NJC

LETTER

View Article Online
View Journal

Cite this: DOI: 10.1039/c7nj03651e

Received 23rd September 2017,
Accepted 1st December 2017

DOI: 10.1039/c7nj03651e

rsc.li/njc

A photoinduced cross-dehydrogenative-coupling (CDC) reaction between aldehydes and *N*-hydroxyimides by a TiO_2–Co ascorbic acid nanohybrid under visible light irradiation†

Fahimeh Feizpour, Maasoumeh Jafarpour * and Abdolreza Rezaeifard *

In this study, we performed a visible light-mediated aerobic photo-cross dehydrogenative coupling (CDC) reaction between aldehydes and *N*-hydroxyimides using TiO_2–AA–Co as a photocatalyst for the synthesis of active esters. The synergistic and selective effects of the cobalt ascorbic acid complex (Co–AA) and TiO_2 nanoparticles on the visible-light photocatalytic activity were explored. The method possesses some advantages such as environmentally friendly conditions, easy work-up procedure, reusability, and scalability.

Quite recently, we improved the visible light photocatalytic properties of TiO_2 by functionalization with a Co–ascorbic acid complex. The modified TiO_2 nanoparticles improved significantly the selective aerobic benzylic C–H oxidation of alcohols and hydrocarbons as well as epoxidation of various olefins in ethyl acetate.[1,2] Our results[1] revealed that the efficiency of oxidation is dependent on the NHPI amount, which acts as a free radical oxidation co-catalyst.[3,4] During the examination of NHPI concentration in the aerobic benzylic C–H oxidation of alcohols,[1] in some cases we observed the pertinent carboxylic acid and *N*-hydroxyesters as by-products. This observation induced us to develop a novel aerobic photocatalytic system to access *N*-hydroxyesters, which are of extreme interest and widely used in organic synthesis as reactive acylating reagents.

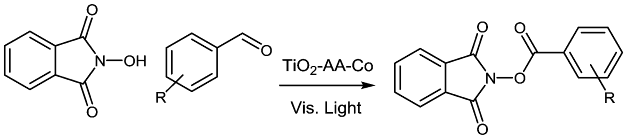
These active esters have been employed profusely for the generation of the amide bond in peptides and proteins *via* *N*-acylation.[5] The traditional approach involving the acylation of alcohols with activated carboxylic acids or coupling of *N*-hydroxyimides with carboxylic acids suffers from serious problems during the separation of by-products, particularly in industrial scale-up.[6] Thus, the development of effective and environmentally benign methods for this transformation under mild reaction conditions is needed.

The cross-dehydrogenative coupling reaction between an aldehyde and *N*-hydroxyimide can be employed for the synthesis of active esters with high atomic efficiency and does not require additional synthetic steps. Therefore, development of methods for the cross-dehydrogenative coupling (CDC; or oxidative cross-coupling) is of importance in modern organic chemistry and represents a promising approach for reducing the by-products as well as the number of synthesis steps.[7–26]

In the present study, we performed a visible light-mediated aerobic photo-cross dehydrogenative coupling (CDC) reaction between aldehydes and *N*-hydroxyimides using TiO_2–AA–Co as a photocatalyst for the synthesis of active esters (Scheme 1), which could be one of the straightforward alternatives to traditional coupling that produces minimum by-products.

The study was initiated by screening of the solvent nature, temperature, catalyst and NHPI amounts and oxidant nature under visible light (Fig. 1). 4-Chloro benzaldehyde was used as a substrate to optimize the conditions. For the conversion of 4-chloro benzaldehyde to the corresponding active ester, we observed that an excellent isolated yield of 97% (100% conversion) could be realized using TiO_2–AA–Co (0.06 mol%) as a catalyst with a 1 : 0.5 molar ratio of aldehyde : NHPI in ethyl acetate (1 mL) for 45 min at 60 °C under air and visible light. Replacing the air with O_2 did not change the reaction yield and selectivity; nevertheless, other oxidants such as H_2O_2 (10% yield), UHP (90% yield), Oxone® (30% yield) and TBAOX (60% yield) reduced considerably the yield and selectivity of the products as given in parentheses. Air was preferred as an ideal oxidant because it is easy, convenient and economical to use.

