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COMMUNICATION

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Metal-free aerobic oxidative esterification of aromatic aldehydes promoted by potassium fluoride (KF)

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Abstract

We investigated the oxidative esterification of aldehydes with alcohols/phenols to produce a range of esters. In this approach, we conducted the reaction under metal-free conditions at room temperature. The reactions were promoted by potassium fluoride (KF) as the additive, resulting in the desired product in good to high yields. This procedure was found to be effective for the production of *aryl* esters, which are challenging in most of the available reports. It is vital for this procedure not to exclude air as the source of oxygen.

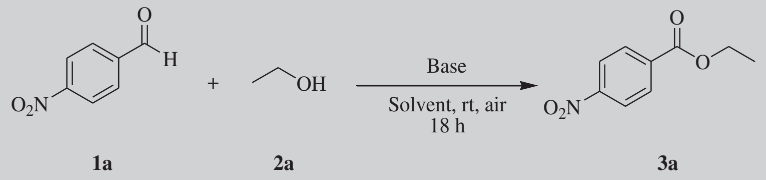
KEYWORDS
metal-free, oxidative esterification, potassium fluoride

1 | INTRODUCTION

Ester functionality occurs abundantly in many synthetic and natural products.[1] Hence, searching for new synthetic methods for the interconversion of different functional groups into esters is highly valued. The traditional methods for the synthesis of esters are Fischer esterification[2] and Schotten–Baumann reaction.[3] The former includes an acid-catalyzed reaction between a carboxylic acid and an alcohol, while the latter involves the base-catalyzed reaction between an acid chloride and an alcohol. In addition, Williamson-type esterification reaction between a carboxylate and an activated carbon is another classical reaction for the synthesis of esters.[4] As an alternative approach, the direct conversion of aldehydes to esters via the oxidative process have attracted significant attention.[5] In this methodology, different catalysts have been used, such as copper,[6] nickel,[7] palladium,[8] etc.[9] In addition to the metal-catalyzed reactions, a literature survey shows that this transformation could be accomplished under metal-free conditions in the presence of organocatalysts such as *N*-heterocyclic carbenes (NHCs),[10] acetone cyanohydrin,[11] *N*-iodosuccinimide,[12] trichlorocyanuric acid (TCCA),[13] etc.[14] Furthermore, cyanide-promoted reactions,[15] along with oxone-[16] and iodine-promoted,[17] reactions are also available in the literature for the conversion of aldehydes into esters. Here, we report an alternative approach for the conversion of aldehydes to esters under metal-free conditions at room temperature.

We began our optimization studies with the reaction of 4-nitrobenzaldehyde and ethanol at room temperature under air atmosphere (Table 1). Initially, we used 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU) as the base and N,N-dimethylformamide (DMF) as the solvent. The reaction failed under these conditions, and no product was observed after an 18-hr reaction time (Table 1, entry 1). Changing the base to CS_2CO_3 and K_3PO_4 resulted in the formation of the desired product in 34 and 56% isolated yields, respectively (Table 1, entries 2, 3). Recently, Zeng et al. used the fluoride ion to promote the conversion of amides to esters.[18] Inspired by this work, we used potassium fluoride (KF) as the base for our model reaction. Under these conditions, the desired ester was isolated in 69% yield (Table 1, entry 4). No product was obtained when changing the solvent to CH_3CN, EtOH, and water (Table 1, entries 5–7). Therefore, we have selected KF as the best base and DMF as the solvent of choice. We have also checked the effect of the amount of KF in the reaction. Increasing the amount of KF

TABLE 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	Yield (%)
1	DBU	DMF	—
2	Cs_2CO_3	DMF	34
3	K_3PO_4	DMF	56
4	KF	DMF	69
5	KF	CH_3CN	—
6	KF	EtOH	—
7	KF	H_2O	—
8[b]	KF	DMF	73
9[c]	KF	DMF	87
10	NaF	DMF	—

[a] *Reaction conditions*: 4-nitrobenzaldehyde (0.5 mmol), EtOH (1 mmol), base (1 mmol), solvent (3 mL) at room temperature.

[b] KF (2 mmol) was used.

