Fe(III)/Pyridine-Mediated Decarboxylative Nitration of α,β-Unsaturated Acids with Iron Nitrate

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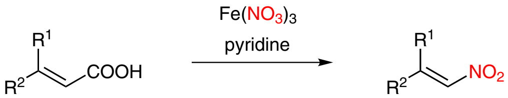

Yield up to 95%, 20 examples
$Fe(NO_3)_3$ as the catalyst and nitro source
R^1 = phenyl, alkyl and H
R^2 = aryl and heteroaryl

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Abstract A novel and efficient method for the synthesis of (*E*)-nitroolefins in moderate to excellent yields is developed by Fe(III)/pyridine-mediated decarboxylative nitration of α,β-unsaturated acids with iron nitrate. A series of α,β-unsaturated acids are well tolerated in this procedure.

Key words nitroolefins, decarboxylative, nitration, α,β-unsaturated acids, iron nitrate

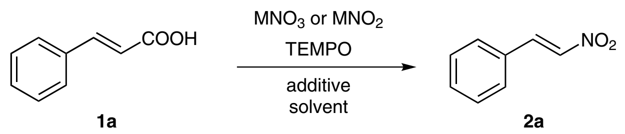
As a useful strategy for the selective formation of C–C and C–hetero bonds, the transition-metal-catalyzed decarboxylative cross-coupling reaction has attracted much attention from organic scientists.[1] One of the advantages of the strategy is that the carboxylic acid derivatives are used as coupling regents instead of aryl halides or organometallic derivatives, which is green and economic.[2] Furthermore, carboxylic acid derivatives, as cross-coupling reagents, are stable, cheap, and easy to prepare, and are receiving more and more attention in organic chemistry.[3] Among them, α,β-unsaturated acids have become a useful olefination reagent for the synthesis of many important compounds.[4]

Nitroolefins are important C–N bond-containing compounds in medicinal chemistry, synthetic organic chemistry, and materials science.[5] Several methods have been reported for the synthesis of nitroolefins from α,β-unsaturated acids. HNO_3 is used as the nitro agent in the traditional synthesis of nitroolefins.[6] Alternatively, variety of nitration agents such as *tert*-butylnitrite (*t*-BuONO), KNO_3, $NaNO_2$, $Cu(NO_3)_2$, and $Ni(NO_3)_2$ have also been employed in the decarboxylative nitration process.[7] Although these methods have been reported, there are some problems, such as harsh conditions, the formation of mixtures of *E* and *Z* isomers, expensive reagents, and limited reaction scopes.

Maitiand co-workers reported an efficient and highly selective nitration of olefins with $AgNO_2$/2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) for the synthesis of nitroolefins, and these protocols have great significance in this field.[8] Recently, a copper-nanoparticle-catalyzed decarboxylative nitration using $Bi(NO_3)_3{\cdot}5H_2O$ as the nitro source for nitroolefins has been developed.[9] However, the application of $Fe(NO_3)_2{\cdot}9H_2O$ as the nitro source for nitroolefins in the reaction of direct decarboxylative nitration is still unexplored. Here, we disclose Fe(III)/pyridine-mediated decarboxylative nitration synthesis of nitroolefin derivatives from the corresponding α,β-unsaturated acids.

Our investigation started with the decarboxylative cross-coupling reaction between cinnamic acid (**1a**) and nitrating agents in the presence of TEMPO (20 mol%) in dichloroethane (DCE; Table 1).[8] After heating at 80 °C for 12 hours when using $Fe(NO_3)_3{\cdot}9H_2O$ as the nitrating agent, the desired β-nitroolfin (**2a**) was obtained in low yield (28%, Table 1, entry 1). Further, nitrate sources such as $Co(NO_3)_2{\cdot}6H_2O$, $AgNO_3$, $Ni(NO_3)_2{\cdot}6H_2O$, and $Bi(NO_3)_3{\cdot}5H_2O$ were used, resulting a lower yield of the nitro product **2a** (Table 1, entries 2–5), and nitrite sources such as $NaNO_2$ failed to give the nitro product **2a** (Table 1, entry 6). There was no generation of product when benzoquinone (BQ) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were used as oxidant instead of TEMPO (Table 1, entry 7). Control experiments without TEMPO confirmed its necessity to obtain the desired outcome of the reaction (Table 1, entry 8). Subsequently, increasing the amount of TEMPO resulted in a significant increase in terms of product yield (Table 1, entry 9). Meanwhile, using a combination of TEMPO/$K_2S_2O_8$ as the oxidant, the yield of **2a** was decreased (Table 1, entry 10). The effect of base was investigated on the model reaction by using Na_2CO_3, pyridine, and Ag_2CO_3, and the results showed that an increase in the yield to give desired product **2a** was obtained by using pyridine as the base (Table 1, entries 11–13). And when the trifluoroacetic acid (TFA) was added, only 20% yield was observed (Table 1, entry 14). Further screening of solvents revealed that toluene was the best solvent, and other solvents, such as dioxane, THF, PEG-400, MeCN, and MCB (chlorobenzene) were also effective, and produced **2a** in good yields (Table 1, entries 13, 15–20). When the $Fe(NO_3)_3 \cdot 9H_2O$ loading was reduced from 2.0 equivalents to 1.2 equivalents, the reaction afforded the desired product in 55% yield (Table 1, entry 21). Without TEMPO, 1.0 equivalent of pyridine led to an excellent substrate conversion and the highest yield (95% yield for **2a**; Table 1, entry 22).

