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DABCO-mediated synthesis of aromatic esters from phenols, naphthols or 3-hydroxypyridines and aryl acyl peroxides at room temperature

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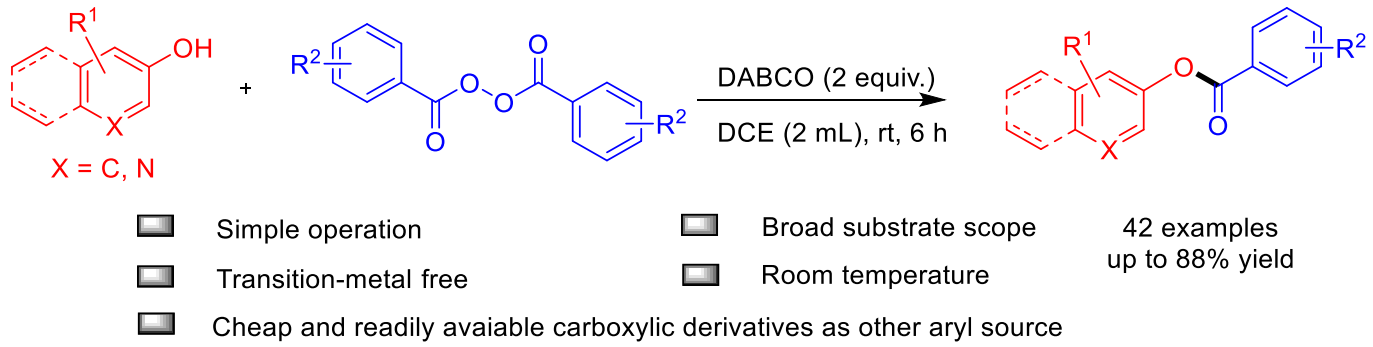
Abstract

An efficient and practical method for the synthesis of aromatic esters from aryl acyl peroxides and phenols, naphthols or 3-hydroxypyridines at room temperature was realized. A series of aromatic esters were synthesized in high yields and with excellent selectivity in the presence of 1,4-diaza[2.2.2]bicyclooctane (DABCO) without the use of transition-metals or acid catalysts. This operation is simple, and it has a good compatibility with various functional groups, especially with heterocyclic pyridine substrates.

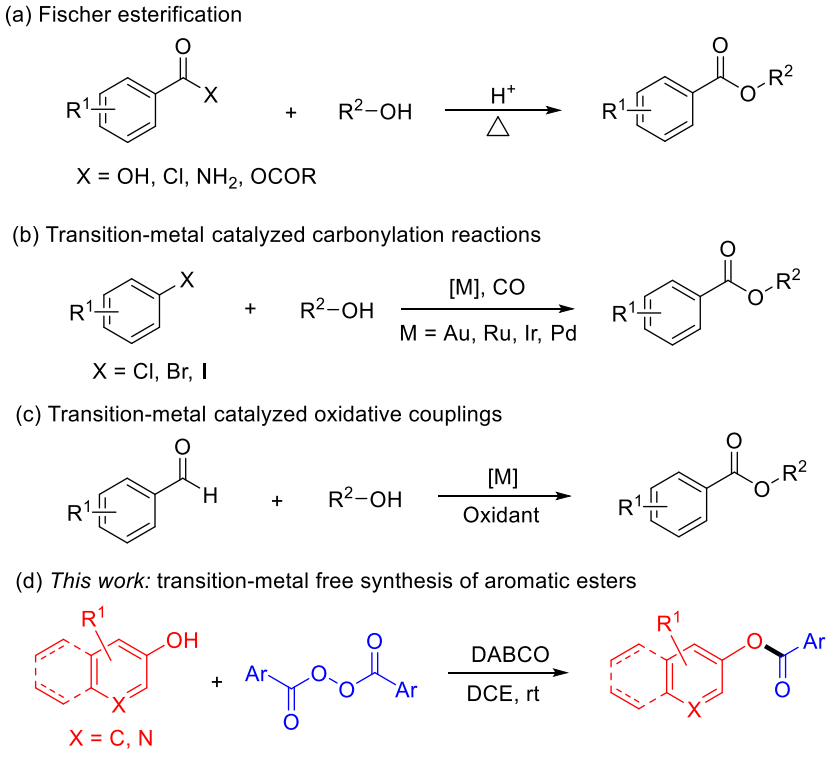


Keywords: 1,4-diaza[2.2.2]bicyclooctane, aryl acyl peroxides, phenols, naphthols, 3-hydroxypyridines, aromatic esters, room temperature