The amount of catalyst and the molar ratio of aldehyde : NHPI are also important determinants of the success of the reaction.



Scheme 1 Synthesis of active esters.

Catalysis Research Laboratory, Department of Chemistry, Faculty of Science, University of Birjand, Birjand, 97179-414, Iran. E-mail: mjafarpour@birjand.ac.ir, rrezaeifard@birjand.ac.ir; Fax: +98 5632202065; Tel: +98 5632202065

† Electronic supplementary information (ESI) available: Synthesis and characterization of catalyst, experimental details and spectral data of all products. See DOI: 10.1039/c7nj03651e

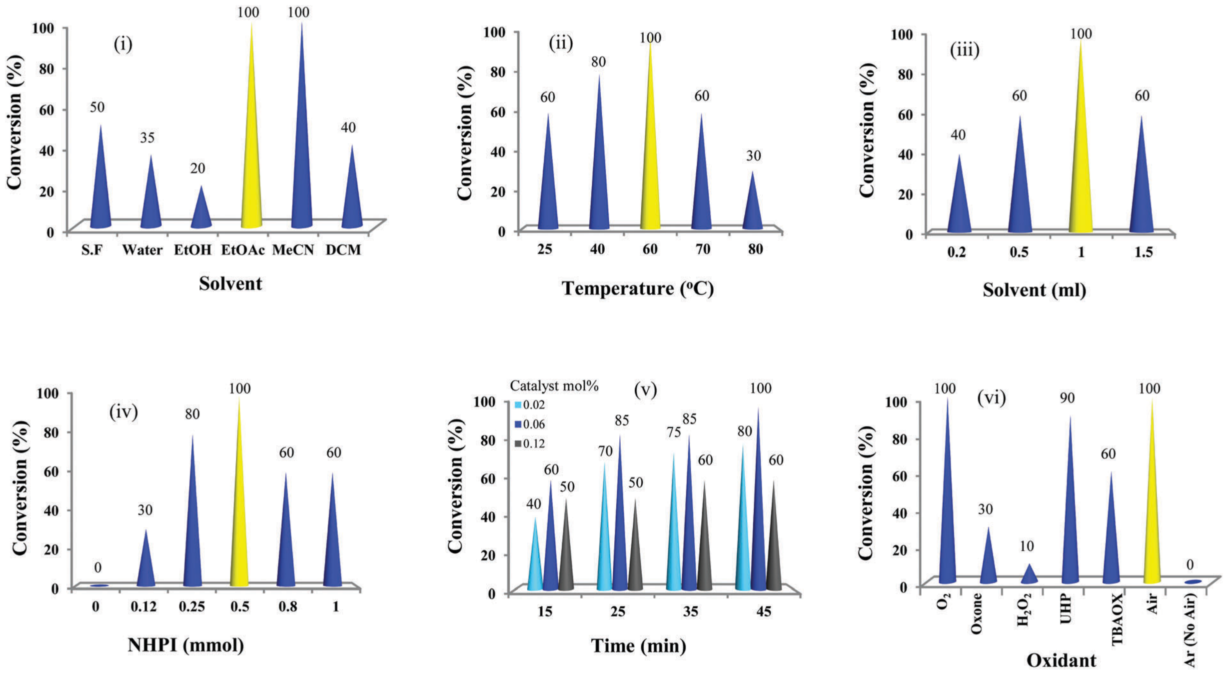


Fig. 1 (i) Screening of solvent [0.06 mol% catalyst, 0.5 mmol NHPI, temp. 60 °C], (ii) temperature [0.06 mol% catalyst, 0.5 mmol NHPI, EtOAc], (iii) solvent amount [temp. 60 °C, 0.06 mol% catalyst, 0.5 mmol NHPI], (iv) NHPI amount [temp. 60 °C, 0.06 mol% catalyst, 1 mL EtOAc], (v) catalyst amount [temp. 60 °C, 0.5 mmol NHPI, 1 mL EtOAc] in air and visible light and (vi) oxidant nature on the cross coupling reaction of 4-chlorobenzaldehyde (1 mmol) and NHPI in the presence of TiO_2–AA–Co after 45 min.