Table 1 DecarboxylativeNitration: Optimization of Reaction Conditions[a]



Entry	Nitrating agents	Addition	Solvent	Yield (%)[b]
1	$Fe(NO_3)_3 \cdot 9H_2O$	–	DCE	28
2	$Co(NO_3)_2 \cdot 6H_2O$	–	DCE	trace
3	$AgNO_3$	–	DCE	trace
4	$Ni(NO_3)_2 \cdot 6H_2O$	–	DCE	NR
5	$Bi(NO_3)_3 \cdot 5H_2O$	–	DCE	trace
6	$NaNO_2$	–	DCE	trace
7[c]	$Fe(NO_3)_3 \cdot 9H_2O$	–	DCE	NR
8[d]	$Fe(NO_3)_3 \cdot 9H_2O$	–	DCE	15
9[e]	$Fe(NO_3)_3 \cdot 9H_2O$	–	DCE	56
10	$Fe(NO_3)_3 \cdot 9H_2O$	$K_2S_2O_8$	DCE	trace
11	$Fe(NO_3)_3 \cdot 9H_2O$	Na_2CO_3	DCE	trace
12	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	DCE	60
13	$Fe(NO_3)_3 \cdot 9H_2O$	Ag_2CO_3	DCE	18
14	$Fe(NO_3)_3 \cdot 9H_2O$	TFA	DCE	20
15	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	dioxane	50
16	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	THF	29
17	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	toluene	71
18	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	PEG-400	40
19	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	MeCN	trace
20	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	MCB	34
21[f]	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	toluene	55
22[g]	$Fe(NO_3)_3 \cdot 9H_2O$	pyridine	toluene	95

[a] Reaction conditions: **1a** (0.2 mmol), nitrating agents (0.4 mmol), TEMPO (20 mol%), addition (0.2 mmol), solvent (2.0 mL), in air atmosphere for 12 h at 80 °C.
[b] GC yield was based on the amount of **1a**.
[c] BQ and DDQ were used instead of TEMPO.
[d] Without TEMPO.
[e] TEMPO (100 mol%) was used.
[f] Without TEMPO, nitrating agents (1.2 equiv) were used.
[g] Without TEMPO, at 100 °C.

Under the optimal reaction conditions, the decarboxylative nitration of a range of α,β-unsaturated acids to generate (*E*)-nitroolefins was performed. As shown in Scheme 1, the corresponding (*E*)-nitroolefins were obtained in good yields. The α,β-unsaturated acids bearing several functional groups such as Me, OMe, Cl, F, NO_2, and CF_3 were examined with $Fe(NO_3)_2 \cdot 9H_2O$, giving the coupling products **2a–j**,**l**,**p** in moderate to excellent yields. However, when the OH group was used, the reaction failed to give the corresponding product **2k**. Moreover, heteroaryl α,β-unsaturated acids gave the corresponding products with moderate yields (**2m**,**n**). Meanwhile, 3-(naphthalen-2-yl)acrylic acid under the reaction conditions resulted in the formation **2o** in good yield. The reactions with the β,β-disubstituted acrylic acids were successful as well, giving the products **2q–t** in moderate to good yields.