Introduction

Esterification is one of the most important reactions in organic synthesis, and is widely used in the chemical and pharmaceutical industry.[1-4] The Fischer esterification is the traditional method of ester synthesis. In addition, the reaction of alcohols with various carboxylic acid derivatives is also a common method for synthesizing esters (Scheme 1a).[5-8] Esters can be synthesized through transition-metal catalyzed carbonylation reactions using an aryl halide and an alcohol in the presence of CO (Scheme 1b).[9-11] However, such methods generally require precious metals such as gold,[12,13] ruthenium,[14,15] rhodium,[16,17] iridium[18,19] or palladium.[20,21] Recently, oxidative esterification of aldehydes has emerged as the most attractive alternative to the traditional synthesis of esters (Scheme 1c).[22,23] Although so far many significant esterification methods have been developed, there are still some limitations, such as the use of noble metal catalysts and ligands, harsh reaction conditions and poor functional group compatibility. Therefore, it is of great practical significance to develop a greener and milder method to synthesize esters.

In recent years, aryl acyl peroxides have been widely used in organic synthesis, for the asymmetric α-benzoyloxylation of cyclic ketones[24] and direct arylation of inactivated benzene. [25] However, it has been found that aroylation by-products are occasionally formed during these reactions, and therefore aroyl peroxides are rarely used as aroylation reagents, as for example in the esterification of primary and secondary alcohols and phenols.[26] In 2020, Dong et al. realized the cobalt-catalyzed aroylation of primary amines, using aryl acyl peroxides as the acyl source, without additional base or oxidant, and the synthesis of amides was realized with high efficiency and high selectivity.[27] Based on the application of DABCO in organic synthesis, including domino reactions, Michael additions, reductive couplings, and cyclization reactions,[28-31] we proposed an efficient DABCO-mediated synthesis of aromatic esters from phenols, naphthols or 3-hydroxypyridines and aryl acyl peroxides at room temperature (Scheme 1d).

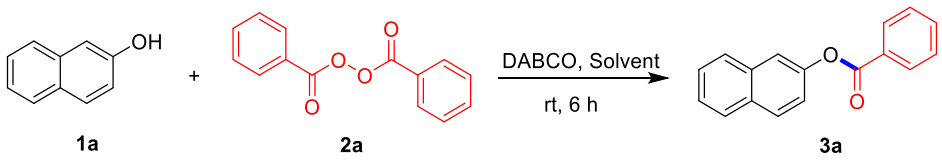


Scheme 1. Methods towards the synthesis of aromatic esters.

Results and Discussion

Initially, 2-naphthol (**1a**) and benzoyl peroxide (**2a**) were selected as model substrates in the presence of DABCO, and the desired product (**3a**) (Table 1, entry 1) was obtained in 38% yield in ethyl acetate at room temperature. In addition, the effect of other solvents was also examined (entries 2-8). It was shown that the reaction works well in chlorinated solvents. When dichloromethane (DCM) and 1, 2-dichloroethane (DCE) are used as solvents (entries 2 and 8), 48% and 49% isolated yields were obtained, respectively. In addition, low yields were obtained with 1,4-dioxane, CH_3CN, DMSO, H_2O as the solvent (entries 3, 4, 6, 7). Furthermore, other polar and non-polar solvents were also screened (*n*-hexane, DMF, EtOH, NMP, DMA), however no further improvement was observed (See Supporting Information, Table S1, entries 8-12). Subsequently, we screened the molar ratio of **1a** to **2a**. To our delight, further study showed that the molar ratio of **1a** to **2a** greatly affects the reaction (entries 9-16). However, increasing the amount of **2a** has little effect on the reaction (entries 9 and 10). As the amount of **1a** increased, the yield of **3a** also increased (entries 11-16). When the amount of **1a** was increased to 1.0 mmol, the yield of **3a** reached 85%, but further increase of the amount of **1a**, did not improve the yield of **3a** (entry 16). Taking into account the economic benefits, we chose the dosage of **1a** (1.0 mmol) and **2a** (0.2 mmol) as the optimal reaction mole ratio.

