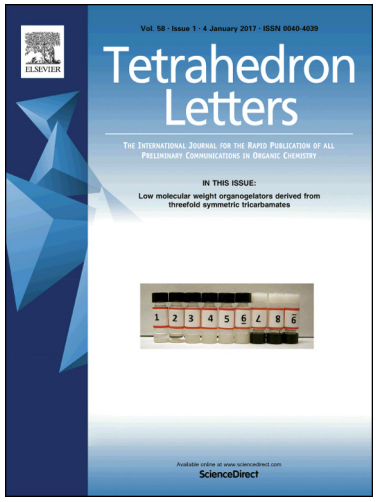

Atmospheric Oxidative Catalyst-Free Cross-Dehydrogenative Coupling of Aldehydes with *N*-hydroxyimides

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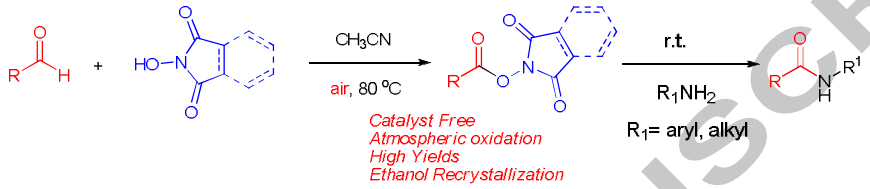

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Atmospheric Oxidative Catalyst-Free Cross-Dehydrogenative Coupling of Aldehydes with *N*-hydroxyimides

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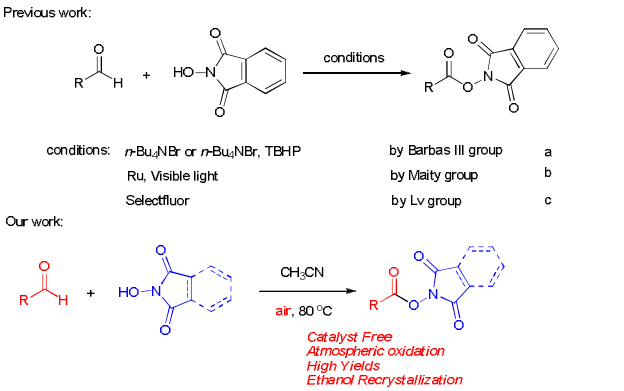
ABSTRACT

Cross-dehydrogenative coupling (CDC) reactions of aldehydes with *N*-hydroxyimidates such as *N*-hydroxysuccinimide (NHSI), *N*-hydroxyphthalimide (NHPI) under catalyst-free conditions is described. Moreover, the desired products can be obtained simply by recrystallization from ethanol. This method is also applicable to the synthesis of amides in excellent yields. A radical mechanism of the type shown in Scheme 4 is proposed based upon the inhibition of the reaction in the presence of TEMPO.

Introduction

Nowadays, cross-dehydrogenative coupling (CDC) has been considered as a green method to construct C-C[1] and C-O[2] bonds due to its high atom efficiency and avoidance of the prefunctionalization of substrates. Generally, CDC reactions requires the use of co-oxidants such as tert-butylhydroperoxide, H_2O_2, potassium persulfate ($K_2S_2O_8$), 2,3-dichloro-5,6-dicyano-para-benzoquinone (DDQ) and so on.[2,3] Compared to the C-C cross-coupling, oxidative C-O coupling reactions were much lesser developed, especially for the aldehydes involved C-O[4] coupling reaction since aldehydes are prone to side oxidation and fragmentation reactions giving carboxylic acids or carbonyl compounds. *N*-hydroxyamide ester, which is an active intermediate, can be used to synthesize amides and esters.[5] Traditionally, *N*-hydroxyamide ester was prepared *via* direct coupling of carboxylic acids with *N*-hydroxyimides in the persence of carbodiimide as an activating reagents,[6] which suffers from poor atom efficiency and difficult purification process of product. Fortunately, a few of CDC reactions of aldehyde with *N*-hydroxyimide have been developed as an effective alternative to solve this problem. In 2012, Tan and co-workers developed an *n*-Bu_4NBr or *n*-Bu_4NI catalyzed cross-coupling reaction of aldehydes with *N*-hydroxyimides using tert-butyl hydrogen peroxide (TBHP) as oxidant. Later on, Barbas III (Scheme 1 a)[7a], Maity (b)[7b] and Lv (c)[7c] groups have also successfully achieved this transformation, respectively. However, these methods still suffer from the use of specific oxidants and heavy-metal catalysts. Therefore, milder and more environmentally benign synthetic methods are still required for the synthesis of *N*-hydroxyamide ester.

