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Regioselective synthesis of 3-nitroindoles under non-acidic and non-metallic conditions†

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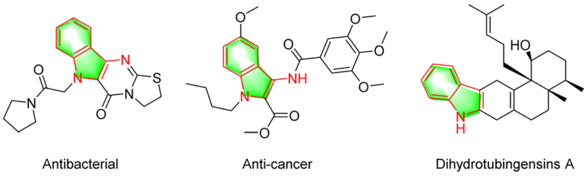
An electrophilic substitution reaction, without acid and metal, of indole with ammonium tetramethylnitrate for accessing 3-nitroindole has been developed. In this protocol, trifluoroacetyl nitrate (CF_3COONO_2) was produced by metathesis of ammonium tetramethyl nitrate and trifluoroacetic anhydride at sub-room temperature. Trifluoroacetyl nitrate (CF_3COONO_2) is an electrophilic nitrating agent for a variety of indoles, aromatic and heterocyclic aromaticity. Meanwhile, this strategy could be applied to construct the skeleton structure of many kinds of bioactive molecules. Interestingly, 3-nitroindole can be further derivatived as a pyrrolo[2,3-*b*]indole.

Introduction

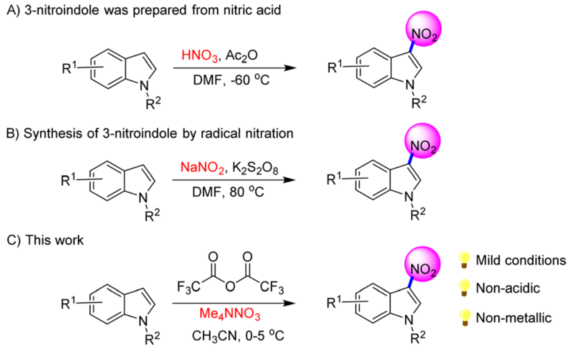
Indole and its derivatives are important structural motifs in organic chemistry.[1] In particular, 3-nitroindole is an important intermediate that has been widely used by scientists for the synthesis of organic molecules[2] with biological activity (Scheme 1).[3] However, the synthesis of 3-nitroindole still faces many challenges, including the lack of classical methods and low yield, and the use of nitric acid in the reaction process is not friendly to the environment.

Therefore, it is of great significance to develop efficient and green methods for the synthesis of 3-nitroindole. At present, the preparation methods of 3-nitroindole and its derivatives mainly include strong acid,[4] radical,[5] electrochemistry[6] and other methods (Scheme 2).[7] Although there are some methods to prepare 3-nitroindole and its analogues, there are some defects. For example, the use of concentrated nitric acid has potential safety hazards and great harm to the environment, low yield of prepared products, poor functional group compatibility. Therefore, the convenient and efficient synthesis of 3-nitroindole and its analogues from simple starting materials still faces great challenges.

Nitration is one of the most common and earliest organic reactions. The 1834 discovered the direct nitration of benzene to nitrobenzene. With the development of printing and dyeing industry,[8] pharmaceutical industry[9] and materials science industry,[10] nitrification has been widely used in organic synthesis industry.[11] Nitro compound by mixing acids is still the mainstream method.[12] But the reaction's regioselectivity, by-products, and functional group tolerance have long puzzled scientists. In recent years, many nitration methods have been developed, including free radical,[13] transition metal catalysis,[14] electrochemistry,[15] microwave[16] and other methods.[17] Although there are many nitrification reactions at present, the development of efficient, rapid and environment-friendly nitrification methods is still facing great challenges.



Scheme 1 Biological compounds derived from 3-nitroindoles.



Scheme 2 3-Nitroindoles was prepared from indoles.

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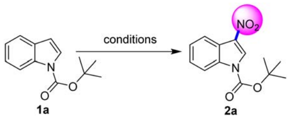
According to literature, ammonium nitrate can react with anhydride to form nitrates.[18] We suspect that nitrates can further react with indole to form 3-nitroindole. Therefore, we tried the reaction with *N*-Boc indole and obtained the target product in medium yield. Herein, we have developed a method for the preparation of 3-nitroindole without acid.

