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ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C6RA22653A

Journal Name

COMMUNICATION

# Metal-free Intermolecular C–O Cross-Coupling Reactions: Synthesis of *N*-hydroxyimide esters

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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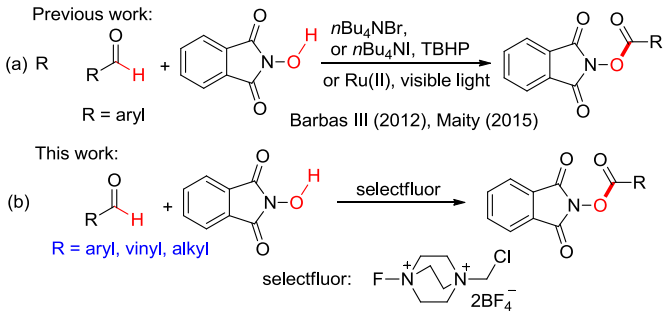
**Selectfluor-mediated intermolecular C–O cross coupling reaction for the synthesis of *N*-hydroxyimide esters was developed for the first time. The reaction is applicable to the coupling of readily available aryl and alkyl aldehydes with *N*-hydroxyphthalimide (NHPI) and *N*-hydroxysuccinimide (NHSI). The resulting active esters can be directly converted into amides in one pot.**

Carboxylic acid esters of *N*-Hydroxyphthalimide (NHPI) are widely used as activated carboxylic acid derivatives to promote the reaction with most common heteronucleophiles such as amines, alcohols and thiols in the synthesis of natural products[1] and their analogues, particularly affinity labels for cell receptom.[2] *N*-hydroxyimide esters are traditionally synthesized from carboxylic acids and *N*-hydroxyphthalimide in the presence of *N*,*N*′-dicyclohexylcarbodiimide.[3] However, this method suffers from several drawbacks such as the allergenic potential of the coupling agent, poor atom economy, and the formation of urea as byproduct that may make difficult the isolation of pure NHPI esters. In this context, the most simple and efficient route for the synthesis of *N*-hydroxyimide esters might be the oxidative C–O bond coupling reaction between C–H bonds in aldehydes and O–H bonds in NHPI. While oxidative C–O bond coupling reaction for their synthesis have been reported,[4] the development of conceptually different synthetic approaches is still of great interest. In 2012, Barbas III and co-workers reported an organocatalytic cross-coupling reaction of aldehydes with *N*-hydroxyimides.[5a] In 2015, A stepwise procedure was developed by Maity and co-workers for the synthesis of *N*-hydroxyimide esters via visible light photoredox catalysis (Scheme 1, eqn a).[5b] Although the above-mentioned elegant methods appear to be general and efficient, but these methods are still restricted to aryl aldehydes. Hence, practical and efficient approaches to obtain *N*-hydroxyimide esters from readily available starting material are still required.

On the other hand, selectfluor is not only one of the most reactive fluorinating reagents available, but it is also safe, nontoxic, and easy to handle.[6] In 2012, Lectka and co-workers reported C($sp^3$)–H fluorination employing a combination of selectfluor, a copper(I) bisimine complex, an anionic phase-transfer catalyst and NHPI.[7a] In 2013, Inoue and co-workers reported direct C($sp^3$)–H fluorination using a catalytic system consisting of selectfluor and *N*,*N*-dihydroxypyromellitimide (NDHPI).[7b] In recent years, selectfluor has been also utilized as a versatile mediator or catalyst for various other functionalisations of organic compounds.[8] Recently, we reported selectfluor-mediated highly selective radical dioxygenation of alkenes[9a] and direct reductive amination of tertiary anilines with aldehydes.[9b] It serves as a strong oxidant for these "fluorine-free" functionalizations. It is possible for selectfluor to oxidize aldehydes and NHPI to produce *N*-hydroxyimide esters. To the best of our knowledge, there is no precedence of selectfluor-mediated methodology with readily available aldehydes and NHPI as precursors for the synthesis of *N*-hydroxyimide esters via a CDC approach under metal-free conditions. Herein, we disclose the first example of selectfluor-mediated intermolecular C–O cross-coupling reactions of simple aldehydes with NHPI without using any metal catalyst (Scheme 1, eqn b).