Oxygen has been used as an ideal oxidant in many chemical processes due to its abundance and environmental friendiness.[8] In the presence of O_2, NHPI could be oxidized to PINO, which could initiate the following radical oxidative reactions.[9] Herein, we envisioned that O_2 could be used as oxidant for the coupling of aldehydes with NHPI under catalyst-free conditions.



Scheme 1. Various apporoaches for CDC reaction of aldehydes with *N*-hydroxyimides

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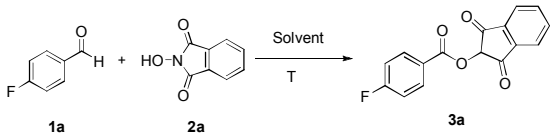
Results and discussion

Initially, a model reaction between *p*-fluorobenzaldehyde **1a** and NHPI **2a** was chosen to explore optimal reaction conditions and the results are summarized in Table 1. Firstly, the reaction was conducted in THF at 60 °C in open air and a trace amout of desired coupling product **3a** was detected (entry 1). However, no product was observed when DMF, DMSO, CH_2Cl_2, toluene and acetone were used as solvents (entries 2-6). When the reaction was carried out in CH_3CN, the yield of **3a** was increased dramatically to 94% (entry 7). By switching to alternative greener solvents such as EtOAc and diethyl carbonate (DEC), the products were obtained in moderate yields (entries 8-9). Furthermore, lower reaction temperature led to the decrease of yield (entry 10). Then the quantities of *p*-fluorobenzaldehyde was also studied, revealed that 2.0 equiv of the **1a** was sufficient to complete the conversion (entries 11-12). It is noteworthy that the reaction did not proceed well under N_2 (entry 13), indicating that oxygen was necessary for this transformation.

Table 1. Optimization of the reaction conditions[a]

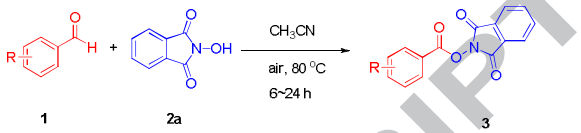


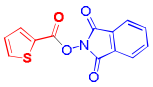
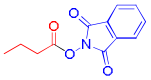
Entry	Solvent	T. (°C)	t. (h)	Yield (%)[b]
1	THF	60	6	trace
2	DMF	100	6	N.R.
3	DMSO	100	6	N.R.
4	CH_2Cl_2	30	6	N.R.
5	toluene	100	6	N.R.
6	acetone	56	6	N.R.
7	CH_3CN	80	6	94
8	EtOAc	77	10	75
9	DEC	100	18	83
10	CH_3CN	70	6	83
11[c]	CH_3CN	80	6	50
12[d]	CH_3CN	80	6	93
13[e]	CH_3CN	80	6	trace

[a.] Reactions were conducted with **1a** (1.0 mmol) and **2a** (0.5 mmol) in 3 mL solvent under open air conditions, unless otherwise noted.
[b.] Isolated yields after ethanol recrystallization based on **2a**.
[c.] **1a** (0.5mmol)
[d.] **1a** (1.5mmol)
[e.] Under N_2. N.R.= no reaction

With the optimized reaction conditions in hand, we then investigated the scope of this coupling reaction between NHPI and various aldehydes, and the results are summarized in Table 2. The reactions of NHPI with aldehydes bearing electron-withdrawing groups, such as CF_3, F, Cl, and Br at the ortho- and para-positions of benzene rings proceeded well under the optimized reaction conditions and gave excellent yields (90-94%) of coupling products (**3a**-**3h**). Aldehydes with electron-donating groups, such as methyl and methoxy afforded desired products (**3i**-**3k**) in better yields (94-95%). These results suggest that the electronic effect of substituents on phenyl ring (para-, meta-, and ortho- position) in the aldehydes did not affect the efficiency of the coupling reactions. The optimized conditions were successfully applied to thiophene-2-carbaldehyde and moderate yield of desired coupling product (**3m**) was obtained. It is noteworthy that sensitive functional group such as ester group was well tolerated in the reaction and desired product **3n** was obtained in 88% yield (entry 14), however, other sensitive group such as hydroxyl on the aldehyde (ortho-, meta- and para-positions) and 3-(4-methoxyphenyl)acrylaldehyde did not process well with NHPI. Aliphatic aldehydes turned out to be poor substrates for this transformation (entry 15).

