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Regioselective C5 nitration of *N*-protected indolines using ferric nitrate under mild conditions

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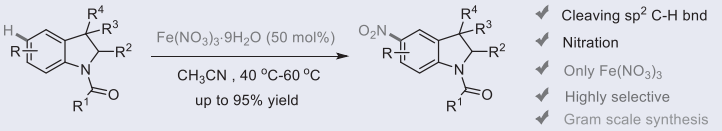
ABSTRACT

An efficient and facile process has been developed for the regioselective C5 nitration of the N-protected indolines using ferric nitrate as the nitrating reagents. The reaction proceeded smoothly in moderate to excellent yields with high efficiency and broad substrate scope under mild conditions. In addition, the synthesized nitration products can be further transformed to 5-nitroindolines and C5-nitroindole derivatives. The method is operationally simple, efficient, and might have potential application in industry production.

GRAPHICAL ABSTRACT



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KEYWORDS
Indolines; C5 nitration; ferric nitrate; nitrating reagents; 5-nitroindolines

Introduction

Nitroarenes are widely utilized in various fields such as pharmaceuticals, explosives, dyes, and materials.[1] Furthermore, aromatic nitro compounds are important building blocks for organic synthesis because they can be easily transformed into amines and ketones.[1d,1e,2] Traditionally, the classical approach to synthesize the aromatic nitro compounds is the direct electrophilic nitration, using conc. HNO_3–H_2SO_4, conc. HNO_3-mixed anhydrides, and $NaNO_3$–TFA as the nitrating reagents.[3] However, these processes often suffer from poor selectivity, harsh reaction conditions, and limited functional group tolerance.[4] Moreover, undesirable by-products and large quantities of hazardous acids are generated through these procedures. Therefore, it remains a challenge to develop new strategy for the direct nitration reaction.

Nitroindolines and its derivatives have been used as photolabile protective groups, photochemically activated coupling reagents.[5] Some of nitro-substituted indoles have potent activity against tuberculosis.[6] Thus, the synthesis of nitroindolines continues to be attractive in the synthetic community due to the unavailability of suitable methods.

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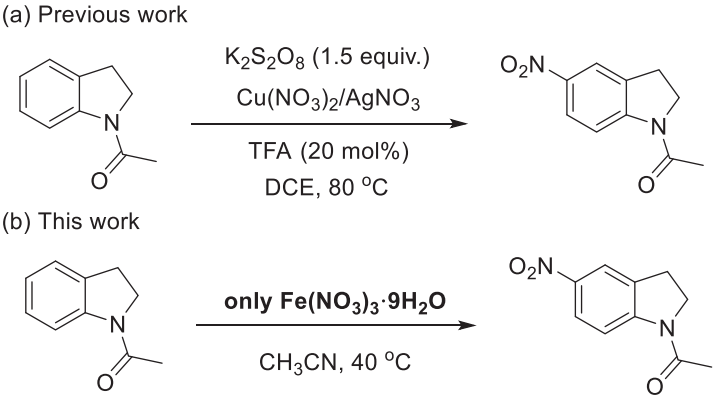


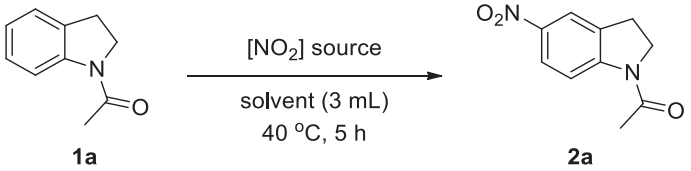
Figure 1. C5 nitration of *N*-acetyl indoline. (a) Our regioselective C5 nitration approach under mild conditions. (b) Mal's mono-nitration approach C–H nitration.

