Silica-supported ceric ammonium nitrate catalyzed chemoselective formylation of indoles

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ABSTRACT

Selective formylation of free (N–H) indoles at C3 can be achieved by using formylating species generated from hexamethylenetetramine (HMTA) and silica-supported ceric ammonium nitrate (CAN–SiO$_2$). The use of a catalytic amount of this solid-supported reagent was found to be compatible with a range of substituents on the indoles and generated the corresponding products with good yields. A plausible mechanism for the formylation involving an electron transfer process is discussed.

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The C-formylation of indoles is a very useful key step in the preparation of biologically active natural products, including cryptosanguinolentine,[1] homofascaplysin C,[2] FR-900482,[3] and indole alkaloids.[4] A number of synthetic methods have been reported in the literature for the formylation of indoles and various reagents are available for use in this reaction. Traditionally, the Vilsmeier–Haack reagent (e.g., POCl$_3$ + DMF) was efficient for such transformation, but it is not environmentally benign.[5] The Duff,[5a] Reimer–Tiemann,[6] and Gattermann–Koch reactions[7] are also powerful methods leading to formylated products, which generally require heating at elevated temperatures with an excess of strong base or acid in the work-up processes. Nevertheless, these indole formylation methods are not compatible with functional groups that are labile under acidic or basic conditions. Catalytic formylations have received considerable attention due to their mild, safe and environmentally friendly characteristics. Hence, the development of novel access to formylindoles using environmentally benign reagents under mild conditions is still of much significance. A reaction utilizing *N*-methylaniline as the carbonyl source has been reported for the Ru[8] or *n*Bu$_4$NI[9] catalyzed formylation of indoles. More recently, Fei and coworkers reported the formylation of indoles using DMSO as the carbonyl source.[10]

The development of non-toxic, low cost, eco-friendly, recyclable catalyst systems has received significant attention in organic synthesis.[11] Cerium(IV) ammonium nitrate (CAN) has proved to be very useful with advantages such as low toxicity, ease of handling, and solubility in a number of organic solvents.[12] Ceric(IV) reagents can function as a one-electron transfer catalyst in various organic reactions.[12] Recently, CAN supported on silica gel has been reported for bromination,[13] removal of protecting groups,[14] and oxidation reactions.[15]

In the search of an eco-friendly procedure using an inexpensive and reusable catalytic system, we report for the first time the use of silica-supported CAN as a mild and highly efficient, recyclable catalyst for the C-formylation of indoles.

The study was initiated by carrying out the formylation of indole with hexamethylenetetramine (HMTA) by screening a variety of catalysts (SiO$_2$, CAN, and CAN–SiO$_2$)[17] in CH$_3$CN under refluxing conditions.[18] The results from the optimization studies are summarized in Table 1. We found that catalysts including SiO$_2$ and CAN were either ineffective or less effective than CAN–SiO$_2$ (entries 1–6). The effect of the solvent on the reaction efficiency was also studied (entries 7–10). Among the tested solvents, CH$_3$CN gave the best result (entry 1).
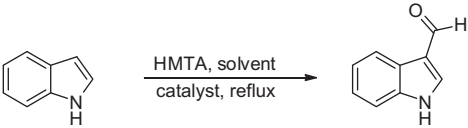
Further, to check the effectiveness of the catalyst, the reaction was carried out in the presence of various amounts of the CAN–SiO$_2$ in CH$_3$CN (Table 2). The results showed no improvement in the product yield using different amounts of CAN–SiO$_2$. The number of equivalents of HMTA was also studied (Table 2, entries 8–10). The yield of 3-formylindole increased when using 2.5 and 3.0 equiv of HMTA (87% and 88%, respectively).

With the optimized reaction conditions in hand, we next explored the substrate scope using CAN–SiO$_2$ as the catalyst. The

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Table 1
Formylation of indole with various catalysts and solvents

Entry[a]	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	CAN–SiO$_2$[c]	CH$_3$CN	22	81
2	CAN	CH$_3$CN	7	29
3	SiO$_2$	CH$_3$CN	24	Trace
4	AlCl$_3$	CH$_3$CN	24	19
5	FeCl$_3$	CH$_3$CN	24	36
6	Amberlyst-15	CH$_3$CN	24	10
7	CAN–SiO$_2$[c]	MeOH	7	10
8	CAN–SiO$_2$[c]	EtOH	4	20
9	CAN–SiO$_2$[c]	DMF	24	58
10	CAN–SiO$_2$[c]	THF	24	Trace

[a] Reaction conditions: indole (1 mmol), HMTA (2 mmol), catalyst (10 mol %), solvent (5 mL).
[b] Isolated yield.
[c] 10% (by weight) of CAN.