Table 2. Reaction of **2a** with various aldehydes[a]

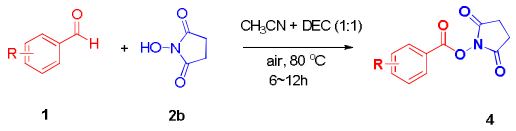


Entry	R	t. (h)	3	Yield (%)[b]
1	4-F	6	**3a**	94
2	2-F	8	**3b**	93
3	4-Cl	8	**3c**	94
4	2-Cl	10	**3d**	92
5	2,4-Cl	10	**3e**	90
6	4-Br	8	**3f**	93
7[c]	2-Br	8	**3g**	90
8	4-CF_3	10	**3h**	94
9	4-CH_3	18	**3i**	94
10	3-OCH_3	18	**3g**	95
11	2-OCH_3	10	**3k**	95
12	H	6	**3l**	90
13		18	**3m**	75
14	4-$COOCH_3$	6	**3n**	88
15		24	--	N.R.

[a.] Reactions were conducted with **1** (1.0 mmol) and **2a** (0.5 mmol) in CH_3CN (3 mL) at 80 °C for 6-24h under open air conditions, unless otherwise noted.
[b.] Isolated yields after ethanol recrystallization based on **2a**.
[c.] EtOAc was used as solvent. N.R.= no reaction

Then, we continued to explore the reaction of aldehydes with *N*-hydroxysuccinimide (**2b**, NHSI) under optimized reaction conditions with minor modifications. Gratifyingly, the desired coupling products were obtained when a mixed solvent of CH_3CN and DEC (CH_3CN/DEC = 1/1) was used, and the results are summarized in Table 3. Aldehydes with electron-withdrawing substitutents like CF_3, fluoro, chloro, and bromo were all good substrates and the desired coupling products were obtained in 80-89% yields (**4a**-**4e**). Aldehydes bearing electron-donating groups such as methyl and methoxy gave excellent yields of corresponding products in 90-95% yields (**4f**-**4g**).

Table 3. Reaction of **2b** with various aldehydes[a]

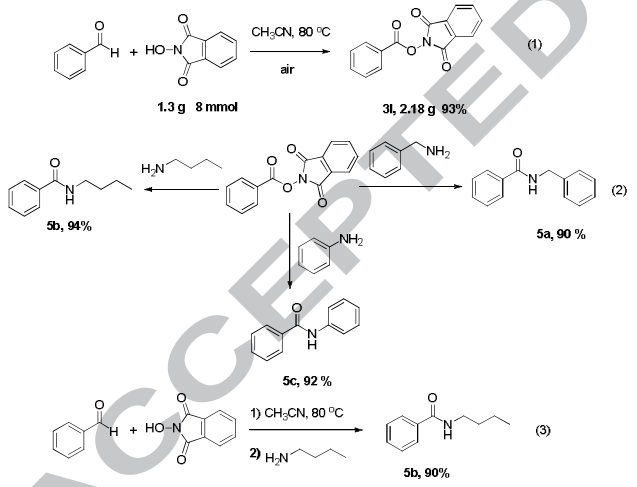


1 2b 4

Entry	R	t. (h)	4	Yield (%)[b]
1	4-F	6	**4a**	83
2	2-F	10	**4b**	82
3	4-Cl	10	**4c**	80
4	4-Br	10	**4d**	82
5	4-CF_3	8	**4e**	89
6	4-CH_3	10	**4f**	95
7	3-OCH_3	12	**4g**	90
8	H	10	**4h**	80

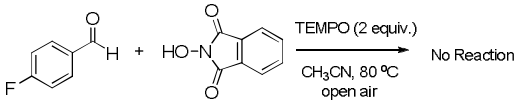
[a.] Reactions were conducted with **1** (1.0 mmol) and **2b** (0.5 mmol) in CH_3CN/DEC (1:1 3 mL) at 80 °C for 6-12h under open air conditions .
[b.] Isolated yields after ethanol recrystallization based on **2b**

