica.

^dDicyclohexylamine.

Finally, the desired product **5a** was obtained in 89% isolated yield under the typical conditions, that is, 1.0 equiv of indole and 1.2 equiv of NaNO₂ as substrates and 1.1 equiv of CH_3SO_3H -SiO₂ as solid acid. Pyridine was the reaction solvent at room temperature in the air.

With the optimal reaction conditions in hand, the substrate scope of indoles for this three-component coupling was examined. The results are summarized in Table 2. From Table 2 it was found that various substrates were converted into the corresponding products in good to excellent yields, with the molecular structure of **5b** confirmed by x-ray crystallography (Fig. 2). As depicted in Fig. 2, the values of the N(1) = C(7) bond length (1.313 Å) and N(3) = C(8) bond length (1.273 Å) are consistent with the localization of the double bond.

The method turned out to be tolerant toward a broad range of functional groups at the 4, 5, 6, and 7 positions of indoles, such as halogen, nitrile, amide, ester, ether, or amine. For the substituted indoles, the electronic effect of the

Table 2. Reaction scope of indoles with $NaNO_2^a$



Entry	R	Ν	Time (h)	Yield $(\%)^b$
1	Н	5a	10	89
2	5-Br	5b	24	62
3	5-F	5c	24	60
4	5-CH3	5d	10	91
5	5-OCH3	5e	10	92
6	5-OBn	5f	10	89
7	5-NH2	5g	10	78
8	5-NHAc	5h	10	85
9	5-NO2	5i	24	54
10	5-CN	5i	24	68
11	5-CO ₂ CH ₃	5k	24	76
12	6-F	51	24	67
13	6-Cl	5m	24	77
14	7-Cl	5n	24	62
15	7-CH ₃	50	10	90
16	7-OCH ₃	5p	10	95
17	7-OBn	5q	10	91
18	4-CH ₃	5r	10	72

 $^{a}Reaction$ conditions: $CH_{3}SO_{3}H\text{-}SiO_{2}$ (0.55 mmol), indole (0.50 mmol), NaNO_{2} (0.60 mmol), pyridine (1 mL), rt.

^bIsolated yield.

substituent groups could affect the reactivity of the substrates. In general, electron-donating substituents were more beneficial for this transformation, whereas the electron-withdrawing groups decreased the reaction yields. For instance, 5-methoxy-1*H*-indole containing an electron-donating group (OCH₃) showed high reactivity and the corresponding product **5e** was obtained in 92% yield (Table 2, entry 5), whereas 5-nitro-1*H*-indole containing strongly electron-withdrawing groups (NO₂) showed poor reactivity and the corresponding product **5i** was obtained in 54% yield (Table 2, entry 9). Furthermore, we found that the position of substituents on C5, C6, and C7 of the indole ring did not have a significant effect on the formation of **5**.

To explore more the scope of this reaction, N-CH₃ indole was also investigated. It was found that under the optimized conditions, 3-nitroso-2,3'-biindole **8** was obtained in excellent yield (Scheme 2).

Finally, the practical applicability of this three-component coupling reaction is also demonstrated. We used indole as a test substrate and worked on a gram scale. A 50 mmol (5.85 g) reaction of indole was performed with CH_3SO_3H -SiO₂ (110.00 g, 55 mmol) and NaNO₂ (4.10 g, 60 mmol) in pyridine (60 mL) under the atmosphere



Figure 2. ORTEP representation of the molecular structure of 5b.

and the mixture was stirred at room temperature for 10h. The desired product was obtained in 86% yield. This result indicates that the present approach is a practical process for three-component coupling of indoles with NaNO₂.

Although the reaction mechanism has not been clear up to now, a possible process is proposed in Scheme 3. First, indole reacts with $NaNO_2$ in the presence



Scheme 2. Reaction of N-CH₃ indole with NaNO₂ using CH₃SO₃H-SiO₂ as the solid acid.



Scheme 3. Plausible mechanism for the one-pot, three-component coupling reaction.

of CH_3SO_3H -SiO₂ as the solid acid, leading to the formation of intermediate 9, which readily tautomerizes the isomeric 3-oxime intermediate 10. Subsequently, the highly reactive species 10 is trapped by second indole to give dimer 11. Finally, the intermediate 11 is further oxidized (likely by NaNO₂) to result in the formation of the desired product 5.

In summary, we have successfully developed a practical, operationally simple, economical, and environmentally friendly procedure for the synthesis of (E)-2-, 3'-bi(3H-indol)-3-one oximes via one-pot, three component-coupling reactions. Moreover, it has several advantages: (1) an inexpensive and environmentally friendly CH₃SO₃H-SiO₂ has been used as the solid acid, (2) a wide variety of functional groups, including electron-rich and electron-withdrawing groups, can survive, (3) it is highly regioselective (2,3'-linkage), (4) this tandem reaction proceeded smoothly without exclusion of moisture or air from the reaction mixture, which gives a rapid access to a variety of substituted (E)-2,3'-bi(3H-indol)-3-one oximes in good to excellent yields at room temperature, and (5) in comparison with the homogeneous reactions using CH₃SO₃H as an acid, the heterogeneous reactions give better reaction yields. Further study in this area is going on in our laboratory to develop cross-coupling of indoles.

EXPERIMENTAL

Preparation of the Silica Gel-Supported Methylsulfonic Acid (CH₃SO₃H-SiO₂)

To a suspension of silica gel (10.0 g, 200–300 mesh) in tetrahydrofuran (THF) (35 mL), CH₃SO₃H (480 mg, 5 mmol) was added. The mixture was stirred magnetically for 60 min at rt. The THF was removed under reduced pressure, and the residue was dried at 110 °C for 2 h to afford CH₃SO₃H-SiO₂ (0.5 mmol g⁻¹) as a white powder.

Typical Experimental Procedure for the Preparation of (*E*)-2,3'-Bi(3*H*-indol)-3-one Oxime (5a)

CH₃SO₃H-SiO₂ (1.1 g, 0.55 mmol) was added to a solution of indole (59 mg, 0.50 mmol) and NaNO₂ (41 mg, 0.60 mmol) in pyridine (1 mL) under the atmosphere, and the mixture was stirred at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:1) to yield the corresponding product **5a** (58 mg, 89%).

Characterization Data of (E)-2,3'-Bi(3H-indol)-3-one Oxime (5a)

Red-brown solid, mp: 243–244 °C (from EtOAc/PE = 1:1) (lit,^[16] mp: 243–244 °C). IR (KBr) (ν_{max} : 3172, 3050, 1548, 1438, 1008, 753 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*6): δ 13.34 (s, 1H), 11.82 (s, 1H), 8.51 (d, J=8.0 Hz, 1H, Ar-H), 8.32 (d, J=4.0 Hz, 1H, Ar-H), 8.04 (d, J=4.0 Hz, 1H, Ar-H), 7.49 (d, J=8.0 Hz, 1H, Ar-H), 7.43 (m, 2H, Ar-H), 7.22 (m, 3H, Ar-H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 162.6, 157.2, 155.4, 136.9, 132.2, 132.1, 127.2, 126.5,

125.8, 123.1, 122.9, 121.6, 121.5, 119.9, 112.5, 109.0. MS (ESI): 262 (M + H⁺, 100), 284 (M+Na⁺, 5). These assignments matched with those previously published.^[17]

SUPPORTING INFORMATION

Full experimental detail, ¹H and ¹³C NMR spectra for the compounds **5–8**, copies of ¹H and ¹³C NMR spectra for all compounds, and x-ray data of compound **5b** can be found via the Supplementary Content section of this article's Web page.

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