To study the mechanism of this decarboxylative nitration process, several control experiments were carried out. The reaction was also carried out in the presence of 2.0 equivalents of TEMPO under the standard conditions, only 11% yield of product **2a** was observed which favors the formation of nitroolefins through the radical mechanistic pathway (Scheme 2). However, when the reaction without $Fe(NO_3)_3 \cdot 9H_2O$ was carried out under the standard conditions, the desired product **3a** was not observed. This result suggests that the decarboxylation likely occurs on Fe(III) before radical addition.

On the basis of the above experimental results and literature precedent,[10] the radical mechanism shown in Scheme 3 is proposed. The nitro radical ($^{\bullet}NO_2$) can be generated from $Fe(NO_3)_3 \cdot 9H_2O$ under standard conditions.[11] The cinnamic acid would react with the $Fe(NO_3)_3 \cdot 9H_2O$ in order to generate a compound **a**.[12] This compound **a** can be translated to β-nitroolefin via two plausible pathways. In path 1, the decarboxylation may occur on Fe(III) before free-radical addition,[13] and in path 2, the free-radical addition likely occurs on compound **a** before the decarboxylation.

In summary, an efficient decarboxylative nitration reaction of α,β-unsaturated acids with $Fe(NO_3)_2 \cdot 9H_2O$ as the nitro source has been developed to afford (*E*)-nitroolefins.[14] A wide range of α,β-unsaturated acids were compatible under these conditions, affording (*E*)-nitroolefins in good yields. The effect of Fe(III)/pyridine-mediated decarboxylative nitration reaction on the stereoselectivity of nitroolefin was also proposed. Furthermore, applications of this decarboxylative nitration protocol for the formation of C–C or C–hetero bonds are currently under investigation in our laboratory.

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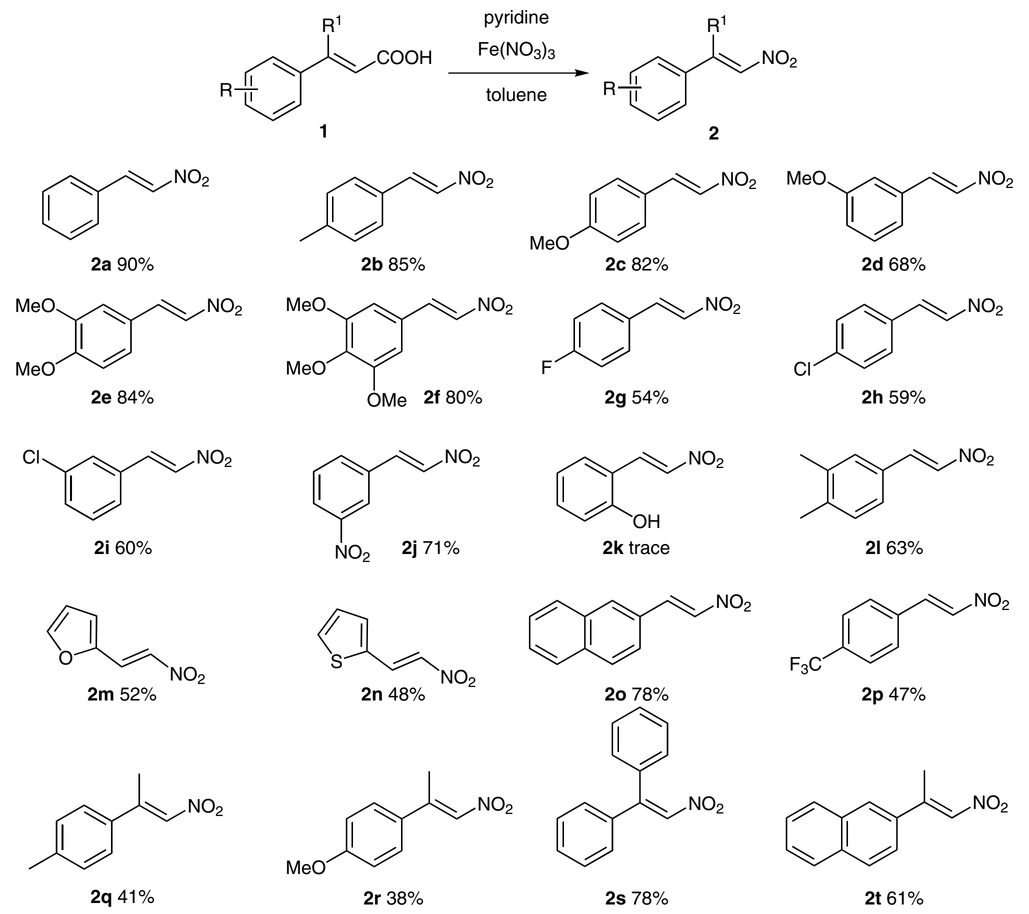
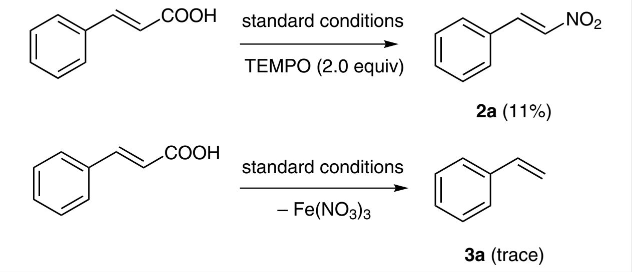