In recent years, ipso-nitration[7] and transition-metal-catalyzed C − H bond functionalization reactions[1f,8] have been developed to achieve the aromatic nitro compounds. Meanwhile, various metal nitrate salts have emerged as new nitrating agents, such as $AgNO_3$,[9] $Bi(NO_3)_3{\cdot}5H_2O$,[10] $Fe(NO_3)_3{\cdot}9H_2O$,[11] $Ca(NO_3)_2$,[12] $Ni(NO_3)_2{\cdot}6H_2O$,[13] and so on. Most recently, Mal group[14] reported C–H mono-nitration of indolines with a complex systems (Figure 1a). Inspired by these elegant studies and our interest in C − H bond functionalization,[15] herein, we report the highly regioselective nitration of indolines only with the cheap metal nitrate salts to afford C5-nitroindolines (Figure 1b).

Results and discussion

At the outset of our study, *N*-acetyl indoline (**1a**) was chosen as a model substrate to optimize the reaction conditions, including various nitrating agents, solvents, and temperature (Table 1). It is known that iron is a nontoxic and inexpensive metal, and iron nitrate nonahydrate ($Fe(NO_3)_3{\cdot}9H_2O$) can generate nitrogen dioxide radical ($NO_2{\cdot}$) through the thermal decomposition.[12] In general, $Fe(NO_3)_3{\cdot}9H_2O$ has been used as a clean nitration source frequently. Therefore, in our initial study, we first chose $Fe(NO_3)_3{\cdot}9H_2O$ as nitrating reagent. To our delight, the reaction proceeded smoothly, giving the C5 nitration product **2a** in 89% yield at 40 °C under an air atmosphere for 5 h (Table 1, entry 1). Then, we examined various metal nitrate salts including $Bi(NO_3)_3{\cdot}5H_2O$, $AgNO_3$, $Cu(NO_3)_2{\cdot}3H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $Ce(NH_4)_2(NO_3)_6$, and KNO_3. However, only $Cu(NO_3)_2{\cdot}3H_2O$ gave 8% yield, the remaining agents could not react (Table 1, entries 2–7). Other nitrating agents such as NH_4NO_3, $NaNO_2$[16], and *tert*-butyl nitrite (TBN) were also explored, but both of them could not give a better yield than $Fe(NO_3)_3{\cdot}9H_2O$ (Table 1, entries 8–10). Moreover, when the temperature was dropped from 40 °C to room temperature, the yield of **2a** became lower even if the reaction time was prolonged to 12 h (Table 1, entry 11). In addition, the effect of solvent was also explored. Disappointingly when 1,2-dichloroethane (DCE), CH_2Cl_2, toluene (PhMe), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and 1,4-dioxane were employed as the solvent, but all of them proved to be deleterious to the reaction

Table 1. Optimization of reaction conditions.[a]



1a **2a**

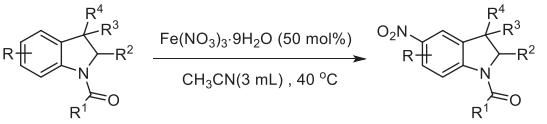
Entry	[NO_2] source (equiv.)	Solvent	Yield (%)[b]
1	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	CH_3CN	89%
2	$Bi(NO_3)_3{\cdot}5H_2O$ (0.5eq.)	CH_3CN	trace
3	$AgNO_3$ (1.5eq.)	CH_3CN	0%
4	$Cu(NO_3)_2{\cdot}3H_2O$ (0.5eq.)	CH_3CN	8%
5	$Co(NO_3)_2{\cdot}6H_2O$ (0.5eq.)	CH_3CN	0%
6	$Ce(NH_4)_2(NO_3)_6$ (0.25eq.)	CH_3CN	0%
7	KNO_3 (1.5eq.)	CH_3CN	0%
8	NH_4NO_3 (1.5 eq.)	CH_3CN	0%
9[c]	$NaNO_2$ (1.5 eq.)	CH_3CN	31% (48%)
10	TBN (1.5eq.)	CH_3CN	58%
11[d]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	CH_3CN	72%
12	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	DCE	66%
13	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	CH_2Cl_2	59%
14	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	PhMe	0%
15	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	DMF	0%
16	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	DMSO	0%
17	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5eq.)	1,4-dioxane	0%