For example, when 0.02 or 0.12 mol% catalyst was used *versus* 0.06 mol% under the optimized conditions, the conversion reaction decreased from 100 to 80 and 60%, respectively. Likewise, when the ratio of aldehyde : NHPI was varied from the optimized 1 : 0.5 ratio to, for example, 1 : 0.8 and 1 : 1, in both cases, the yields decreased to 60%. It is noteworthy that by varying the aldehyde : NHPI ratio from the optimized ratio of 1 : 0.5 the corresponding carboxylic acid as a by-product was obtained.

With an improved procedure for successful ester formation in hand, we then focused on the evaluation of the substrate scope. First, a set of structurally diverse aldehydes was coupled with NHPI under air and visible light (Table 1). A broad range of NHPI esters were successfully formed with moderate to excellent yield using this protocol (Table 1). It was observed that the electronic properties of the substituents on the aromatic aldehydes displayed effects on the reaction efficiency. When the phenyl substrate was substituted with electron donor groups such as 4-Me and 4-OMe (entries **3b** and **3c**), as well as halogens (**3d**, **3e**, and **3g**), excellent yields were observed (90–94%). Nevertheless, with electron-withdrawing substituents such as $-NO_2$ (**3f**, **3h**), moderate yields of 40–46% were obtained. Similarly, the heterocyclic aromatic aldehydes (**3m** and **3n**) exhibited low yields (35 and 41%), which may be a consequence of the electron-withdrawing effect of the intermediates or transition states of the reaction. It is also apparent that the steric bulkiness in the molecule retards reactivity and produces a lower product (**3g**–**3k**).

Furthermore, cinnamaldehyde participated successfully in this reaction to provide ester **3l** with 62% yield. Although aromatic aldehydes were suitable substrates toward photo-CDC reactions, aliphatic ones such as acetaldehyde failed to produce any product under the optimized conditions.

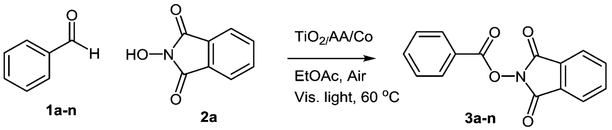
After successful results of photo-CDC reaction with NHPI as a coupling partner, we replaced NHPI with NHSI under the optimal reaction conditions. It produced the corresponding NHSI ester in a comparable yield and selectivity, albeit in a longer reaction time (Table 2). The lower reactivity of NHSI than NHPI might be attributed to the higher bond dissociation energy (BDE) of the NO–H bond in the former during the generation of the reactive N–O radical.[27]

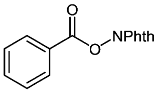
Next, we screened the photocatalytic effect of TiO_2 at the core of the title nanohybrid on the photo-CDC efficiency as we investigated previously on the oxidation of some organic compounds.[1,2] For this purpose, we replaced the title nanohybrid with other nanosized oxometals and their nanocomposites. The product yield and selectivity reduced under standard conditions (Table 3).

The photocatalytic property of TiO_2 at the core of the title nanohybrid was further supported by performing the CDC reactions of NHPI with aryl aldehydes under UV and visible light as well as in the dark (Table 4). The reactions accelerated under light radiation particularly UV light confirming once again the photocatalytic effect of the TiO_2 core on the CDC efficiency of the TiO_2–AA–Co nanohybrid.

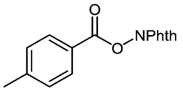
Taking into account the data published in the literature,[26,28] the pathway for the formation of oxidative cross-coupling products **3** and **4** may be proposed (Scheme 2). It is believed that the photo excited Co(II) oxidized NHPI to a phthalimide *N*-oxyl

Table 1 Photo-cross dehydrogenative coupling reaction between aldehydes and NHPI using TiO_2–AA–Co[a,b,c]