N-hydroxyimide esters (**3** or **4**) are usually used as active esters for amidation process. To demonstrate the practical utility of this coupling reaction, the reaction of benzaldehyde with NHPI was performed at an 8 mmol scale and the product **3l** was still obtained in excellent yield [Scheme 2, eq. (1)]. Next, **3l** was used as active esters to synthesize amides, providing amidation products in excellent yields [Scheme 2, eq. (2)]. Meanwhile, one-pot synthesis of amide directly from aldehyde, NHPI and amine was investigated. After the oxidative coupling of benzaldehyde and NHPI, butan-1-amine was added directly to the reaction mixture, and the desired product **5b** was obtained in 90% yield [Scheme 2, eq. (3)].

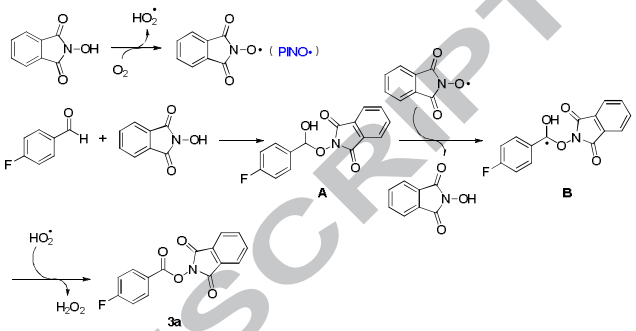


Scheme 2. Synthesis of various amides.

In order to gain a good insight into the mechanism of reaction, one control experiment of 4-fluorobenzaldehyde (**1a**) with NHPI (**2a**) was conducted in the presence of TEMPO under the standard reaction conditions and the desired product **3a** was not detected (Scheme 3), indicating that the reaction might proceed in a radical way. Based on the results of this experiment and the literature reported,[7,8] a plausible reaction pathway was illustrated in Scheme 4. Initially, in the presence of molecular oxygen and under heating, NHPI could afford PINO radical, which subsequently abstracts one hydrogen atom from **A** and forms radical **B**. Further oxidation of **B** affords the final product **3a.**



Scheme 3. Coupling of *p*-fluorobenzaldehyde with NHPI in the presence of TEMPO.



Scheme 4 Proposed mechanism for CDC reaction of *p*-fluorobenzaldehyde with NHPI

In conclusion, we have developed a novel and efficient approach for the synthesis of *N*-hydroxyimide esters *via* cross-dehydrogenative coupling (CDC) of aldehydes with NHPI under oxidative catalyst-free conditions. Notably, the use of molecular oxygen (air) as the terminal oxidant and simple purification process make this method environmentally friendly and practical. Moreover, this approach was successfully used for the straightforward synthesis of various amides. Further studies on this CDC reactions between other aromatic aldehydes and *N*-hydroxyimides and its mechanism are currently underway.

Acknowkedgment

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10. Typical experimental procedure: *p*-Fluorobenzaldehyde (**1a**) (124.0 mg, 1.0 mmol, 1.0 equiv.) and NHPI (**2a**) (82.0 mg, 0.5 mmol, 0.5 equiv.) were dissolved in CH_3CN (3 mL) and then stirred under reflux for 6 h under open air conditons. After the reaction was completed (monitored by TLC), the reaction mixture was concentrated under vacuum. The residue was purified by ethanol recrystallization to give the product **3a** (134.7 mg, 94% yield) as a white solid, m. p. 193-195 °C (lit.[7c] 194-195°C). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ = 8.25 (dd, J = 8.8, 5.2 Hz, 2H), 8.03-8.01 (m, 2H), 7.98-7.96 (m, 2H), 7.52 (t, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ = 166.1 ($^1J_{C\text{-}F}$ = 253.3 Hz), 161.53, 161.45, 135.4, 133.1 ($^3J_{C\text{-}F}$ = 10.1 Hz), 127.9, 123.9, 120.6 ($^4J_{C\text{-}F}$ = 2.1 Hz), 116.8 ($^2J_{C\text{-}F}$ = 22.4 Hz).

Highlights

1. Catalyst-Free protocol
2. Air as the terminal oxidant
3. Simple purification
4. Gram synthesis
5. One-pot synthesis amides