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Vitamin B1-catalyzed aerobic oxidative esterification of aromatic aldehydes with alcohols†

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A straightforward aerobic oxidative esterification of aryl aldehydes with alcohols has been developed for the synthesis of substituted esters by employing vitamin B1 as a cost-effective, metal-free, and eco-friendly NHC catalyst. Air is used as a green terminal oxidant. The reaction is a useful addition to the existing NHC-catalytic oxidative esterification.

Introduction

Vitamin B1 (VB1), also known as thiamine, is one of the eight water-soluble B vitamins. In the human body, VB1 plays an essential role in the synthesis of nucleic acids (*e.g.*, DNA), the conduction of nerve impulses, and the production of energy from food.[1] The structure of VB1 contains a thiazole ring and a pyrimidine ring linked by a methylene bridge (Fig. 1). As an important subarea of biocatalysis, VB1 and its analogs have been widely used as non-toxic, low cost, and stable catalysts in diverse organic transformations[2] including oxidation,[3] cyclization,[4] Michael addition, C–X bond coupling,[5] benzoin condensation,[6] Knoevenagel condensation,[7] *etc.*[8] Despite this impressive progress which has been achieved, reports related to the C–O bond formation by employing this renewably biobased catalyst are still highly desirable, offering benefits from an environment point of view.

The esters have been found a myriad of applications in fields ranging from agrochemistry, pharmacochemistry, and materials science to organic synthesis, mainly owing to their unique biological and chemical properties.[9] The development of efficient strategies towards ester functionality has inspired chemists for more than 100 years, therefore, a variety of well-established methods are developed. Classical condensation of carboxylic acids with alcohols is carried out under strongly acidic conditions in the presence of a large excess of either substrate.[10] In addition, esterification can also be achieved through the stoichiometric activation of the corresponding acids (*e.g.*, acid halides, anhydrides, or activated esters) following nucleophilic substitution with appropriate alcohols. On the other hand, transition metal-catalyzed direct oxidative functionalization of aldehydes provides a powerful platform for ester synthesis over the past decades (Scheme 1A). Despite advances, these transformations commonly suffered from harsh reaction conditions, the use of costly metal catalysts, stoichiometric oxidants, and extra additives, which constitute drawbacks for large-scale applications and late-stage modifications.[11] Alternatively, N-heterocyclic carbenes (NHCs) derived from thiazolium ions have the capability to accomplish the oxidative esterification with the assistance of various oxidants, such as MnO_2,[12] nitroarene,[13] TEMPO,[14] NFSI,[15] diphenoquinone,[16] azobenzene,[17] phenazine,[18] CCl_3CN,[19] and O_2/air (Scheme 1B).[20] From a viewpoint of green chemistry, a metal-free NHC-catalyzed one-pot esterification of aldehydes under air has become more sought after. In this regard, most of the existing methods relied on the preformed NHC catalysts which required multi-step synthesis. Continuing with our interests in green chemistry,[21] herein we introduce the commercially available VB1 as an efficient catalyst for oxidative esterification (Scheme 1C). As a result, a cost-effective, metal-free, eco-friendly, and catalytic route that minimizes hazardous waste is developed for the synthesis of esters by employing a variety of aryl aldehydes and alcohols as coupling partners or reaction solvents. This metal-free approach offers a valuable alternative when compared to the above-mentioned methods: (i) biocompatible VB1 is used as an NHC catalyst; (ii) transition metal and expensive oxidant are not necessary; (iii) DABCO serves as

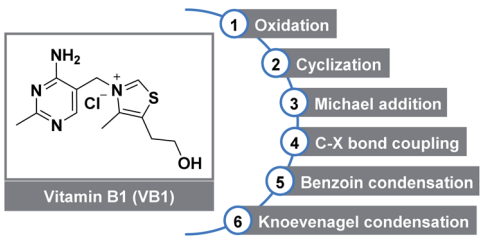

Fig. 1 Thiamine (VB1) as a versatile catalyst in organic transformations.