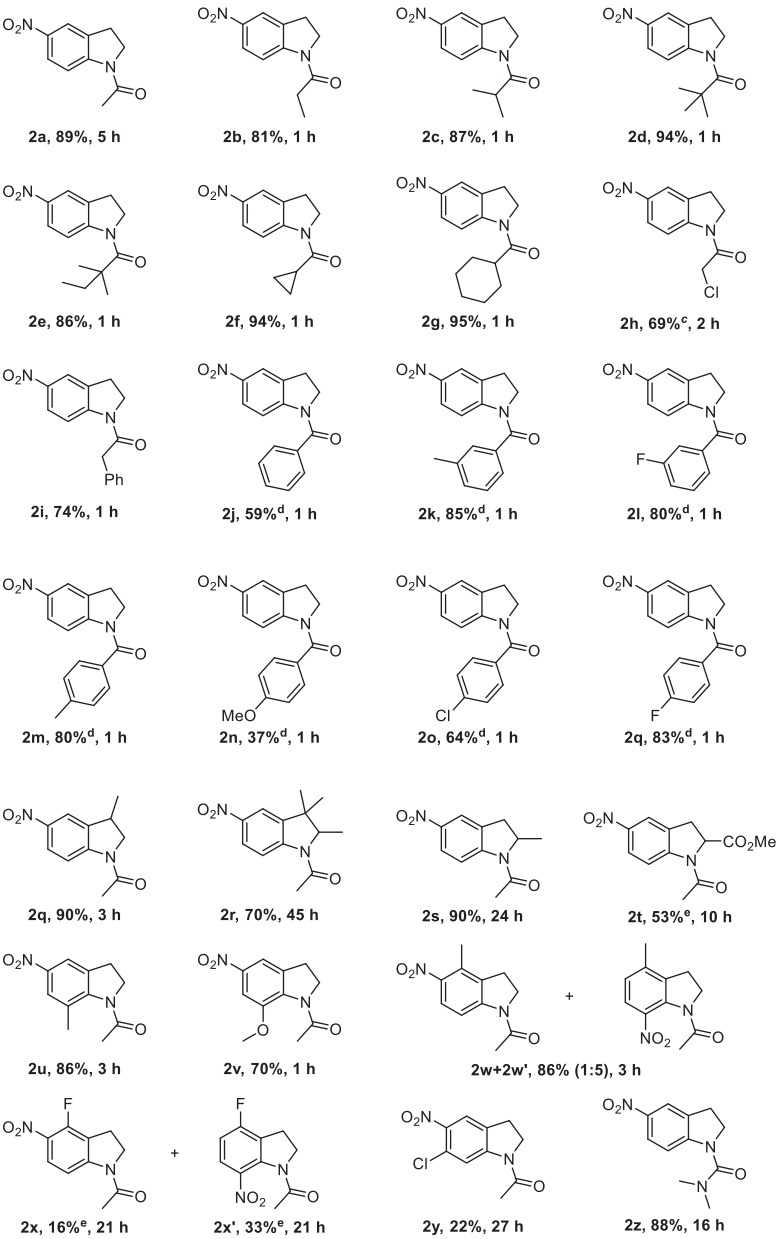
[a]Unless otherwise specified, all reactions were carried out with 0.3 mmol of **1a**, and nitrating agent in 3 mL of solvent under an air atmosphere at 40 °C for 5 h.
[b]Isolated yield.
[c]1.5 eq. CF_3CO_2H was added; when CF_3CO_2H (1 mL) and CH_3CN (2 mL) were as solvent, the yield was given in parentheses.
[d]At 25 °C, 12 h.

(Table 1, entries 12–17). Therefore, the use of *N*-acetyl indoline 50 mol% of $Fe(NO_3)_3{\cdot}9H_2O$ at 40 °C in CH_3CN was chosen as the optimal reaction conditions.