Table 1. Optimization of reaction conditions [a]



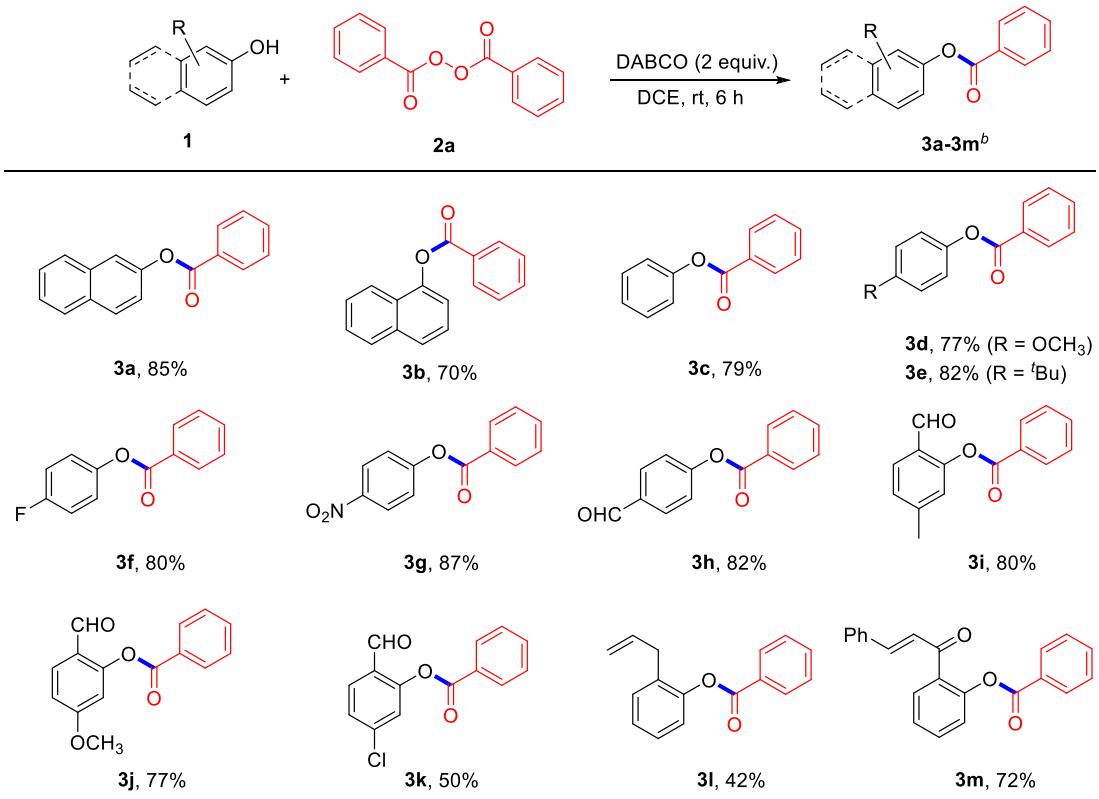
1a 2a 3a

Entry	**1a** (mmol)	**2a** (mmol)	Solvent	Yield (%)[b]
1	0.2	0.3	EA	38
2	0.2	0.3	DCM	48
3	0.2	0.3	Dioxane	18
4	0.2	0.3	CH_3CN	15
5	0.2	0.3	THF	26
6	0.2	0.3	DMSO	trace
7	0.2	0.3	H_2O	trace
8	0.2	0.3	DCE	49
9	0.2	0.4	DCE	51
10	0.2	0.6	DCE	45
11	0.2	0.2	DCE	59
12	0.4	0.2	DCE	69
13	0.6	0.2	DCE	77
14	0.8	0.2	DCE	80
15	1.0	0.2	DCE	85
16	1.2	0.2	DCE	85

[a] Reaction conditions: **1** (1.0 mmol), **2a** (0.2 mmol), DABCO (0.4 mmol), DCE (2 mL), at room temperature for 6 h. [b] Isolated yields.

With the optimized conditions in hand, the scope and compatibility of phenolic compounds were investigated. It was found that phenols substituted with various functional groups were well tolerated, and a series of aromatic esters were obtained in moderate to excellent yields. The results are shown in Table 2. Excitingly, the sterically hindered 1-naphthol could still participate well in the reaction, and the corresponding target ester compound **3b** was obtained in 70% yield. Phenol was also able to give **3c** in 79% yield. When examining the effect of substituents on the benzene ring, we found that both electron-donating and electron-withdrawing groups on the benzene ring can generate the corresponding aromatic esters **3d-3m** in good yields. With methyl, *tert*-butyl and strong electron withdrawing groups such as F, NO_2, and CHO in the para position, the reactants were well compatible, and no other side reactions occur. In addition, when the benzene ring contains both electron-withdrawing aldehyde groups and electron-donating methyl or methoxy groups, the corresponding target compounds **3i** and **3j** can still be obtained. However, when the substrates with sensitive chlorine atoms participate in the reaction, only 50% yield was obtained. But, when we used alkyl alcohol substrates, such as methanol, ethanol, isopropanol, *tert*-butanol, for the reaction, no target product was observed.