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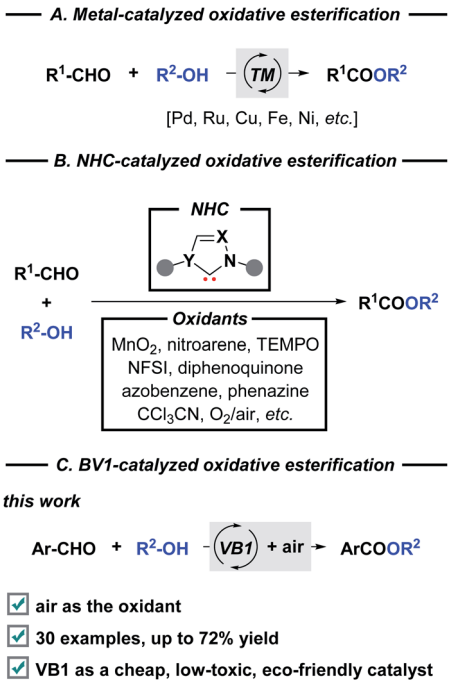


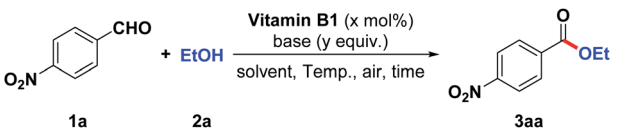
Scheme 1 General routes for the oxidative esterification.

a basic promoter. In particular, aerobic oxidation using dioxygen gas as a green oxidant is attractive.

Results and discussion

We commenced the study by investigating the model reaction of 4-nitrobenzaldehyde (**1a**) with ethanol (**2a**) (Table 1). Gratifyingly, the reaction proceeded smoothly in the presence of VB1 (20 mol%) as a catalyst and triethylenediamine (DABCO, 2 equiv.) as a base at 40 °C for 6 h under air, leading to the desired coupled product **3aa** in 58% yield (entry 1). In contrast, eroded efficiency was observed when the amount of VB1 was increased from 20 mol% to 30 mol% (entry 2), or when the amount of DABCO was increased from 2 equiv. to 3 equiv. (entry 3). Based on the control experiments, the necessity of adding catalyst and base were adequately demonstrated for the present reaction (entries 4 and 5). Subsequently, variations of various reaction parameters, including base, reaction temperature, reaction time, and solvent, were also carried out. It was found that DABCO was the base of choice, as the same reactions performed with other bases (including Na_2CO_3, Et_3N, and NaOH) produced the corresponding product **3aa** in low yields (entries 6–8). Furthermore, evaluation of reaction temperature and reaction time showed that the isolated yield of product **3aa** could be increased to 65% when the reaction was performed at 80 °C for 12 h (entry 9). Interestingly, a low equivalent of ethanol (1 mmol) in $CHCl_3$ did not considerably reduce the yield efficiency (49% yield, entry 10). Further screening of other solvents (*e.g.*, DMSO, toluene, THF, and acetone) revealed that the reaction performance could be improved in acetone as the solvent (57% yield, entry 14). Finally, it was found that 63% yield could be obtained by carrying out the reaction at 60 °C in acetone for 12 h

Table 1 Optimization of reaction conditions[a]



