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Graphical Abstract

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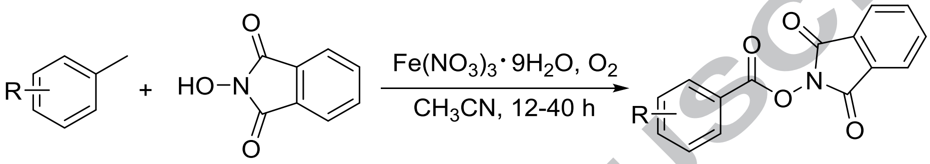

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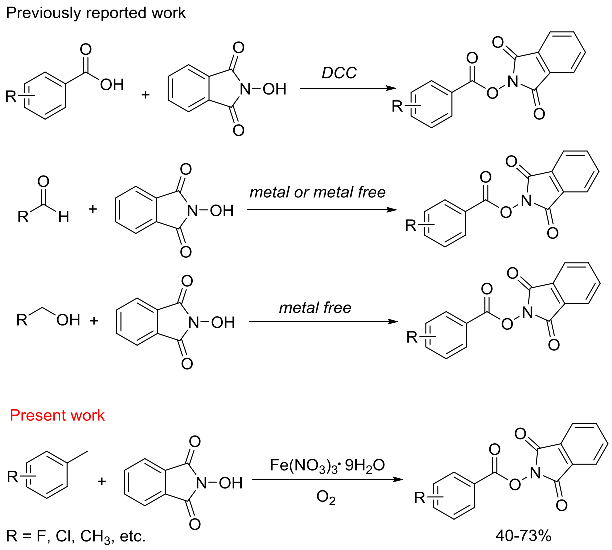
ABSTRACT

A ferric nitrate-promoted cross-dehydrogenative coupling reaction of *N*-hydroxyphthalimide (NHPI) with toluene derivatives is reported. The reaction proceeded smoothly using molecular oxygen as an oxidant, providing an efficient method for the synthesis of *N*-hydroxyimide esters. Furthermore, a plausible mechanism was proposed.

Introduction

N-Hydroxyimide esters were active intermediates, which can be used in the synthesis of amides, esters, *O*-substituted hydroxylamines.[1] Over the past years, a series of methods for the preparation of *N*-hydroxyimide esters have been developed. The reported methods are summarized as follows: (1) coupling of carboxylic acids with *N*-hydroxyimide (NHPI) in the presence of *N*,*N'*-dicyclohexylcarbodiimide;[2] (2) oxidative cross-dehydrogenative coupling of aldehydes with NHPI in the presence of a metal catalyst or under metal-free conditions;[3] (3) oxidative cross-dehydrogenative coupling of alcohols with NHPI under metal-free conditions.[4] The above-mentioned methods appear to be general and efficient. However, the cross-dehydrogenative coupling reaction of toluene derivatives with NHPI still remains a major challenge.

In recent years, iron(III) nitrate nonahydrate [$Fe(NO_3)_3·9H_2O$] has been used as a nitration reagent, as well as a catalyst in the oxidation of benzyl alcohols.[5] In our previous work, we have described $Fe(NO_3)_3·9H_2O$ catalyzed synthesis of *N*-hydroxyimide ester by a cross-dehydrogenative coupling reaction of aldehydes or alcohols with NHPI in the air.[6] NHPI has also been used to catalyze the oxidation of toluene for the preparation of *N*-hydroxyimide ester. However, the use of environmentally unfriendly co-catalyst cobalt salts and expensive solvent 1,1,1,3,3,3-hexafluoropropan-2-ol has limited the application of this reaction.[7] Therefore, synthesis of *N*-hydroxyimide esters under simple and efficient reaction conditions using environment benign, cheap and commercially available reagents, such as toluene, $Fe(NO_3)_3·9H_2O$ and O_2 as a green oxidant has received a great interest.



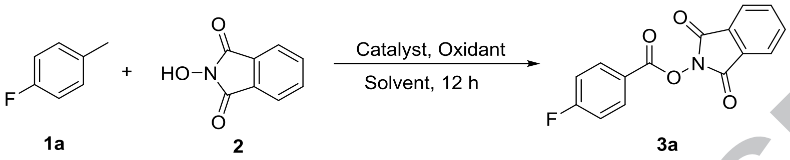
Scheme 1. Design synthesis of *N*-hydroxyamide esters

Results and discussion

Initially, *p*-fluorotoluene **1a** and NHPI **2** were used as the model substrates to explore the optimal reaction conditions. The results are summarized in Table 1. When $Cu(NO_3)_2·3H_2O$ (20 mol%) was used as a catalyst in the presence of oxygen in CH_3CN, the desired product **3a** was obtained in 52% yield (entry 1). Other catalysts such as $Mg(NO_3)_2·6H_2O$ and $NaNO_2$ were found to be less effective (entries 2-3). To our delight, when $Fe(NO_3)_3·9H_2O$ was used as the catalyst, the desired product was obtained in 63% yield (entry 4). Decreasing or increasing the reaction temperature led to lower yields (entries 5-6).