Results and discussion

We initially studied the protocol with *tert*-butyl 1*H*-indole-1-carboxylate (**1a**) under various conditions (Table 1, see ESI for detailed data†). Gratifyingly, when trifluoroacetic anhydride and tetramethylammonium nitrate were used as reaction reagents, *tert*-butyl 3-nitro-1*H*-indole-1-carboxylate (**2a**) was obtained in medium yield (entry 1). Then we investigated other ammonium salts, which only got trace product except tetrabutylammonium nitrate which could get the product in medium yield (entries 2 and 3). We tried to improve the yield of the reaction by changing the type of anhydride. It was regrettable that acetic anhydride was not capable of performing this reaction (entry 4). The triflic anhydride could only get trace amounts of the product (entry 5). The exciting thing was that the yield was unexpectedly increased to 85% when the amount of trifluoroacetic anhydride was two equivalent (entry 6). We also investigated the effects of different solvents on the reaction, most of which could not get ideal results (entries 7 and 8). Interestingly, when acetonitrile was used as a solvent, the yield of the reaction could be dramatically increased to 97% (entry 9). What's more, the reaction was almost impossible when the temperature was reduced to −20 °C (entry 10). Finally, only trace amounts of the product were obtained when the temperature increased to 25 °C (entry 11).

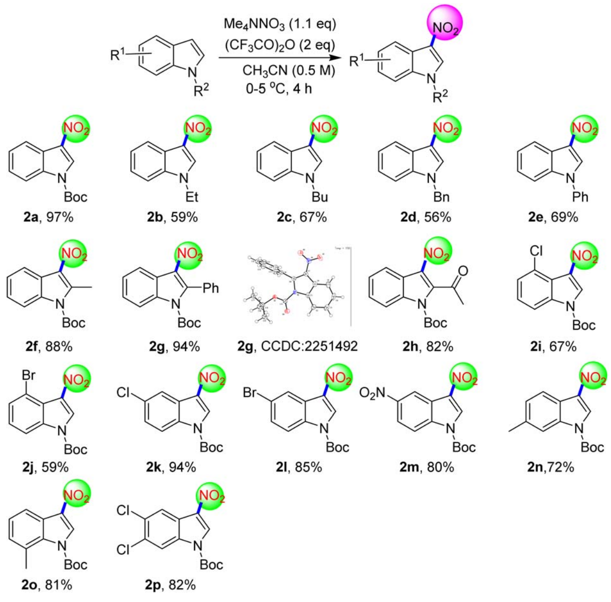
Table 1 Optimization of the reaction conditions[a,b]



Entry	Ammonium salts	Anhydride	Solvent	*T* (°C)	Yield (%), **2a**
1	NMe_4NO_3	$(CF_3CO)_2O$	DCM	0–5	78
2	KNO_3	$(CF_3CO)_2O$	DCM	0–5	Trace
3	NBu_4NO_3	$(CF_3CO)_2O$	DCM	0–5	56
4	NMe_4NO_3	$(Ac)_2O$	DCM	0–5	NR
5	NMe_4NO_3	$(CF_3SO_2)_2O$	DCM	0–5	Trace
6[c]	NMe_4NO_3	$(CF_3CO)_2O$	DCM	0–5	85
7[c]	NMe_4NO_3	$(CF_3CO)_2O$	THF	0–5	41
8[c]	NMe_4NO_3	$(CF_3CO)_2O$	DMSO	0–5	Trace
9[c]	NMe_4NO_3	$(CF_3CO)_2O$	CH_3CN	0–5	97
10[c]	NMe_4NO_3	$(CF_3CO)_2O$	DCM	−20	NR
11[c]	NMe_4NO_3	$(CF_3CO)_2O$	DCM	25	Trace

[a] Reaction conditions: **1a** (0.5 mmol), ammonium salts (0.55 mmol), anhydride (1 mL), solvent (1 mL), 4 h. [b] Yield refers to isolated product. [c] 1 mmol of anhydride was used.

We explored the substrate universality of this protocol according to our preferred optimal conditions (Scheme 3). Therefore, a series of indole derivatives used to prepare derivatives of 3-nitroindole. In addition, X-ray diffraction patterns of **2g** (CCDC: 2251492†) further proved that the nitration took place at position 3 of indole. It should be noted that in the next experiment we expanded the scale of the reaction to 1 mmol. When the indole 1 position was attached to the alkyl or benzyl group of the electron donor, the protocol could prepare the target product in a medium yield (**2b**–**2d**). What's more, the yield of 3-nitro-indole was slightly increased when the 1-position of indole was inserted into the phenyl group of drawing electron (**2e**). Interestingly, when the 2-position of indoles were connected to other substituents, regardless of the electron-donating or electron-withdrawing substitution, could proceed smoothly in this process to deliver corresponding 3-nitroindoles in good to excellent yields (**2f**–**2h**). It was concluded that the effect of 2-position of indole electric property on the reaction was small. In addition, 4-substituted indoles could also deliver the products smoothly. But the yield of *N*-boc-4-bromoindole was lower than that of *N*-boc-4-chloroindole (**2i**–**2j**). Using 4-methyl-Boc-indole as starting material, the nitration product (**2y** see ESI for detailed data†) containing impurities was obtained in a yield of only 33%. This phenomenon showed that the 4-site steric hindrance had an effect on the reaction. Moreover, no matter the 5-position of indole was replaced by the nitro group or halogen, the reaction could proceed smoothly and the derivatives of 3-nitroindole could be obtained in good to excellent yield (**2k**–**2m**). In addition, when indole 6-linked substituents, the protocol can be successfully implemented and the target product can be obtained with a medium yield (**2n**). Gratifyingly, 7-substituted indole was also compatible with the