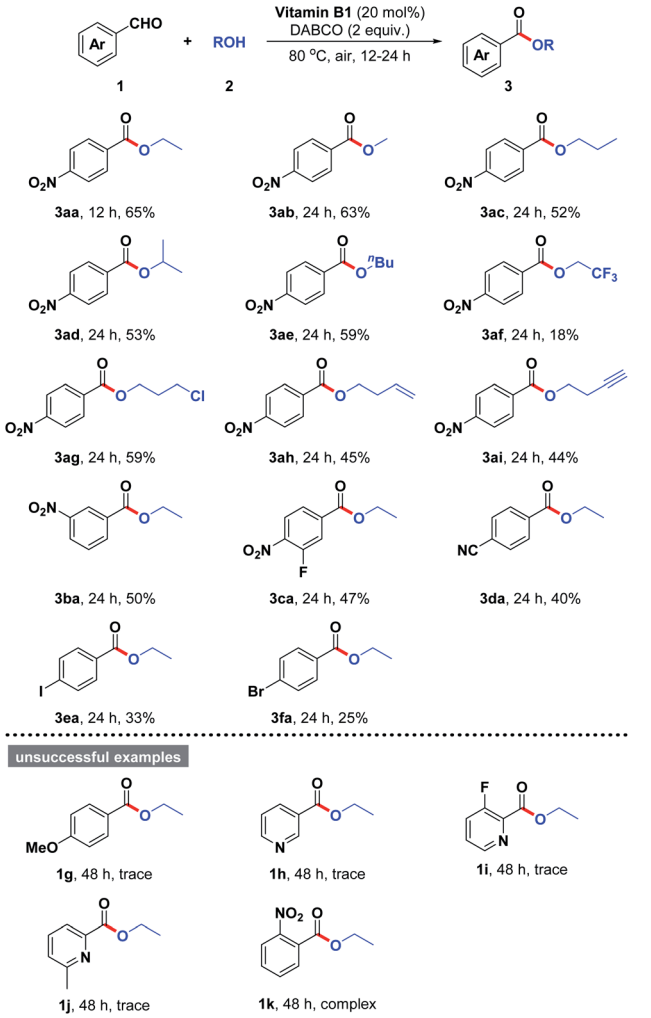
Entry	VB1 (x mol%)	Base (y equiv.)	Solvent	T (°C)	Yield[b] (%)
1	20	DABCO (2)	EtOH	40	58
2	30	DABCO (2)	EtOH	40	49
3	20	DABCO (3)	EtOH	40	47
4	—	DABCO (2)	EtOH	40	0
5	20	—	EtOH	40	0
6	20	Na_2CO_3 (2)	EtOH	40	<10
7	20	Et_3N (2)	EtOH	40	10
8	20	NaOH (2)	EtOH	40	<10
9	**20**	**DABCO (2)**	**EtOH**	**80**	**65**[c]
10	20	DABCO (2)	$CHCl_3$	40	49[d]
11	20	DABCO (2)	DMSO	40	22[d]
12	20	DABCO (2)	Toluene	40	Trace[d]
13	20	DABCO (2)	THF	40	Trace[d]
14	20	DABCO (2)	Acetone	40	57[d]
15	**20**	**DABCO (2)**	**Acetone**	**60**	**63**[d]
16	20	DABCO (2)	Acetone	60	61[d,e]

[a] Reaction conditions: 4-nitrobenzaldehyde (**1a**, 1 mmol), VB1 (0–0.6 mmol), and base (0–3 mmol) in EtOH (**2a**, 2 mL) at 40–80 °C (oil bath) under air for 6 h. [b] Isolated yield. [c] 12 h. [d] Reaction conditions: 4-nitrobenzaldehyde (**1a**, 3 mmol), EtOH (**2a**, 1 mmol), VB1 (0.2 mmol), and DABCO (2 mmol) in solvent (2 mL) at 40–60 °C (oil bath) under air for 12 h. [e] O_2 is used as an oxidant.

(entry 15). However, further improvement of the yield of product **3aa** and diminishment of the undesired process were failed by replacing air with pure O_2 (entry 16).