Furthermore, the effects of different solvents were investigated and CH_3CN was found to be the optimal solvent (entries 7-10). When in the air, 45% yield of **3a** was obtained (entry 11). A similar yield was obtained when TBHP was used as an oxidant (entry 12). However, under a N_2 atmosphere, only 30% yield of **3a** was obtained (entry 13) .The effect of amount of NHPI on the reaction was also studied, it was found that the yield of **3a** reduced when 1.0 equiv. of **2** was used (entry 14). Additionally, changes in the amount of $Fe(NO_3)_3·9H_2O$ did not obviously affected the yield of **3a** (entries 15-16).

Table 1. Optimization of the reaction conditions.[a]



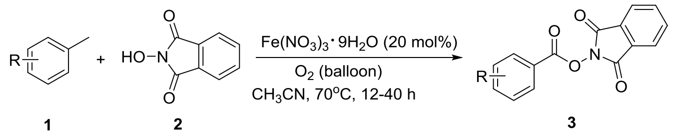
Entry	Solvent	Catalyst	T. (°C)	Oxidant	Yield (%)[b]
1	CH_3CN	$Cu(NO_3)_2·3H_2O$	70	O_2	52
2	CH_3CN	$Mg(NO_3)_2·6H_2O$	70	O_2	37
3	CH_3CN	$NaNO_2$	70	O_2	Trace
4	**CH_3CN**	**$Fe(NO_3)_3·9H_2O$**	**70**	**O_2**	**63**
5	CH_3CN	$Fe(NO_3)_3·9H_2O$	60	O_2	50
6	CH_3CN	$Fe(NO_3)_3·9H_2O$	82	O_2	61
7	H_2O	$Fe(NO_3)_3·9H_2O$	70	O_2	N.D.
8	EtOAc	$Fe(NO_3)_3·9H_2O$	70	O_2	27
9	CH_3CH_2OH	$Fe(NO_3)_3·9H_2O$	70	O_2	10
10	HFIP	$Fe(NO_3)_3·9H_2O$	70	O_2	15
11	CH_3CN	$Fe(NO_3)_3·9H_2O$	70	air	45
12[c]	CH_3CN	$Fe(NO_3)_3·9H_2O$	70	TBHP(6.0)	59
13[d]	CH_3CN	$Fe(NO_3)_3·9H_2O$	70	--	30
14[e]	CH_3CN	$Fe(NO_3)_3·9H_2O$	70	O_2	35
15[f]	CH_3CN	$Fe(NO_3)_3·9H_2O$	70	O_2	52
16[g]	CH_3CN	$Fe(NO_3)_3·9H_2O$	70	O_2	56

[a]Reactions were conducted with **1a** (1.0 mmol), **2** (2.0 mmol) and catalyst (20 mol%) in solvent (4 mL) under O_2 (balloon) for 12 h, unless otherwise noted. [b]Isolated yields based on **1a**. [c]TBHP (70% in water). [d]Under N_2 atmosphere. [e]**2** (1.0 mmol). [f]$Fe(NO_3)_3·9H_2O$ (15 mol%). [g]$Fe(NO_3)_3·9H_2O$ (30 mol%).

With the optimized conditions in hand, the scope of substrates was investigated. As shown in Table 2, a series of toluene derivatives reacted smoothly with NHPI, and the corresponding products were obtained in moderate to good yields. The reaction of NHPI with toluene derivatives bearing electron-withdrawing groups, such as F, Cl, Br and I at the *para*-positions of benzene rings proceeded well under the optimized conditions and gave coupling products **3a-3d** in 43-63% yields (entries 1-4). Due to steric effects, the reaction of the toluene derivatives with a substituent at *ortho*- or *meta*-position of benzene ring provided the products **3e-3j** in slightly lower yields 48-56 % (entries 5-10). The reaction of a toluene derivative with a strong electron-withdrawing group NO_2 generated the corresponding product **3k** in only 40% yield (entry 11). In the cases of electron-donating group, such as OCH_3, at the *para*-, or *othro*- or *meta*-position of toluene, higher yields of products **3l**, **3m**, and **3n** were obtained, being 73, 68, and 58%, respectively (entries 12-14). The reaction with *p*-*tert*-butyl toluene only gave the desired product **3o** in a lower yield (entry 15). Unfortunately, the reaction did not occur when NHPI analogues, such as *N*-hydroxysuccinimide (NHSI) and *N*-hydroxybenzotriazole (HOBt), were used instead of NHPI.