Recently, we have developed metal-free catalyzed C–N and C–O bond formation reactions directly from C–H bonds.[9] As part of our continuing effort towards the development of




**Scheme 1** Synthesis of *N*-hydroxyimide esters from aldehydes and NHPI

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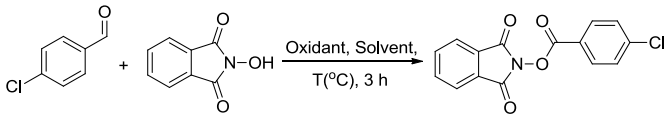
Electronic Supplementary Information (ESI) available: See
DOI: 10.1039/x0xx00000x

**Table 1** Optimization of the Reaction Conditions[a]




1a 2 3a

| Entry | Oxidant | Solvent | T (°C) | Yield(%)[b] |
|---|---|---|---|---|
| 1 | selectfluor | $CH_3CN$ | 60 | 59 |
| 2 | selectfluor | $CH_3CN$ | 25 | 9 |
| **3** | **selectfluor** | **$CH_3CN$** | **90** | **91** |
| 4 | NFSI | $CH_3CN$ | 90 | trace |
| 5 | TBHP[c] | $CH_3CN$ | 90 | 32 |
| 6 | TBHP[d] | $CH_3CN$ | 90 | 21 |
| 7 | $H_2O_2$[e] | $CH_3CN$ | 90 | 0 |
| 8 | selectfluor | $CHCl_3$ | 90 | trace |
| 9 | selectfluor | $CH_2Cl_2$ | 90 | 20 |
| 10 | selectfluor | DMF | 90 | 0 |
| 11 | selectfluor | EtOH | 90 | trace |
| 12 | selectfluor | EtOAc | 90 | 35 |
| 13 | none | $CH_3CN$ | 90 | 0 |

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), oxidant (0.36 mmol), solvent (3.0 mL), 3 h. [b] Yield of the isolated product. [c] TBHP (70% in water). [d] TBHP (5.5 M in decane). [e] $H_2O_2$ (30% in water).

methodologies to construct C–O bonds, we attempted intermolecular C–O cross-coupling of aldehydes with NHPI. Initially, 4-chlorobenzaldehyde **1a** and NHPI **2** were selected as the model substrates to optimize the reaction conditions (Table 1). To our delight, the desired product **3a** was obtained in 59% yield using selectfluor as the oxidant at 60 °C for 3 h (Table 1, entry 1). When the reaction was performed at 25 °C or 90 °C, **3a** was isolated in 9% or 91% yield (Table 1, entries 2 and 3). When *N*-fluorobenzenesulfonimide (NFSI) was used as the oxidant, no desired **3a** was obtained (Table 1, entry 4). Other oxidants such as *tert*-butyl hydroperoxide (TBHP) and 30% $H_2O_2$ did not perform well (Table 1, entries 5–7). Solvent screening indicated that $CH_3CN$ was the most suitable. Other solvents such as $CHCl_3$, $CH_2Cl_2$, DMF, EtOH, and EtOAc gave relatively low yields of **3a** or no **3a** was obtained (Table 1, entries 8–12). In addition, the reaction in the absence of selectfluor did not work (Table 1, entry 13). After sufficient screening, the optimal condition eventually emerged as aldehydes **1a** (1.0 equiv), NHPI **2** (1.2 equiv), selectfluor (1.2 equiv), and $CH_3CN$ (3.0 mL) at 90 °C for 3 h under air (Table 1, entry 3).