With the optimized reaction conditions in hand, we started to investigate the scope and limitation of the reaction. The reaction results are listed in Table 2. Indolines **1a–z** with various protected substituents could afford the nitrated products **2a–z** in moderate to excellent yields. Substrates **1a–g** bearing formyl, acetyl, isopropanoyl, tert-butyryl, pivaloyl, cyclopropionyl, and cyclohexanoyl groups reacted smoothly to give the corresponding products **2a–g** in 81–95% yields. It should be noted that indoline **1h** bearing the strong electron-withdrawing chloroacetyl group could also be functionalized to bring out the desired product, albeit at a relatively low yield with 5% $Cu(OTf)_2$ as catalyst. When **1i** was employed as the substrate, a good yield (74%) was obtained for the C5-nitrated product (**2i**). Gratifyingly, *N*-benzoyl indolines containing electron-neutral substituent (H and Me) or halogen atoms such as F, and Cl reacted smoothly and led to corresponding products (**2j–2m, 2o–2p)** in 59–85% yields, albeit in a slightly low yield even with more solvent and a temperature rise. However, *N*-benzoyl indoline (**1n**) bearing the electron-donating *p*-OMe group only bring out the target product in 37% yield with the generation of other unknown by-products. To expand the substrate scope of the reaction, the optimized reaction conditions were applied to a wide range of indolines with different substituents in the pyrrolidine moiety. To our delight, when indolines substituted with methyl were chosen as the reactants, they could react smoothly to

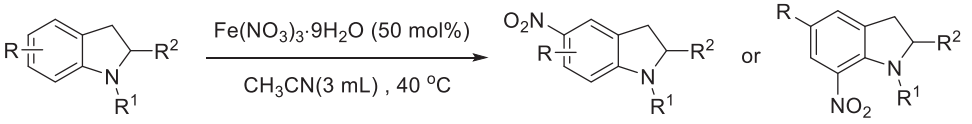
Table 2. Substrate scope of the C5 nitration reaction of *N*-protected indolines.[a,b]

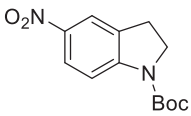


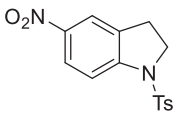


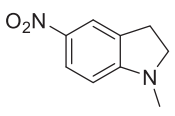
[a]Unless otherwise indicated, all reactions were carried out with 0.3 mmol of indolines, 0.15 mmol of $Fe(NO_3)_3{\cdot}9H_2O$, in CH_3CN (3 mL) at 40 °C.
[b]Isolated yield.
[c]5 mol% $Cu(OTf)_2$ was used.
[d]CH_3CN (6 mL), at 60 °C.
[e]At 60 °C.

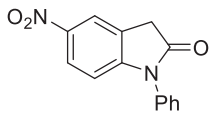
Table 3. Substrate scope of the nitration reaction of *N*-protected indolines.[a,b]