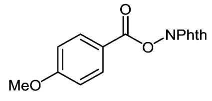




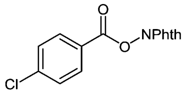
3a, 86%, 1 h



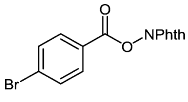
3b, 90%, 1 h



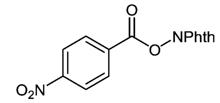
3c, 94%, 1.3 h



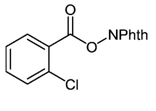
3d, 97%, 45 min



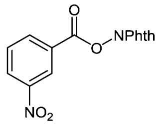
3e, 83%, 1 h



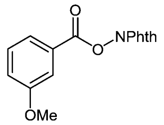
3f, 46%, 2 h



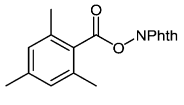
3g, 72%, 1.5 h



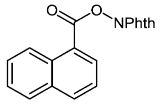
3h, 40%, 2 h



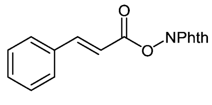
3i, 78%, 1.3 h



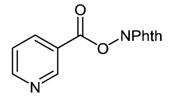
3j, 74%, 1.5 h



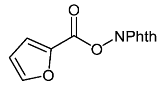
3k, 68%, 1.5 h



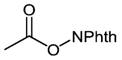
3l, 62%, 2 h



3m, 35%, 2 h



3n, 41%, 2 h



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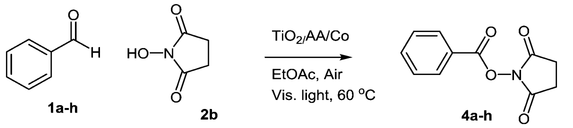
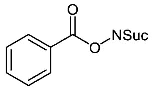
[a] Reaction conditions: aldehyde (1 mmol), NHPI (0.5 mmol), catalyst (0.06 mol%) in EtOAc (1 mL) under air and visible light conditions. [b] The products were identified by ^1H NMR spectroscopy. [c] The reported yields are yields of isolated products.

radical (PINO), a fairly stable but highly reactive free radical. This radical was then intercepted by the aldehyde to form a hemiaminal radical which on oxidation furnished the ester product.

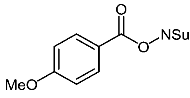
The efficiency of the present photo-CDC reaction could be highlighted by its reusability and scalability. The catalyst was easily separated by centrifugation and reused in five consequent runs in the reaction of 4-chlorobenzaldehyde and NHPI (Fig. S7, ESI†). A slight reduction in the product yields was observed after the 5th run indicating the efficiency and stability of the title nanocatalyst. Also, the leaching of the catalyst was screened by centrifugation and decantation of the reaction mixture. No catalytic activity was observed in the filtrate solution and based on the ICP-AES results, the amount of Co in the catalyst after recycling is comparable with that of the fresh catalyst. Much evidence for this issue was observed by comparing the FT-IR and TEM images of the used catalyst with the fresh one (Fig. S8, ESI†). The structure, size and morphology of the catalyst remained intact after recycling. In support of the scalability of this method, we conducted the reaction on 10 times scale, whereupon the product was obtained with almost the same yield.

Table 2 Photo-cross dehydrogenative coupling (CDC) reaction between aldehydes and NHSI using TiO_2–AA–Co[a,b,c]

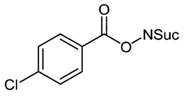




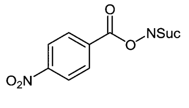
4a, 84%, 2 h



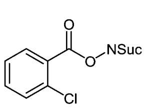
4b, 89%, 2 h



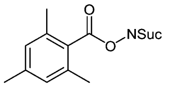
4c, 93%, 1.3 h



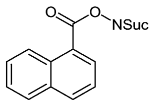
4d, 45%, 3 h



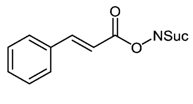
4e, 68%, 2 h



4f, 76%, 2 h



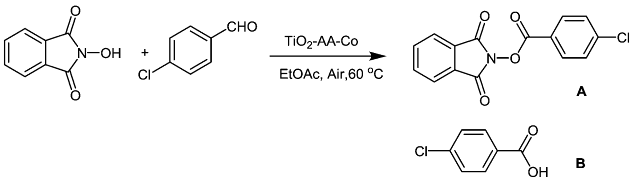
4g, 70%, 2 h



4h, 41%, 3 h

[a] Reaction conditions: aldehyde (1 mmol), NHSI (0.5 mmol), catalyst (0.06 mol%) in EtOAc (1 mL) under air and visible light conditions. [b] The products were identified by ^1H NMR spectroscopy. [c] The reported yields are yields of isolated products.