Table 2. Substrate scope of phenolic and naphtholic substrates [a]



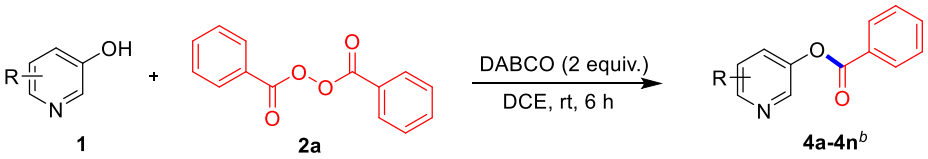
[a] Reaction conditions: **1** (1.0 mmol), **2a** (0.2 mmol), DABCO (0.4 mmol), DCE (2 mL), at room temperature for 6 h. [b] Isolated yields.

It is well known that alkenes are prone to radical addition reactions, especially in the presence of the radical initiator BPO. However, when an allyl-containing phenol was involved in the acylation reaction, no ring-closed product was found by radical addition, and an aromatic ester compound **3l** with a terminal double bond was obtained in 42% yield in this case. 2-Hydroxychalcone is an important intermediate of flavonoids, a low molecular weight polyphenol widely distributed in plants. A large number of studies have shown that 2-

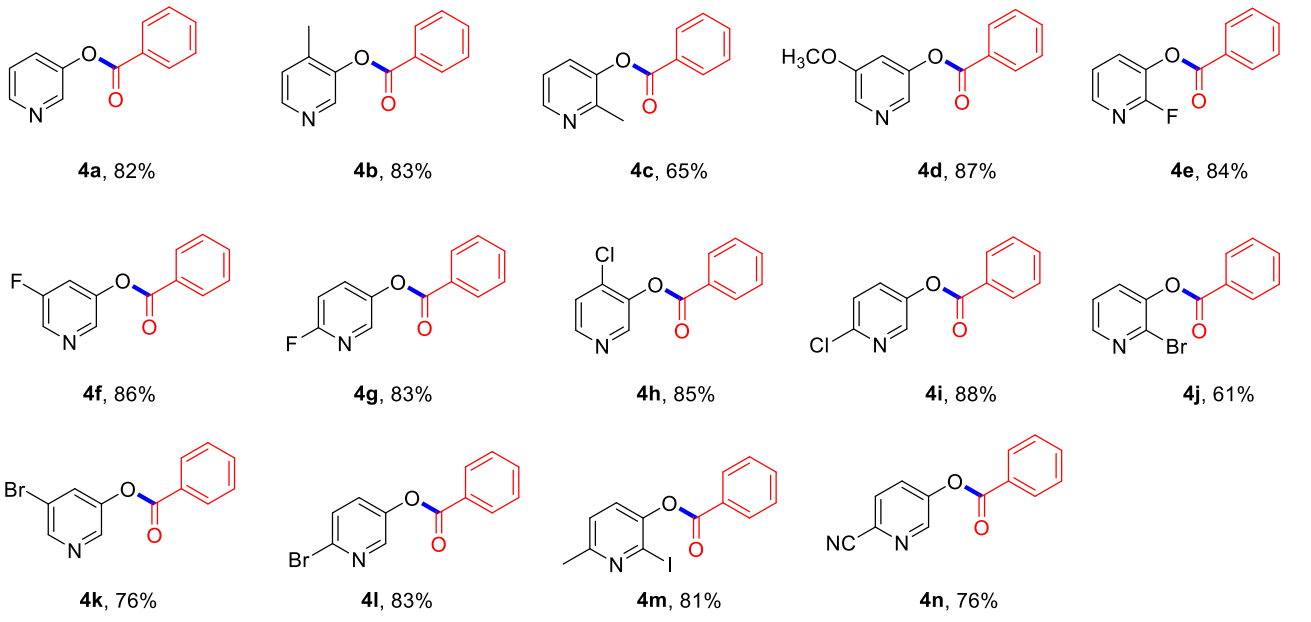
hydroxychalcone possess bioactive properties and pharmacological effects, such as anti-oxidant, anti-cancer, anti-allergic, anti-inflammatory and antiviral activity. When 2-hydroxychalcone was involved in this reaction, the acylated product **3m** was synthesized in 72% yield.