Table 2
Evaluation of the catalytic activity of ceric ammonium nitrate on silica gel (CAN–SiO$_2$) in the formylation of indole

Entry[a]	%wt.	CAN[c] (mol %)	HMTA (equiv)	Time (h)	Yield[b] (%)
1	10% CAN–SiO$_2$	5	2	26	63
2	10% CAN–SiO$_2$	10	2	22	81
3	10% CAN–SiO$_2$	15	2	22	81
4	5% CAN–SiO$_2$	5	2	22	57
5	15% CAN–SiO$_2$	15	2	20	78
6	5% CAN–SiO$_2$	10	2	22	81
7	15% CAN–SiO$_2$	10	2	20	73
8	10% CAN–SiO$_2$	10	1.5	22	79
9	10% CAN–SiO$_2$	10	2.5	20	87
10	10% CAN–SiO$_2$	10	3	20	88

[a] Reaction conditions: indole (1 mmol), HMTA, catalyst, CH$_3$CN (5 mL), reflux.
[b] Isolated yield.
[c] Amount of CAN in the reaction.
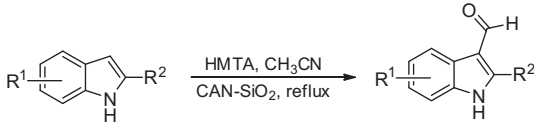
Table 3
Synthesis of 3-formylindole derivatives

Entry[a]	R^1	R^2	Time (h)	Yield[b] (%)
1	H	H	20	87
2	4-MeO	H	9	65
3	5-MeO	H	15	60
4	6-MeO	H	6	70
5	7-MeO	H	12	77
6	H	Ph	12	88
7	H	4-MeOC$_6$H$_4$	12	78
8	H	4-MeC$_6$H$_4$	12	70
9	H	3-MeOC$_6$H$_4$	12	81
10	5-MeO	Ph	12	89

[a] Reaction conditions: indole (1 mmol), HMTA (2.5 equiv), 10% CAN–SiO$_2$ (10 mol % of CAN in reaction), CH$_3$CN (5 mL), reflux.
[b] Isolated yield and products were identified by comparison of their ^{1}H NMR and ^{13}C NMR spectral data with those reported in the literature.

Table 4
The recycling of CAN–SiO$_2$ in the formylation with indole

Entry[a]	No. of cycles	Time (h)	Yield[b] (%)
1	1	20	87
2	2	22	81
3	3	24	68
4	4	24	65

[a] Reaction conditions: indole (1 mmol), HMTA (2.5 equiv), 10% CAN–SiO$_2$ (10 mol % of CAN in the reaction), CH$_3$CN (5 mL), reflux.
[b] Isolated yield.

CAN–SiO$_2$ catalyzed C3-selective formylation of free N–H indoles was compatible with a range of substituents on the benzene and pyrrole ring of indole, and generated the corresponding products with reasonable to good yields (Table 3, entries 1–10). In addition, we also studied the reusability of the catalyst after filtration, washing with EtOAc[18] and drying. The results of the recycling show that the catalyst can be recycled once (87% and 81% yield, respectively, Table 4).

The adsorption of HMTA on to the silica gel impregnated with CAN could bring the substrates and the catalyst into close proximity.[16] This facilitates the electron transfer process between CAN and the substrates. The use of silica gel as a support could also increase the effective surface area and constrain both the substrate and the reactant in pores thus decreasing the entropy of activation for electron transfer.[14] We propose a mechanism in Scheme 1 for the formylation of indole using CAN–SiO$_2$. HMTA was adsorbed on CAN–SiO$_2$ to afford **I**. The proximity of HMTA to CAN in **I** results in a favorable entropy of activation and, consequently, a rate enhancement of the reaction. Oxidation of HMTA in **I** gives the corresponding radical cation in **II**, while reduction of Ce(IV) to Ce(III) takes place. The radical cation then undergoes fragmentation to give an iminium cation and an amine radical as shown in **III**. The reduction of the amine radical **III** to amine anion **IV** allows

regeneration of Ce(IV) from Ce(III). Meanwhile, protonation of the amine anion **IV** gives an iminium ion **V** and allows regeneration of CAN–SiO$_2$. The nucleophilic aromatic substitution of indole with iminium **V** generates **VI**.