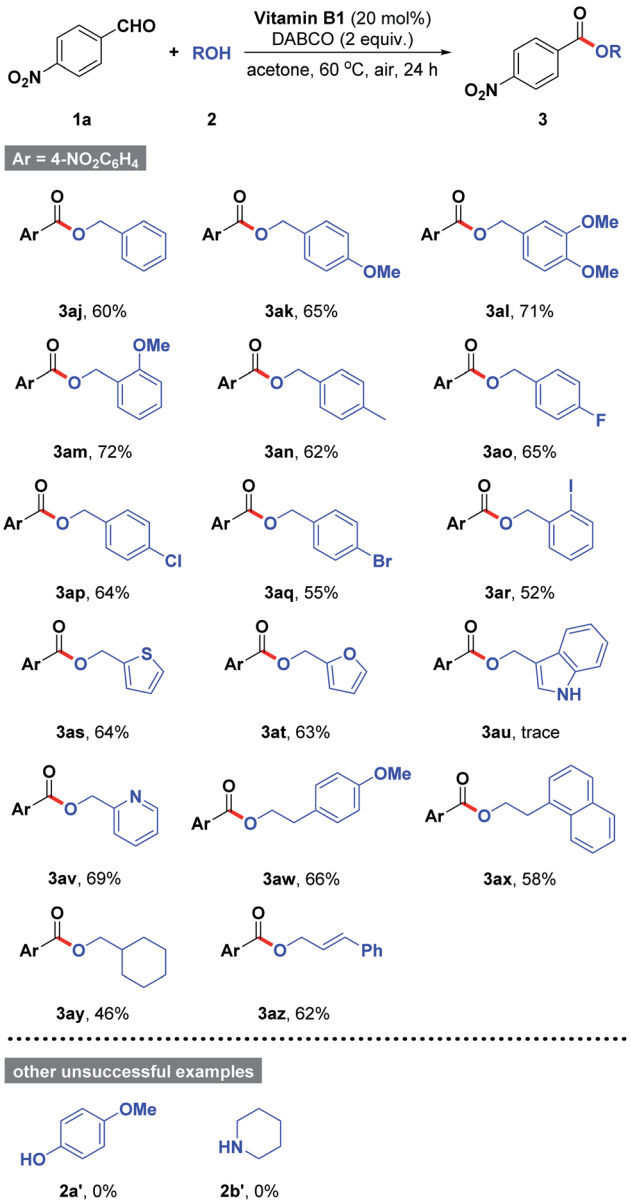
With this optimized result in hand, we continued to study the substrate scope of the present esterification by employing a wide variety of structurally varied alcohols and aryl aldehydes as starting materials, and the results were summarized in Table 2. The aerobic oxidative esterification of 4-nitrobenzaldehyde (**1a**) worked equally well when the reactions were performed in different alcohols **2** as the solvents at 80 °C for 12–24 h, furnishing the corresponding esters **3aa–3aj** in 18–65% yields. Interestingly, the chain length of the alkyl alcohols only had a slight impact on the reaction outcome (**3aa–3ae**, 52–65% yields). Notably, a sterically hindered secondary alcohol could be employed as substrate with equal ease (**3ad**, 53% yield). However, 2,2,2-trifluoroethan-1-ol with a strong electron-withdrawing CF_3 group obviously reduced the reactivity presumably because of its low nucleophilicity (**3af**, 18% yield). To our delight, alcohols containing functional groups such as Cl atom (**2g**), alkene (**2h**), and alkyne (**2i**) were compatible with the mild reaction conditions, providing the anticipated products **3ag–3ai** in 44–59% yields. Moreover, aryl aldehydes **1** bearing various substituents successfully underwent oxidative coupling with ethanol. In most cases, the cross-coupled products were produced in moderate yields (**3ba–3fa**). In addition to 4-nitrobenzaldehyde, aryl aldehydes possessing F, CN, I, and Br in the

Table 2 Substrate scope of various alcohols and aryl aldehydes[a]



[a] Reaction conditions: aryl aldehyde **1** (1.0 mmol), VB1 (0.2 mmol), and DABCO (2.0 mmol) in alcohol **2** (2.0 mL) at 80 °C (oil bath) for 12–24 h under air; isolated yields.