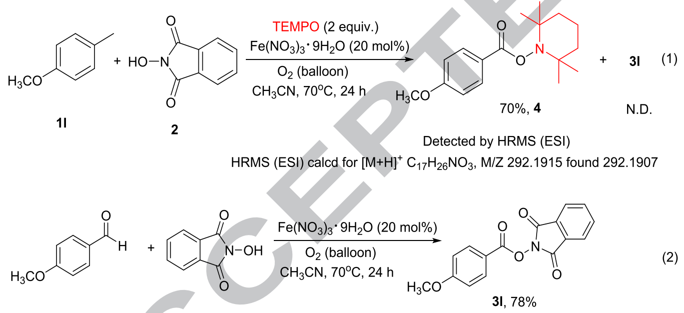
Using the established method, a control experiment was performed. Under the standard conditions, the esterification of 4-methoxytoluene **1l** with NHPI **2** was conducted in the presence of TEMPO. The desired product **3l** was not detected and a TEMPO-captured product **4** was obtained in 70% yield (Scheme **2**, eq. 1), which indicated that the reaction might proceed in a radical way. Besides, when 4-methoxybenzaldehyde was used instead of 4-methoxytoluene under the standard conditions, luckily, 78% yields of desired product was obtained (Scheme **2**, eq. 2). This result also demonstrated that aldehyde was the reaction intermediate. Based on the results of this experiment and the previous reports,[6,8] a plausible reaction pathway was illustrated in Scheme **3**. In this proposed mechanism, ferric nitrate functions as a radical initiator. Hydrolysis of ferric nitrate yields HNO_3, the latter undergoes thermal decomposition to generate NO_2. Then NO_2 captures a hydrogen atom from NHPI to form PINO, the latter absorbs a hydrogen atom from toluene to produce the corresponding radical **A**, which subsequently reacts with molecular oxygen, producing peroxide radical **B**. Then **B** captures a hydrogen atom from NHPI to produce the intermediate **C**,[9] which is converted to the benzaldehyde intermediate **D** after losing water.[10] Next, PINO obtains a hydrogen atom from aldehyde to produce the corresponding radical **E**, which further reacts with PINO to produce the *N*-hydroxyimide ester **3**.

Table 2. Reaction of **2** with toluene derivatives.[a]



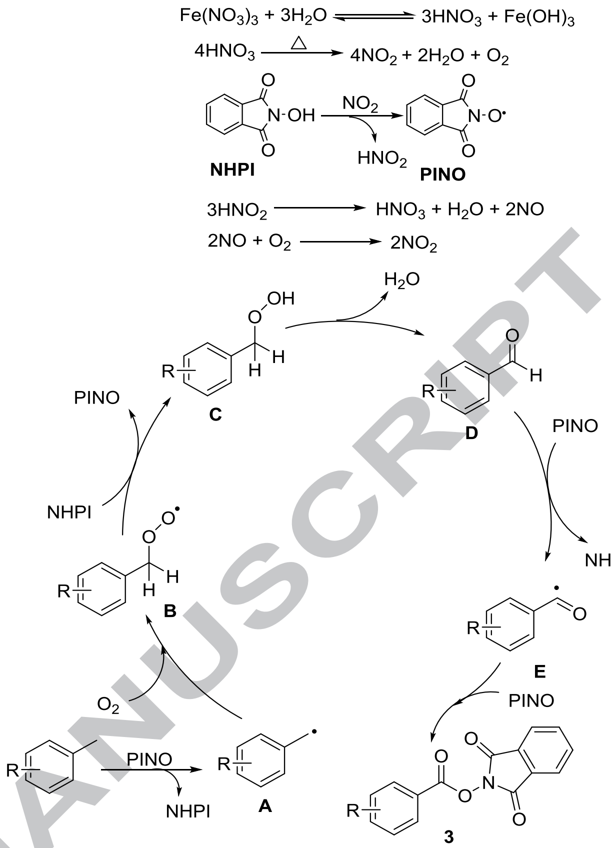
Entry	R	t (h)	3	Yield (%)[b]
1	4-F	12	**3a**	63
2	4-Cl	12	**3b**	60
3	4-Br	12	**3c**	59
4	4-I	36	**3d**	43
5	2-F	16	**3e**	48
6	2-Cl	12	**3f**	50
7	2,4-Cl	16	**3g**	51
8	2-Br	16	**3h**	53
9	3-Br-4-F	16	**3i**	50
10	3-Br	16	**3j**	56
11	4-NO_2	40	**3k**	40
12	4-OCH_3	24	**3l**	73
13	3-OCH_3	24	**3m**	68
14	2-OCH_3	24	**3n**	58
15	4-^{t}Bu	24	**3o**	54

[a]Reactions were conducted with **1** (1.0 mmol), **2** (2.0 mmol) and $Fe(NO_3)_3 \cdot 9H_2O$ (20 mol%) in CH_3CN (4 mL) at 70°C for 12–40 h under O_2 (balloon) conditions. [b]Isolated yields based on **1**.



Scheme 2. Control experiment

In conclusion, we have developed a novel and efficient method for the synthesis of *N*-hydroxyimide esters. This is the first report that describes the use of toluene derivatives as the coupling partners for NHPI to give the corresponding esters. In addition, other advantages of this methodology include using inexpensive $Fe(NO_3)_3 \cdot 9H_2O$ as a radical initiator and O_2 as an oxidant. Further studies on the coupling reaction of amine with *N*-hydroxyimide esters are underway.



Scheme 3. Proposed mechanism

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