Removal of the amine groups from **VI** with CAN–SiO$_2$ could proceed through a similar mechanism. The first step involves the oxidation of the secondary amine in **VI** after coordination to CAN–SiO$_2$. The resultant radical cation in **VIII** could then undergo a ring-opening reaction to give **IX**. Regeneration of Ce(IV)–SiO$_2$ from Ce(III)–SiO$_2$ during reduction of the amine radical in **IX** affords the amine anion **X**. Protonation of **X** then gives the primary amine **XI**. Intermediate **XI** undergoes a 1,5-hydrogen shift to give iminium ion **XII**, followed by hydrolysis to give the 3-formylindole. Another plausible mechanism is given in the Supporting information.

In summary, we have demonstrated the formylation of a variety of indoles under mild conditions. The formylating species generated from HMTA and CAN–SiO$_2$ is highly reactive, and the formylation of indoles proceeded smoothly to provide the corresponding aldehydes with good yields. The reaction might be useful for the synthesis of highly functionalized indoles.

Acknowledgments
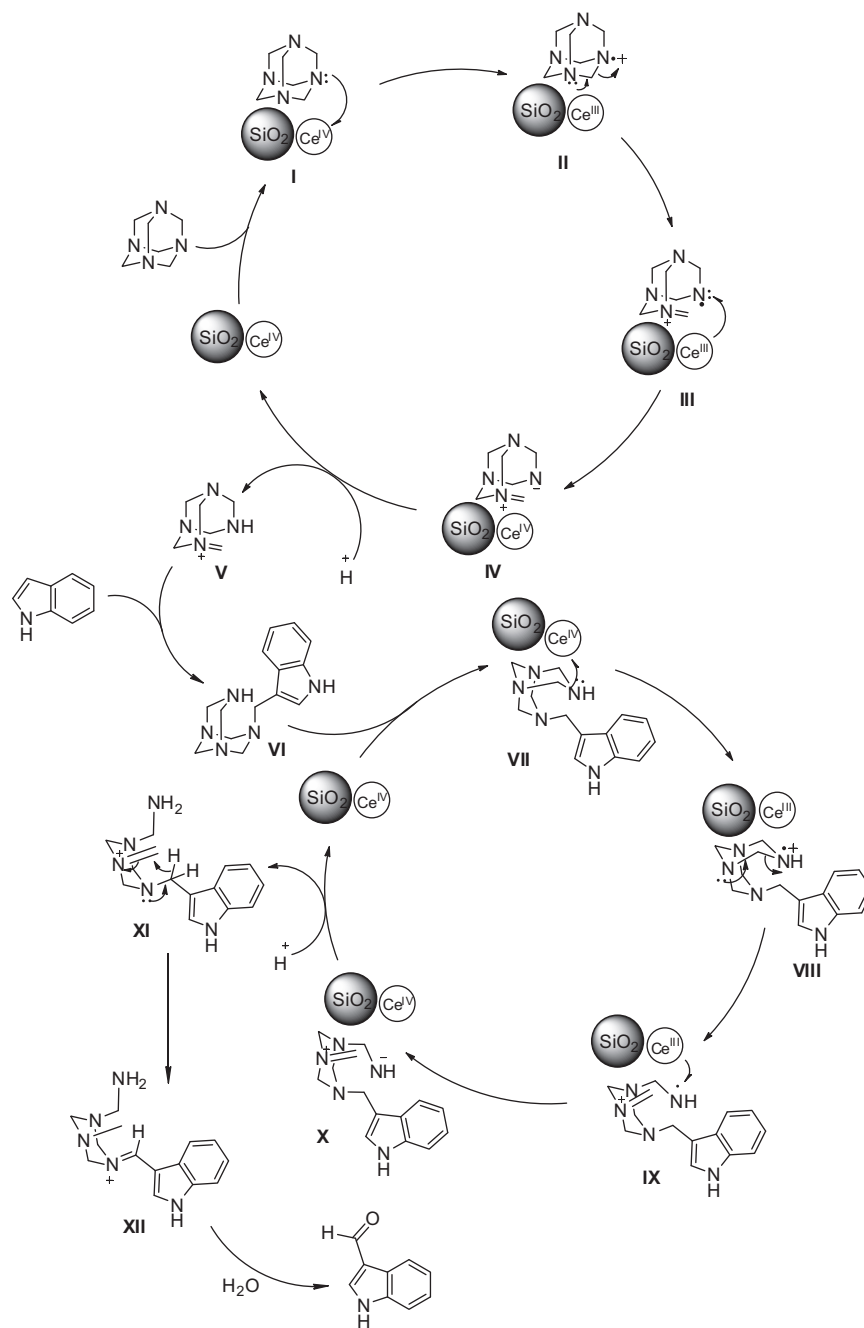
Scheme 1. Proposed mechanism.