Table 3 The comparison of catalytic activity of TiO_2–AA–Co with other nanocomposites and nanooxometals in photo-CDC reaction between aldehydes and NHPI



Entry	Catalyst	Conversion[a] (%) (A, B)	Selectivity %
1	TiO_2–AA–Co	100 (A)	100
2	TiO_2–AA	25 (A)	100
3	AA–Co	60 (30, 30)	50
4	TiO_2–Co	20 (15, 5)	75
5	TiO_2	50 (40, 10)	80
6	ZrO_2	40 (20, 20)	50
7	Fe_2O_3	30 (25, 5)	83
8	Fe_2O_3–AA	50 (40, 10)	80
9	Fe_2O_3–AA–Co	50 (40, 10)	80
10	MoO_3	20 (10, 10)	50
11	MoO_3–AA	35 (30, 5)	85
12	MoO_3–AA–Co	45 (25, 20)	55
13	TiO_2–OA–Co	60 (45, 15)	75
14	$Co(OAc)_2$	65 (30, 35)	46
15	AA	<5	—
16	No catalyst	—	—

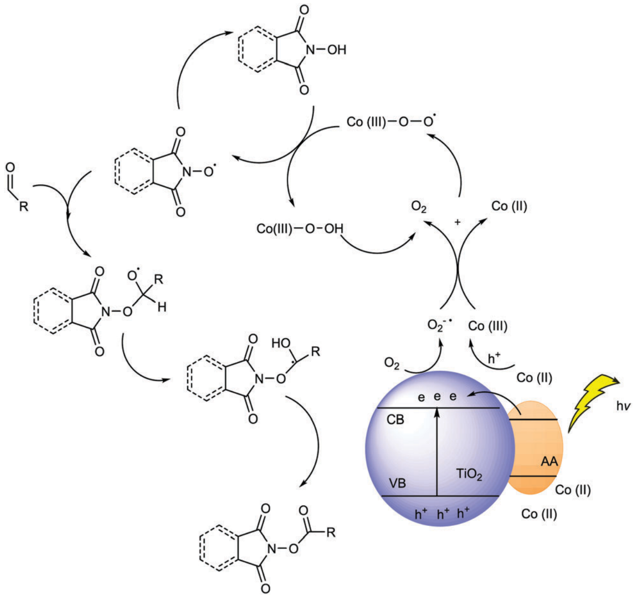
[a] Reaction conditions: aldehyde (1 mmol), NHPI (0.5 mmol), catalyst (0.06 mol%) in EtOAc (1 mL) at 60 °C after 45 min. Under air and visible light (Fig. S6, ESI).

In conclusion, we have developed an aerobic photocatalytic cross-dehydrogenative coupling reaction of aldehydes with *N*-hydroxyimides, which provides active esters in moderate to

Table 4 Screening of the photocatalytic activity of TiO_2–AA–Co[a]

Entry	Catalyst	Condition	Yield[b] (%)	Time (min)
1	TiO_2	UV[c]	40	45
2	TiO_2–AA	UV	30	45
3	TiO_2–AA–Co	UV	95	30
4	TiO_2	Visible light[d]	50	45
5	TiO_2–AA	Visible light	25	45
6	TiO_2–AA–Co	Visible light	97	45
7	TiO_2	Darkness	30	90
8	TiO_2–AA	Darkness	15	90
9	TiO_2–AA–Co	Darkness	35	90

[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol), NHPI (0.5 mmol), catalyst (0.06 mol%) in EtOAc (1 mL) at 60 °C under air. [b] Isolated yield. [c] λ = 200–290 nm. [d] Fluorescent lamp (CFL: 40 W, 1.1 W m^{-2}).



Scheme 2 Proposed mechanism for the synthesis of *N*-hydroxyimide esters.

excellent yields without by-products under visible light irradiation conditions. This new method offers an attractive and potentially general alternative to the more standard procedures to make *N*-hydroxyesters of aromatic aldehydes starting with aromatic carboxylic acids or acid halides. The environmentally friendly reaction conditions, easy work-up procedure, reusability of the catalyst and scalability to the multi-mmole scale make the title catalytic method amenable to industrial processes. With these benefits, we believe that this method will help to develop a new strategy toward the development of photocatalysis-based organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Support for this work by Research Council of University of Birjand and "Iran National Sience Fundation" is highly appreciated (Grant No. 96004509).

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