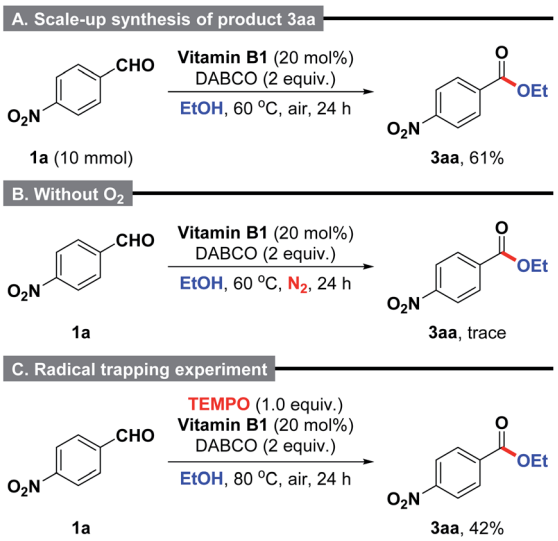
Table 3 Substrate scope of various alcohols 2 [a]



[a] Reaction conditions: 4-nitrobenzaldehyde (**1a**, 3.0 mmol), alcohol **2** (1.0 mmol), VB1 (0.2 mmol), and DABCO (2.0 mmol) in acetone (2.0 mL) at 60 °C (oil bath) for 24 h under air; isolated yields.

benzene ring were also proven to be appropriate substrates for the reaction (**3ca–3fa**). Unfortunately, further examination revealed that 4-methoxybenzaldehyde (**1g**) and heterocyclic aldehydes **1h–1j** were reluctant to participate in the titled transformation. The failures could be attributed to the electronic effect. However, the reaction of 2-nitrobenzaldehyde (**1k**) with alcohol also failed to give the desired product, mainly owing to the negative effect of steric hindrance.

Encouraged by the above results, the generality of the substrate scope was further evaluated by applying different alcohols in acetone. As summarized in Table 3, benzyl alcohols **2** possessing either electron-donating group (*e.g.*, Me, Me) or electron-withdrawing group (*e.g.*, F, Cl, Br, and I) smoothly underwent the present organic transformations to give the desired esters **3ak–3ar** in moderate to good yields. Notably, halogen functionality was satisfactorily compatible with the mild reaction conditions, which could be allowed for further divergent late-stage modifications (**3ao–3ar**). Similarly, thiophen-2-ylmethanol (**2s**), furan-2-ylmethanol (**2t**), and pyridin-2-ylmethanol (**2v**) were proven to be good candidates, affording the anticipated products **3as**, **3at**, and **3av** in 63–69% yields. However, other heterocyclic substrate such as (1*H*-indol-3-yl)methanol (**2u**) could not participate into the reactions with 4-nitrobenzaldehyde (**1a**). In addition, we were able to accomplish the conversion of alkyl alcohols such as 2-(4-methoxyphenyl)ethan-1-ol (**3aw**), 2-(naphthalen-1-yl)ethan-1-ol (**3ax**), and cyclohexylmethanol (**3ay**) to the coupled products **3aw–3ay** in 46–66% yields. Remarkably, (*E*)-3-phenylprop-2-en-

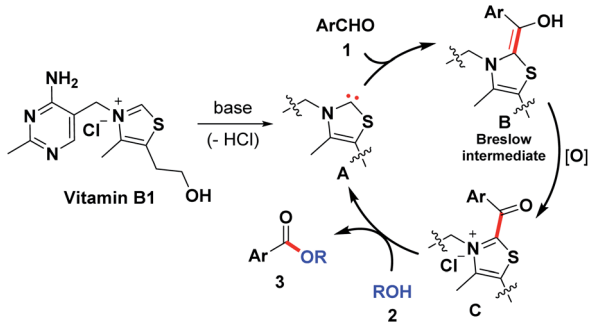


Scheme 2 Scale-up synthesis of product **3aa** and control experiment.