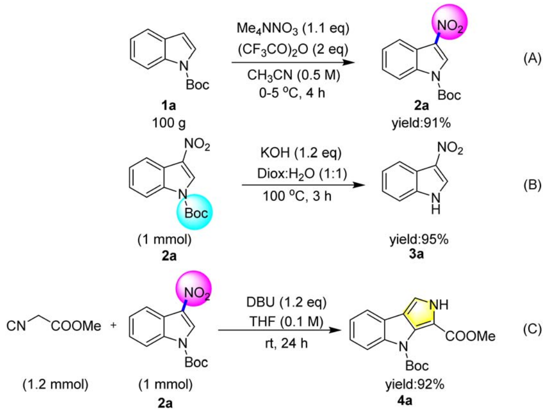
a) Reaction conditions: **1a** (1 mmol), NMe_4NO_3 (1.1 mmol), $(CF_3CO)_2O$ (2 eq), CH_3CN (2 mL), 0-5 °C, 4 h. b) Isolated yields.

Scheme 3 Substrate scope of indoles.[a,b]

protocol and carried out smoothly with good yield (**2o**). Furthermore, under this protocol, the corresponding 3-nitroindole can also be prepared from disubstituted indole in good yield (**2p**). The above cases showed that 5-7-substituted indoles had little influence on the protocol and could be used to prepare 3-nitroindoles in good to excellent yields (**2k**–**2p**).

Next we turned our attention to common aromatic and heteroaromatic hydrocarbons (Scheme 4). Gratifyingly, various aromatic and heteroaromatic hydrocarbons were well applicable in this transformation. Interestingly, benzene was compatible with this protocol and nitrobenzene was prepared in good yield (**2q**). Furthermore, the nitration of naphthalene and phenanthrene could be carried out smoothly under this protocol and the product could be obtained in good to excellent yield (**2r**–**2s**). Additionally, oxygen-containing aromatic hydrocarbons can be delivered successfully in good yields regardless of whether the oxygen atom is conjugated or not (**2t**–**2u**). Finally, sulfur-containing aromatic hydrocarbons are also compatible with the protocol to successfully prepare nitro compound in good yields (**2v**–**2w**). These examples showed that the protocol could be used to efficiently prepare other aromatic and heteroaromatic nitro compounds.

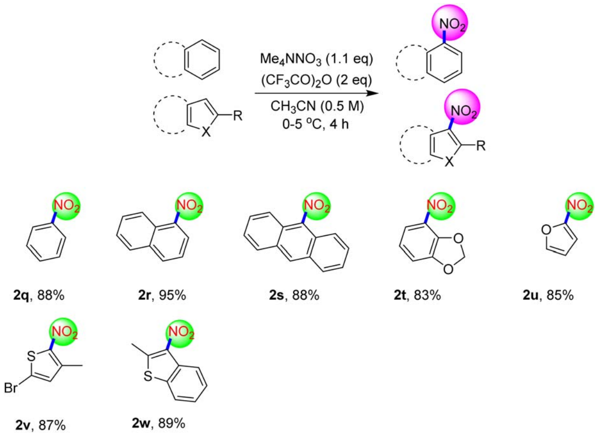
In order to explore the potential application of this protocol, a 100 g scale reaction was carried out with *N*-Boc indole **1a**, and the *N*-boc-3-nitroindole **2a** was isolated in 91% yield (Scheme 5A). 3-Nitroindole is an important intermediate that has been widely used by scientists for the synthesis of organic molecules[2] with biological activity.[3] Although there were several methods for the synthesis of 3-nitroindole.[4–7] However, the synthesis of 3-nitroindole without nitric acid still faces some challenges. Therefore, the deprotection of *N*-boc-3-nitroindole indicated the practical significance of this method (Scheme 5B). It is very challenging to assemble polyindoles in synthetic chemistry and medicinal chemistry.[19] 4-(*tert*-Butyl) 3-methyl pyrrolo[3,4-*b*]indole-3,4(2*H*)-dicarboxylate (**4a**) could be prepared by Barton–Zard reaction of *tert*-butyl 3-nitro-1*H*-indole-1-carboxylate (**2a**) in excellent yield.[4c] This result also reveals another value of the product (Scheme 5C).



Scheme 5 Scale-up reaction and synthetic application.