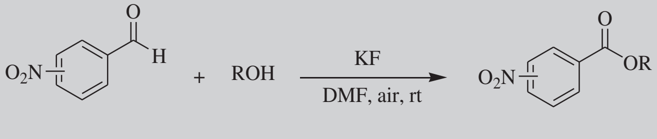
[c] KF (4 mmol) was used.

to 4 eq. resulted in the desired product with 73% yield (Table 1, entry 8). Further increase of KF to 8 eq. improved the yield up to 87% (Table 1, entry 9). To our surprise, the reaction using NaF instead of KF failed, showing the importance of the counterion in this reaction (Table 1, entry 10). This effect is probably due to the higher nucleophilicity of KF in comparison with NaF. Therefore, these conditions were considered optimum.

Using these optimized conditions, we prepared a variety of esters using structurally different alcohols/phenols (Table 2). As mentioned above, the reaction of 4-nitrobenzaldehyde (**1a**) with ethanol (**2a**) proceeded well, giving the desired product **3a** (Figures S1 and S2) with an 87% yield within an 18-hr reaction time (Table 2, entry 1). Changing the alcohol to tetraethyl orthosilicate resulted in the decreased yield of the desired product **3a** to 34% (Table 2, entry 2). The corresponding methyl ester **3b** (Figures S3 and S4) was also synthesized in 85% isolated yields within 16 hr (Table 2, entry 3). The reaction of 4-nitrobenzaldehyde (**1a**) with isoamyl alcohol (**2d**) gave the desired product **3c** (Figures S5 and S6) with 83% isolated yield (Table 2, entry 4). 2-Butanol (**2e**) was also tested in this reaction as a secondary alcohol. In this case, 45% of the product **3d** (Figure S7) was isolated from the reaction mixture (Table 2, entry 5). The reaction of 3-nitrobenzaldehyde with tetraethyl orthosilicate resulted in the formation of the product **3e** (Figure S8) in moderate yield (Table 2, entry 6). As there are only few reports for the synthesis of aryl esters from aldehydes,[8,10,19] we decided to apply our system for the synthesis of aryl esters. For this aim, we used phenol derivatives as the coupling partners (Table 2, entries 7–11). Under the optimized conditions, 4-nitrobenzaldehyde reacted with phenol, giving the corresponding ester **3f** (Figures S9 and S10) with a 64% yield within 21 h (Table 2, entry 7). Likewise, 4-methoxyphenol was also reactive under the same conditions, producing **3g** (Figures S11 and S12) with an 86% yield (Table 2, entry 8). Moderate yield of the product **3h** (Figures S13 and S14) was obtained when using 4-chlorophenol as one of the reactants, leaving the chloride functionality intact (Table 2, entry 9). The reaction failed when bulky 1-naphthol or 2-naphthol were used (Table 2, entries 10, 11).

In order to obtain some information from the reaction mechanism, we performed the reaction of 4-nitrobenzaldehyde with ethanol under inert atmosphere of nitrogen. Analysis of the reaction mixture after 18 h showed that no product was formed, and the starting materials remained intact. This results shows that aerobic oxidation is involved in this reaction. Hence, we propose the mechanism for the reaction as depicted in Scheme 1. Fluoride anion attacks the aldehyde to form intermediate **I**. Aerobic oxidation of **I** produces intermediate **II**, which converts to the target molecule in the presence of an alcohol.

TABLE 2 Reaction of 4-nitrobenzaldehde with different alcohols[a]