1-ol can be easily converted into **3az** in 62% yield. During the course of our studies, other types of nucleophiles including phenol **2a′** and amine **2b′** failed to react under the optimized reaction conditions.

Subsequently, a scale-up reaction was also applied to the model reaction (Scheme 2A). It was found that 10 mmol scale reaction worked with equally high efficiency under the well-established reaction conditions to produce the desired product **3aa** in 61% yield. Additionally, when the reaction of 4-nitrobenzaldehyde and ethanol was performed under N_2 atmosphere, the formation of product **3aa** was almost completely inhibited (Scheme 2B). This result suggests that the presence of O_2 is important for the intermolecular oxidative coupling reaction.[22] Furthermore, a radical trapping experiment by using 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 1.0 equiv.) as a radical inhibitor provided clear evidence that the reaction might not proceed in a radical manner (Scheme 2C).

Based on the control experiment and a literature survey,[12–20] a proposed mechanism is depicted in Scheme 3. Initially, deprotonation of VB1 under the basic condition gives rise to carbene catalyst **A**. Subsequently, the resulting species reacts with aryl aldehyde to produce the Breslow intermediate **B**, which in the presence of air can be further oxidized to acyl azolium intermediate **C**. Next, an intermolecular nucleophilic attack from the alcoholic OH occurred to give the desired product and regenerate the NHC catalyst.



Scheme 3 Proposed mechanism.

Conclusions

In summary, we have developed a vitamin B1-catalyzed aerobic oxidative esterification of aryl aldehydes with alcohols, providing easy access to synthetically important ester derivatives in moderate yields. The reaction proceeds in the air without an external oxidant. Moreover, commercially available VB1 was used as a cost-effective, metal-free, eco-friendly, and green catalyst, complementing the previously reported NHC-catalytic methods for the esterification.

Experimental

General procedure of vitamin B1-catalyzed aerobic oxidative esterification for the synthesis of products 3

Method 1. A solution of aldehyde (1 mmol), vitamin B1 (60.2 mg, 0.2 mmol), and triethylenediamine (DABCO, 224.3 mg, 2 mmol) in alcohol (2 mL) was stirred at 80 °C under air for 12–24 h. The reaction was then quenched by saturated NH_4Cl solution (20 mL) and extracted with EtOAc (20 mL × 3). The organic layer was washed with saturated brine twice, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (300–400 mesh) using petroleum ether/ethyl acetate (100/1–2/1) as eluent to afford the pure products **3**.

Method 2. A solution of 4-nitrobenzaldehyde (453.4 mg, 3 mmol), alcohol (1 mmol), vitamin B1 (60.2 mg, 0.2 mmol), and triethylenediamine (DABCO, 224.3 mg, 2 mmol) in acetone (2 mL) was stirred at 60 °C under air for 24 h. The reaction was then quenched by saturated NH_4Cl solution (20 mL) and extracted with EtOAc (20 mL × 3). The organic layer was washed with saturated brine twice, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (300–400 mesh) using petroleum ether/ethyl acetate (100/1–2/1) as eluent to afford the pure products **3**.

General procedure for the scale-up synthesis of pyridine 3aa

A solution of 4-nitrobenzaldehyde (1.51 g, 10 mmol), vitamin B1 (601.6 mg, 2 mmol), and triethylenediamine (DABCO, 2.24 g, 20 mmol) in EtOH (20 mL) was stirred at 80 °C under air for 24 h. The reaction solvent was removed under reduced pressure, then the reaction mixture was quenched by saturated NH_4Cl solution (20 mL) and extracted with EtOAc (20 mL × 3). The organic layer was washed with saturated brine twice, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (300–400 mesh) using petroleum ether/ethyl acetate (100/1–2/1) as eluent to afford the pure products **3aa** (1.19 g, 61% yield).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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