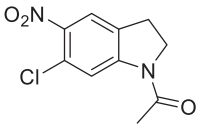


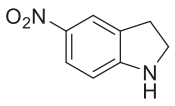

2aa, 76%, 1 h

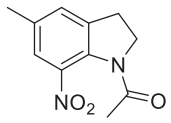

2ba, 61%, 5 h

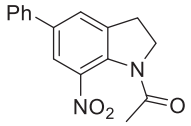

2ca, 0%, 5 h

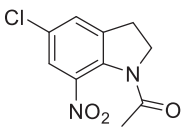

2da, trace, 24 h

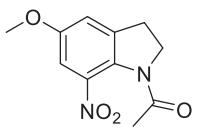

2ea, 0%, 24 h


2fa, 0%, 5 h


2ga, 83%, 2 h


2ha, 72%, 2 h


2ia, 27%, 24 h

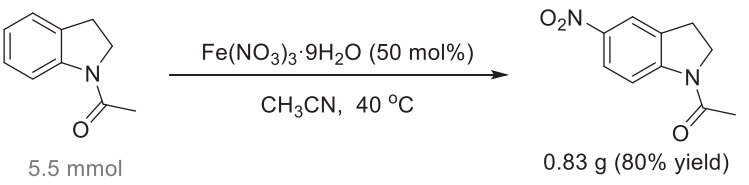

2ja, 18%, 1 h

[a]Unless otherwise indicated, all reactions were carried out with 0.3 mmol of indolines, 0.15 mmol of $Fe(NO_3)_3·9H_2O$, in CH_3CN (3 mL) at 40 °C.
[b]Isolated yield.

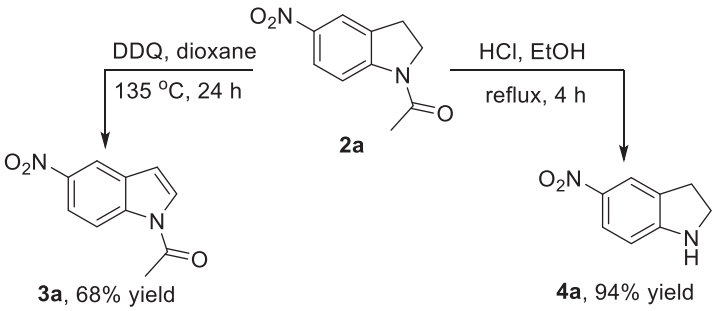
give the corresponding products **2q**, **2r**, and **2s** in 70–90% yields. Subsequently, *N*-acetyl indoline **1t** bearing the electron-withdrawing CO_2Me group could also afford the desired product, albeit in a relatively low yield.

Encouraged by the above results, we began to explore the scope of substitution on the aromatic ring of indoline. Indoline with 7-Me group could proceed smoothly to give the target molecules **2u** in 86% yield, surprisingly, when indoline with 7-OMe group also afford the C5 nitration product in 70% yield. Meanwhile, 4-Me group on the phenyl ring of indoline **1w** was employed as the substrate, a mixed products **2w** and **2w'** (1:5) were obtained probably due to the steric hindrance. Similarly, substrates bearing 4-F group was compatible with this nitration protocol, generating a mixed products **2x** and **2x'** (1:2). Additionally, 1-(6-chloroindolin-1-yl)ethanone **1y** was also tolerant in this transformation, giving the corresponding product in 22% yield. Compared with chloroacetyl group, the *N*,*N*-dimethyl formyl group could afford the target product **2z** in 88% yield under the same experimental conditions.

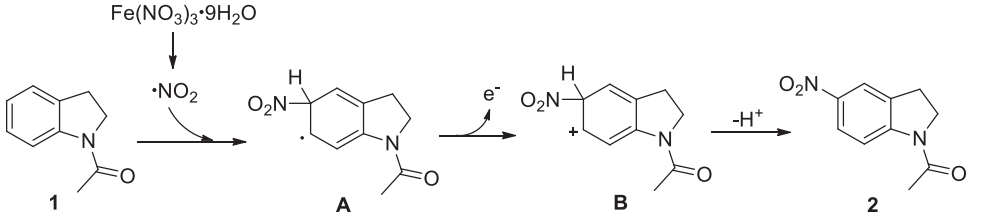
In addition, other *N*-substituted substrates were also examined (Table 3). *N*-protected substituents such as Boc and Ts also could be applied to afford the desired products (**2aa** and **2ab**). However, when 1-methylindoline, 1-phenylindolin-2-one, and 1-acetyl-6-chloroindolin-2-one were employed as reactant, respectively, either no or trace amounts of products were formed. Moreover, 1-H indoline also failed to give any nitrated products. The above results clearly disclose the importance of the N centers of indolines



Scheme 1. Gram-scale synthesis.



Scheme 2. Transformations of C5-nitrated indoline.