With the optimized conditions in hand (Table 1, entry 3), several aldehydes as well as aliphatic aldehydes compounds were examined as substrates to react with NHPI under the optimized reaction conditions (Table 2). Aryl aldehydes with various functional groups were effective. Halosubstituted aryl aldehydes (**1c**, **1d**, **1g**-**i**, **1m**, **1n**, **1s**) were tolerated in the CDC reaction, and could be very useful for further transformations. The steric effects might influence the reaction. Compared to

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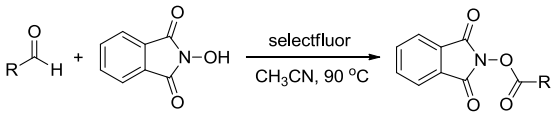
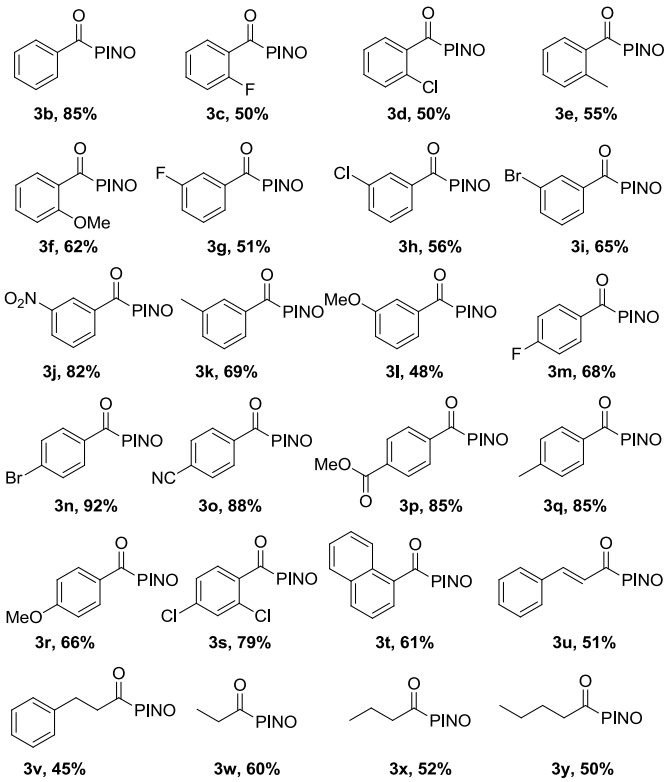
**Table 2** Scope of the reaction of aldehydes with NHPI mediated by selectfluor[a,b]




1 2 3




[a] Standard reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), selectfluor (0.36 mmol), $CH_3CN$ (3.0 mL), 90 °C, 3 h. [b] Yield of the isolated products.

**1a**, the reactions of *o*-, and *m*-chlorobenzaldehyde afforded **3d** and **3h** in 50% and 56% yields, respectively. Slightly decreased but acceptable yields were also achieved for reactions that involved other *ortho*-substituted aldehydes (**3c, 3e, 3f**). Aryl aldehydes substrates bearing electronwithdrawing substituents including such as nitro, cyano, and carboxylate were effectively converted into the corresponding products **3j**, **3o**, **3p**, respectively. Similarly, substrates with electrondonating substituents on the aromatic ring underwent coupling smoothly to afford the desired products (**3e**, **3f**, **3k**, **3l**, **3q**, **3r**) in good yields. In addition, starting from 1-naphthaldehyde (**1t**), cinnamic aldehyde (**1u**) and 3-phenylpropanal (**1v**), **3t**, **3u** and **3v** could be obtained in 45-61% yields. Remarkably, alkyl aldehydes such as propionaldehyde (**1w**), butyraldehyde (**1x**), and pentanal (**1y**) were also effective in providing **3w**-**y** in 50-60% yields. As we know, an example of a direct transformation from alkyl aldehydes and NHPI to *N*-hydroxyimide esters has not been reported until this work.