In order to further examine the compatibility of the reaction, a series of heterocyclic aromatic phenols were screened, as shown in Table 3. 3-Hydroxypyridine compounds are also well compatible in this reaction system. Whether it is an electron-donating group or an electron-withdrawing group, it has little effect on the acylation reaction, and the corresponding pyridine benzoates were obtained in good yields (**4a-4n**, 61%-88%). Halogen atoms (F, Cl, Br, I) are not affected in this transformation. At the same time, the different positions of the substituents on the pyridine ring have a slight effect on the yields, as well as the strong electron withdrawing cyano group has little effect on the reaction, and the target compound **4n** was still obtained in 76% yield. Furthermore, the position of hydroxyl groups on the pyridine ring greatly affects the reaction. When 2-hydroxypyridine and 4-hydroxypyridine were involved in the reaction, no acylated product was obtained, since the starting materials are prone to tautomerization to form 2-pyridone and 4-pyridone.

Table 3. Substrate scope of 3-hydroxypyridines [a]



1 + **2a** → **4a-4n**[b]



4a, 82% **4b**, 83% **4c**, 65% **4d**, 87% **4e**, 84%

4f, 86% **4g**, 83% **4h**, 85% **4i**, 88% **4j**, 61%

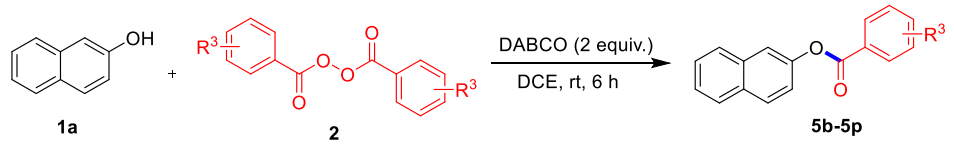
4k, 76% **4l**, 83% **4m**, 81% **4n**, 76%

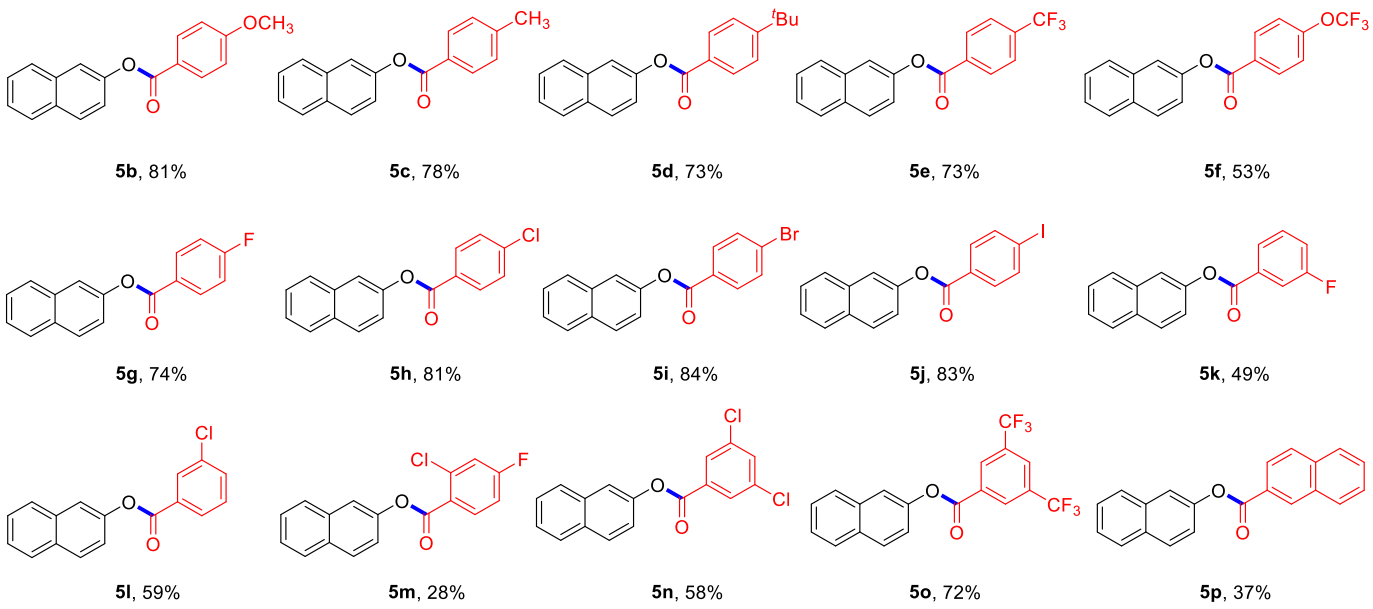
[a] Reaction conditions: **1** (1.0 mmol), **2a** (0.2 mmol), DABCO (0.4 mmol), DCE (2 mL), at room temperature for 6 h. [b] Isolated yields.