1 **2** **3**

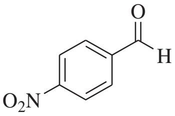
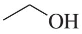
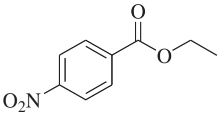
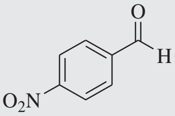
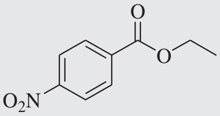
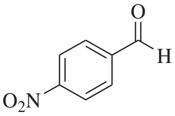
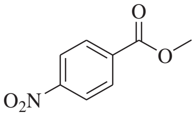
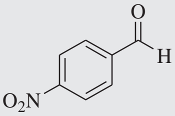
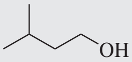
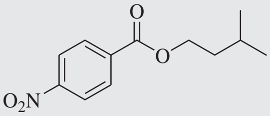
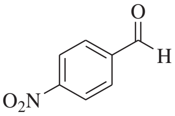
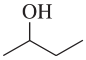
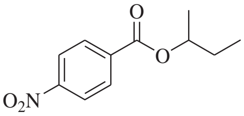
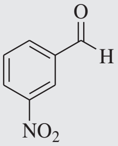
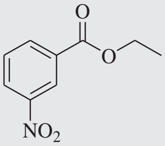
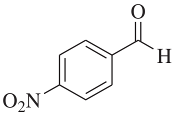
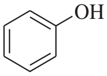
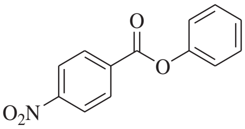
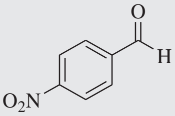
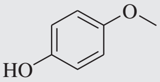
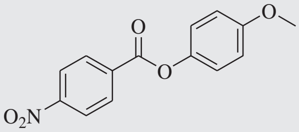
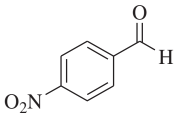
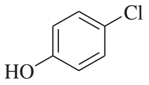
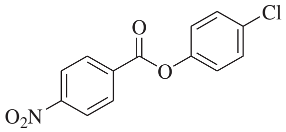
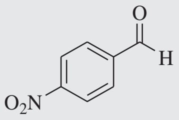
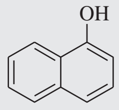
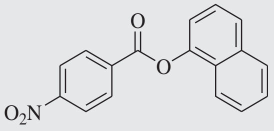
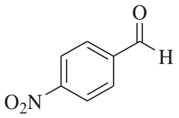
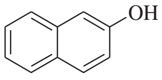
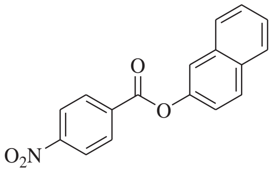
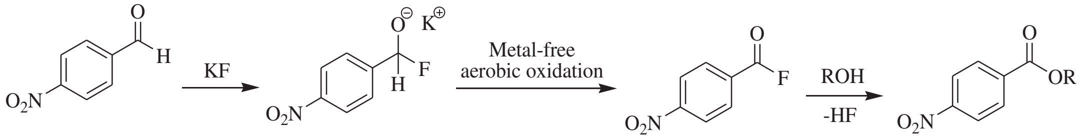
Entry	Aromatic aldehydes	Alkoxy/phenoxy source	Product	Time (hr)	Isolated yield (%)
1	 **1a**	 **2a**	 **3a**	18	87
2	 **1a**	$Si(OEt)_4$ **2b**	 **3a**	18	34
3	 **1a**	CH_3OH **2c**	 **3b**	16	85
4	 **1a**	 **2d**	 **3c**	18	83
5	 **1a**	 **2e**	 **3d**	20	45
6	 **1b**	$Si(OEt)_4$ **2b**	 **3e**	18	40
7	 **1a**	 **2f**	 **3f**	21	64
8	 **1a**	 **2g**	 **3g**	19	86

TABLE 2 (Continued)

1 2 3

Entry	Aromatic aldehydes	Alkoxy/phenoxy source	Product	Time (hr)	Isolated yield (%)
9	 **1a**	 **2h**	 **3h**	24	45
10	 **1a**	 **2i**	 **3i**	24	Trace
11	 **1a**	 **2j**	 **3j**	24	Trace

[a]*Reaction conditions*: 4-nitrobenzaldehyde (0.5 mmol), alcohol/phenol (1 mmol), KF (4 mmol), DMF (3 mL) at rt.



I II

SCHEME 1 Plausible pathway for the aerobic oxidation of aldehydes promoted by KF

2 | CONCLUSIONS

In conclusion, we have reported an effective procedure for the synthesis of esters under metal-free conditions at room temperature. In this approach, KF has been used as the key additive for the reaction to proceed. Utilizing the optimized conditions, different alkoxide sources, including a 2° alcohol, $Si(OEt)_4$, and phenol derivatives, were successfully used to produce a range of esters. Mechanistic studies showed that the oxygen of atmosphere is necessary for the reaction, and the aerobic oxidation is included in the reaction pathway.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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