Encouraged by the above results, we extended the scope of this reaction with aldehydes and *N*-hydroxysuccinimide (NHSI) under optimal reaction conditions (Table 3). To our delight,



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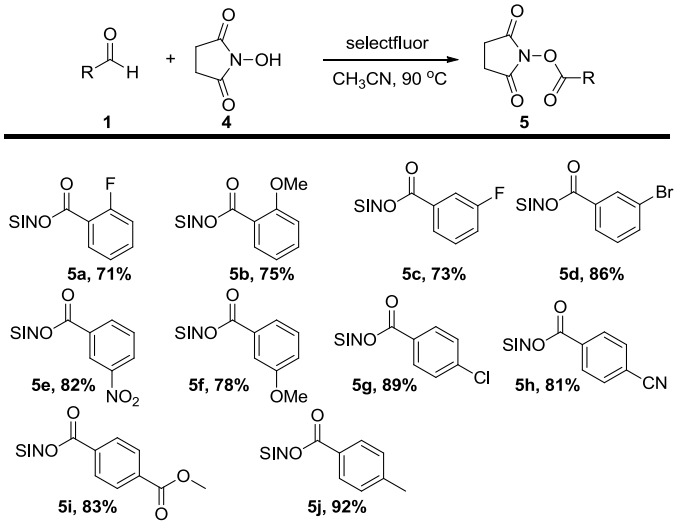
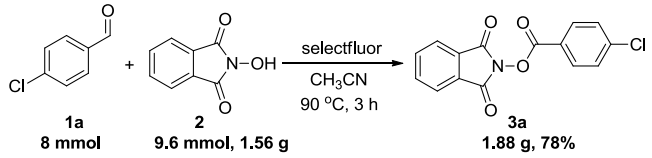
**Table 3** Scope of the reaction of aldehydes with NHSI mediated by selectfluor[a,b]




[a] Standard reaction conditions: **1** (0.3 mmol), **4** (0.36 mmol), selectfluor (0.36 mmol), $CH_3CN$ (3.0 mL), 90 °C, 1 h. [b] Yield of the isolated products.

aldehydes with electron-withdrawing or electron-donating groups could be converted to the desired products in good to excellent yields.

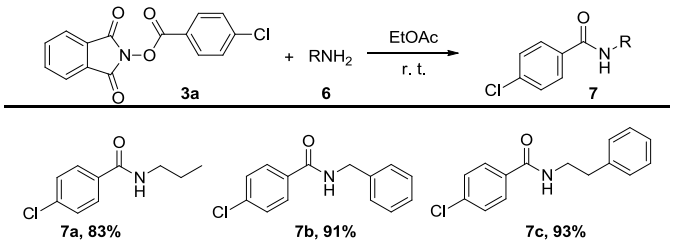
To demonstrate the practicability of this protocol, the C–O cross-coupling reaction was scaled-up to the gram scale. A gram scale oxidation of 4-chlorobenzaldehyde **1a** was easily performed under standard reaction conditions to furnish the desired product in 78% isolated yield (Scheme 2).




**Scheme 2** Gram scale synthesis of *N*-hydroxyimide ester **3a**

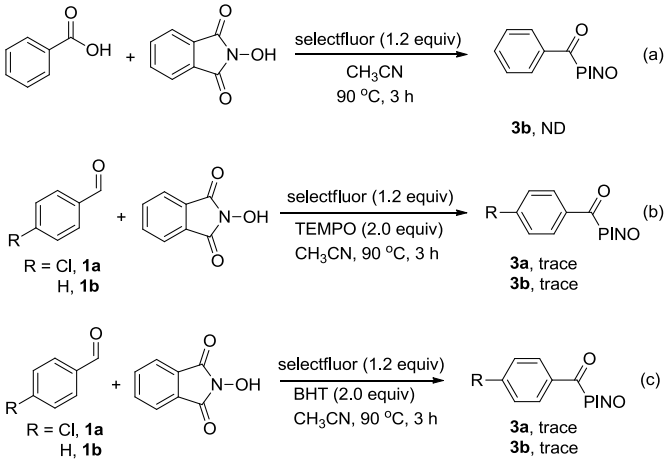
The utility of *N*-hydroxyimide esters as synthons in organic chemistry has expanded significantly in recent years.[4,5,10] For example, treatment of amines, such as 1-propylamine, benzylamine, and 2-phenylethanamine, with the product **3a** in EtOAc at room temperture led to the formation of the amides **7a**, **7b** and **7c** in excellent yield (Table 4).