Scheme 3. Proposed reaction mechanism.

protecting with p-acceptors. Meanwhile, we also attempted several substrates that the C-5 was substituted. Indolines bearing 5-Me or 5-Ph were applied as substrates in this nitration reaction, giving the corresponding C7 products in moderate to good yields. However, when indoline substituted with chloro group at C5 position, the C7 nitration product could be afforded in 27% yield and a large amount of starting material was oxidized. Meanwhile, when the indoline bearing the electron-donating C5-OMe group, we could only get 18% yield of the target product and an unknown by-product.

Finally, the nitration reaction was examined in gram-scale as representative example (Scheme 1). *N*-acetyl indoline (5.5 mmol) reacted with $Fe(NO_3)_3{\cdot}9H_2O$ to afford **2a** 0.83 g (80% yield) after 5 h, which suggests that the protocol is scalable.

Furthermore, to highlight the transformation of C-5 nitrated indolines, we performed the oxidation of **2a** using DDQ to give 5-nitrated indole **4a** in 68% yield. In addition, treatment of **2a** with hydrochloric acid in a solution of ethanol refluxing for 4 h afforded the free (NH)-indoline **3a** in 94% yield (Scheme 2)

To gain more insights into the reaction mechanism, a free radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.0 equiv.), was added to the reaction mixture, no desired target product could be observed under the standard reaction

conditions, indicating that the reaction probably proceeded through a free radical process.

Based on above results and the previously reported reactions,[12] a plausible reaction mechanism is proposed and shown in Scheme 3. First, $Fe(NO_3)_3{\cdot}9H_2O$ generates the NO_2 radical under thermal conditions.[12] And then, the NO_2 radical reacts with *N*-acetyl indoline at the C-5 position to give the intermediate A which is further oxidized to furnish B. Finally, the elimination of a proton from B would produce the desired product. It should be noted that a mechanism involving the aromatic electrophilic substitution (EArS) pathway[14] could not be completely excluded.

Conclusion

In conclusion, we have demonstrated the regioselective C5 nitration of the *N*-protected indolines. This protocol only uses ferric nitrate as the nitrating reagent. The reaction can be applied to a wide range of indolines smoothly in moderate to excellent yields under mild conditions. In addition, the synthesized nitration products can be further transformed to 5-nitroindolines and 5-nitroindole derivatives. The method is operationally simple, efficient, and might have potential application in industry production.

Experimental

Unless otherwise noted, all commercial materials and solvents were used without further purification. Thin-layer chromatography (TLC) was carried out using silica-gel GF254 plates. Products were purified using column chromatography over 300–400 mesh silica gel under a positive pressure of air. ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and residue $CHCl_3$ at 0.00 ppm and 77.16 ppm, respectively. High-resolution mass spectra (HRMS) were measured with ESI-Orbitrap in positive mode.

General procedure (taking the synthesis of 2a as an example)

N-acetylindoline **1a** (0.3 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (60.5 mg, 0.15 mmol), in CH_3CN (3 mL or 6 mL) were added to a 25 mL oven-dried Schlenk tube equipped with a magnetic stirred bar. The reaction was then stirred at 40 °C without charging with inert gas. The reaction was monitored using TLC and stopped at the desired time. Then, the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether and ethyl acetate as the eluent to give desired product **2a** as a brown yellow solid (55.3 mg, 89% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, $J = 9.0$ Hz, 1H), 8.12 (d, $J = 9.0$ Hz, 1H), 8.04 (s, 1H), 4.20 (t, $J = 8.6$ Hz, 2H), 3.30 (t, $J = 8.7$ Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.67, 148.43, 143.65, 132.47, 124.83, 120.40, 116.29, 49.56, 27.48, 24.42. HRMS (ESI-Orbitrap): m/z $[M + Na]^+$ calcd for $C_{10}H_{10}N_2O_3Na$ 229.0584, found 229.0581.

Funding

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