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17. *Preparation of 10% CAN–SiO₂:* a solution of CAN (1.01 g) in H_2O (2.0 mL) was added dropwise to silica gel 60 (9.01 g, Merck Kieselgel 60, particle size 0.063–0.200 mm, 70–230 mesh) under stirring followed by evaporation under reduced pressure at 60 °C for 4 h. A dry yellowish powder was collected and stored in a well-sealed bottle. Other loading ratios of CAN–SiO₂ were prepared by the same method (9.51 g silica gel and 0.51 g CAN for 5% CAN–SiO₂, 8.51 g silica gel and 1.51 g CAN for 15% CAN–SiO₂).
18. Typical procedure: a mixture of indole (1 mmol), HMTA (2.5 mmol), and 10% CAN–SiO₂ was refluxed in CH_3CN (5.0 mL). After the reaction was complete, the mixture was evaporated to give a crude residue of CAN–SiO₂ and product. The crude residue was washed with EtOAc (10 mL × 5) and dried to leave a crude product that was purified by short flash column chromatography (EtOAc/hexane = 1:3).
Spectral data for 2-(3-methoxyphenyl)-1H-indole-3-carbaldehyde (Table 3, entry 9): pale yellow solid; ¹H NMR (300 MHz, CDCl₃): δ = 3.80 (s, 3H, CH₃), 7.19 (dd, J = 2.66, 8.27 MHz, 1H, ArH), 7.35 (d, J = 8.13 MHz, 1H, ArH), 7.39 (m, 1H, ArH), 8.25 (d, J = 7.28 MHz, 1H, ArH), 9.99 (s, 1H, CHO), 11.68 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): 54.9, 111.3, 113.8, 114.7, 114.9, 121.2, 121.9, 122.1, 123.3, 125.6, 129.4, 131.1, 135.7, 148.9, 159.2, 185.9; IR (KBr): 3175, 1628, 1453, 1370, 1239, 1166 cm⁻¹; HRMS: m/z calcd for C₁₆H₁₃NO₂ [M+Na]⁺ 274.0858.
Spectral data for 5-methoxy-2-phenyl-1H-indole-3-carbaldehyde (Table 3, entry 10): pale yellow solid; ¹H NMR (300 MHz, CDCl₃): δ = 3.79 (s, 3H, CH₃), 6.80 (dd, J = 2.21, 8.97 MHz, 1H, ArH), 7.22 (d, J = 8.75 MHz, 1H, ArH), 7.45 (m, 3H, ArH), 7.59 (d, J = 6.2 MHz, 2H, ArH), 7.73 (s, 1H, ArH), 9.91 (s, 1H, CHO), 11.82 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): 55.1, 102.7, 112.2, 113.2, 113.6, 126.4, 128.3, 129.1, 129.9, 130.6, 149.1, 155.75, 185.7; IR (KBr): 3129, 2982, 1624, 1468, 1368, 1259, 1213 cm⁻¹; HRMS: m/z calcd for C₁₆H₁₃NO₂ [M+Na]⁺ 274.0834.