Scheme 1 Decarboxylative nitration of α,β-unsaturated acids. *Reagents and conditions*: **1** (0.5 mmol), $Fe(NO_3)_3·9H_2O$ (1.0 mmol), pyridine (0.5 mmol), toluene (4.0 mL), in air for 12 h at 100 °C. Isolated yields are given.



Scheme 2 Control experiments

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588948.

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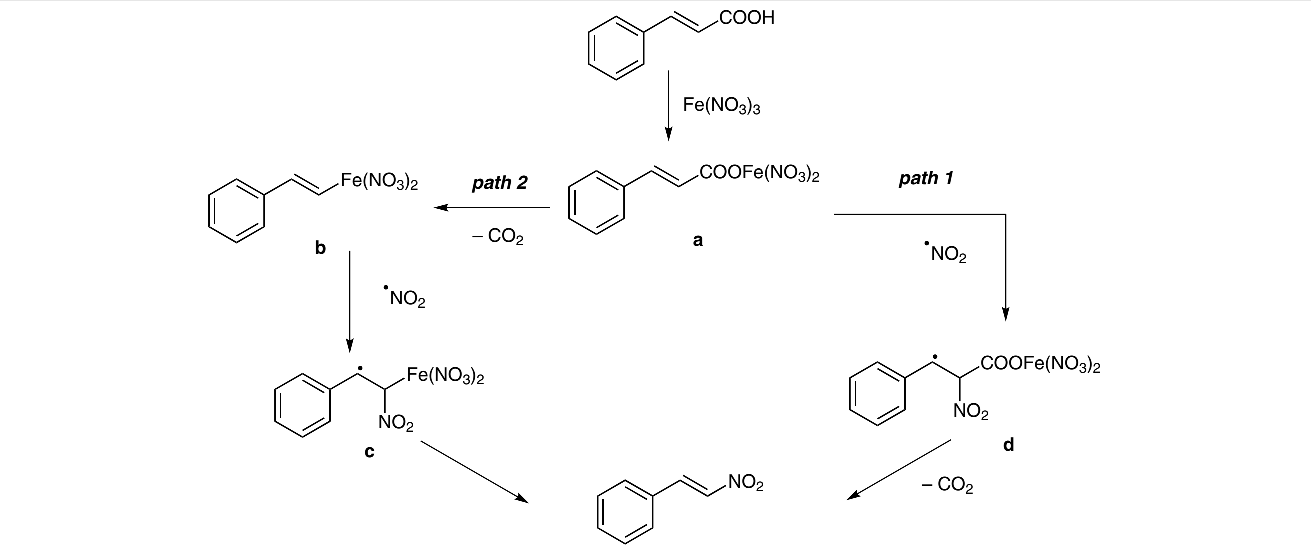

Scheme 3 Proposed mechanism for the decarboxylative nitration process

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(14) **Procedure for the Synthesis of β-Nitrostyrene**
The mixture of cinnamic acid (0.5 mmol), $Fe(NO_3)_3$ (1.0 mmol), pyridine (0.5 mmol), and toluene (2 mL) was stirred at 100 °C for 12 h. After cooling to r.t., the reaction mixture was washed with H_2O (10 mL) and extracted by EtOAc (3×). The organic phase was dried with anhydrous $MgSO_4$. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (15% EtOAc–*n*-hexane) to afford pure product.
Yellow solid (90%, 77 mg). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.57 (m, 5 H), 7.59 (d, $J = 13.7$ Hz, 1 H), 8.01 (d, $J = 13.7$ Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 129.16$, 129.43, 130.14, 132.15, 137.19, 139.06.