**Table 4** Synthetic application of *N*-hydroxyimide esters[a,b]



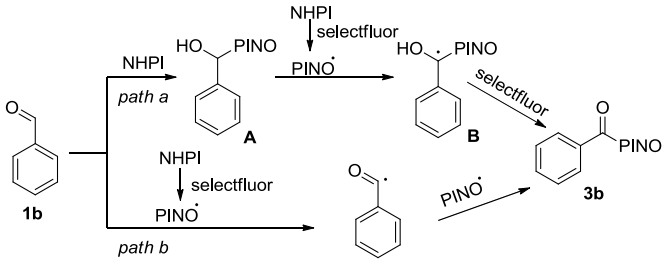

[a] Standard reaction conditions: **3a** (0.2 mmol), **6** (0.6 mmol), EtOAc (2.0 mL), r.t., 3 h. [b] Yield of the isolated products.

Several control experiments were performed to probe the reaction mechanism (Scheme 3). To find out whether benzoic acid was formed *in situ* as active intermediate, benzoic acid was applied to the cross-coupling reaction with NHPI (Scheme 3, a). No *N*-hydroxyimide ester product was obtained under the optimal conditions. When the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv) was added to the reaction of 4-chlorobenzaldehyde **1a** or benzaldehyde **1b** under the optimal conditions, after 3 h, no desired product **3a** or **3b** was detected. (Scheme 3, b). Additionally, the reaction was also inhibited by another radical scavenger, 2,6-di-tert-butyl-4-methylphenol (BHT, 2.0 equiv, Scheme 3, c). All these results suggested a possible radial mechanism.




**Scheme 3** Control experiment

Although the mechanistic details of this transformation are not very clear at the moment, based on the experimental results and literature precedent, a possible mechanism was proposed in Scheme 4. Initially, selectfluor reacts with NHPI to generate PINO radical,[7b,11] a fairly stable but highly reactive free radical.[12] Then the PINO radical abstract a hydrogen atom from the acetal species **A**, which forms from the reaction of the NHPI with **1b**, and the resulting radical species **B**[5] is further oxidized by selectfluor to obtain the PINO adducts **3b** (Scheme 4, path a). On the other hand, we also could not exclude another pathway: the PINO radical induces the homolysis of a benzaldehyde C–H bond to give the acyl radical.[13] Finally, the recombination of the acyl radical and PINO radical will lead to the PINO adducts **3b** (Scheme 4, path b).




**Scheme 4** Plausible mechanism

In conclusion, we have described the first example of a selectfluor-mediated intermolecular C–O cross coupling reaction of simple aldehydes with NHPI and NHSI without using any metal catalyst. The resulting products can be directly converted into amides in one pot. Various aldehydes including aliphatic aldehydes such as propionaldehyde, butyraldehyde, and pentanal were efficient, which made this CDC reaction very attractive. Further investigations to gain a detailed mechanistic understanding of this reaction and apply this strategy in other oxidative coupling reactions are underway in our lab.

We gratefully acknowledge the Science & Technology Foundation of Henan Province, the Foundation of Henan Educational Committee (15A150029), Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis (130028651), Henan province key laboratory of new opto-electronic functional materials and AYNU-KP-A04 for financial support.

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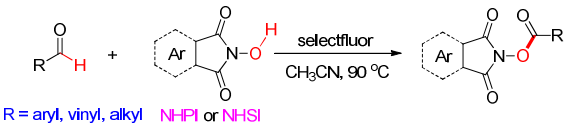


Selectfluor-mediated intermolecular C–O cross coupling reaction for the synthesis of *N*-hydroxyimide esters was achieved under metal-free conditions.