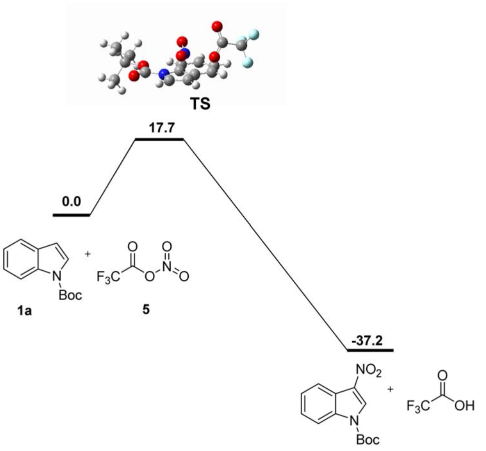
The calculated reaction transition states and processes were shown in Scheme 6. *N*-Boc indole (**1a**) and trifluoroacetyl nitrate (**5**) undergo a highly regioselective *via* TS to form product.

To reveal the mechanism and Regioselectivity of this reaction, we conducted a series of controlled experiments (Scheme 7). The fact that the reaction could not be carried out smoothly when there was no anhydride in this protocol proved that anhydride was an indispensable condition of the protocol. If the indole 3-position is occupied by the methyl group, the reaction can not be carried out smoothly, which shows that the protocol has a strong regioselectivity. Laali had described that nitrate could decompose with trifluoroacetic anhydride to produce trifluoroacetyl nitrate (CF_3COONO_2), and it had strong electrophilic nitrification for many aromatic hydrocarbons.[18] Based on the previous literature and the results of computational chemistry (Scheme 6), we proposed a possible reaction mechanism (Scheme 7). Initially, ammonium tetramethylnitrate and

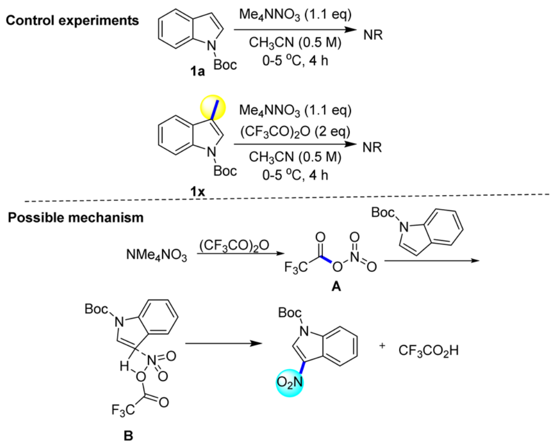


[a] Reaction conditions: **1a** (1 mmol), NMe_4NO_3 (1.1 mmol), $(CF_3CO)_2O$ (2 eq), CH_3CN (2 mL), 0-5 °C, 4 h. [b] Isolated yields.

Scheme 4 Substrate scope of aromatic and heteroaromatic hydrocarbons.[a,b]



Scheme 6 Complete reaction pathway. Free energies are computed at the PCM(dichloromethane)/B3LYP-D3BJ/6-31G(d)level and are in kcal mol^{-1}.



Scheme 7 Control experiments and possible mechanism.

trifluoroacetic anhydride worked together to form trifluoroacetyl nitrate (**A**). Species **A** reacted with *N*-Boc indole to form four-member ring transition state **B**. The trifluoroacetic acid was shed from the transition state to form a product.

Conclusions

In summary, we have developed a practical method for the regioselective nitration of indoles using ammonium tetramethylnitrate under non-acidic and non-metallic conditions. This protocol is not only mild and environmentally friendly, but also reveals the aromatic electrophilic nitration of trifluoroacetyl nitrate, which provides a new method for the further construction of 3-nitroindole and its analogues. Meanwhile, the 3-nitroindole can be further derivatived as a pyrrolo[3,4-*b*] indole. In the future, we will explore the value of 3-nitroindole in pharmaceutical chemistry and synthetic chemistry.

Experimental

General procedure for the synthesis of 2

Add aromatic or heteroaromatic hydrocarbons (1 mmol) and NMe_4NO_3 (150 mg, 1.1 mmol) to the reaction tube and immediately dissolve it with acetonitrile (1 mL). The reaction system was then cooled to 0–5 °C and the trifluoroacetic anhydride solution (420 mg dissolved in 1 mL CH_3CN) was added. The reaction system was incubated at 0–5 °C for 4 hours. At the same time, the reaction was monitored by TLC. When the reaction was completed, the reaction was quenched by saturated sodium carbonate. Extract with EA and transfer to a round bottom flask. Silica gel was added to the flask, and the solvent was evaporated under vacuum. Purified by silica gel column chromatography using ethyl acetate/petroleum ether as eluent to obtain compound **2**.

Conflicts of interest

There are no conflicts to declare.

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