The scope of aroyl peroxides were then investigated under identical reaction conditions, and the results are shown in Table 4. It was found that the aroyl peroxides with electron-donating group in the para position, such as OCH_3, CH_3, *tert*-Bu, lead to the target esters (**5b-5d**, 81%, 78% and 73%, respectively). Meanwhile, aroyl peroxides with electron-withdrawing groups in the para position, such as halogen atoms (F, Cl, Br, I), gave halogen-containing aromatic esters in 74%-83% yields. Among these products, the resulting compounds containing halogens can be used for further functionalization. However, only moderate yields were obtained

for substrates bearing a trifluoromethoxy group in the para position. It was found that the relative position of the halogen on the benzene ring affects the reaction yield. When functional groups such as F and Cl are located at the meta-position, moderate yields of esters are obtained, which generally lower than that of the para position. It was shown that the halogen atoms in the meta-position mainly exhibit an electron-withdrawing inductive effect, so that the efficiency of the acylation reaction was reduced. To our delight, when the benzene ring contains two electron-withdrawing F, Cl and CF_3 substituents at the same time, moderate to good yields could also be obtained. It is noteworthy that only 37% of the target ester **5p** was obtained when the large conjugated group 2-naphthoyl peroxide was involved. Unfortunately, the o-methyl-substituted benzoyl peroxide did not give the desired esterification product, possibly due to steric hindrance.

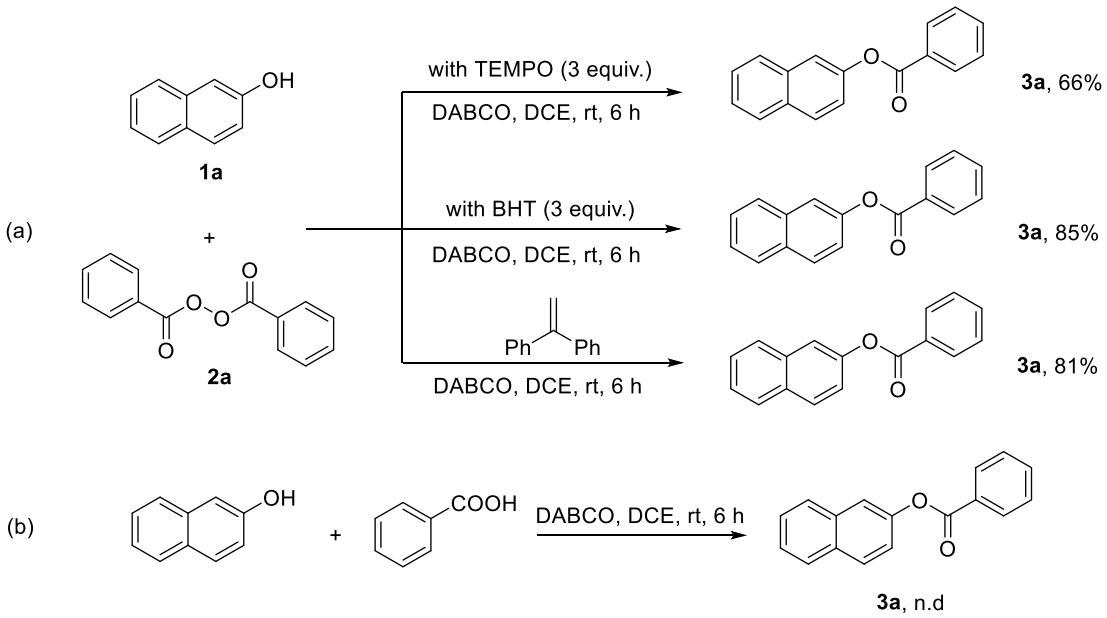
Table 4. Substrate scope of aryl acyl peroxides [a]





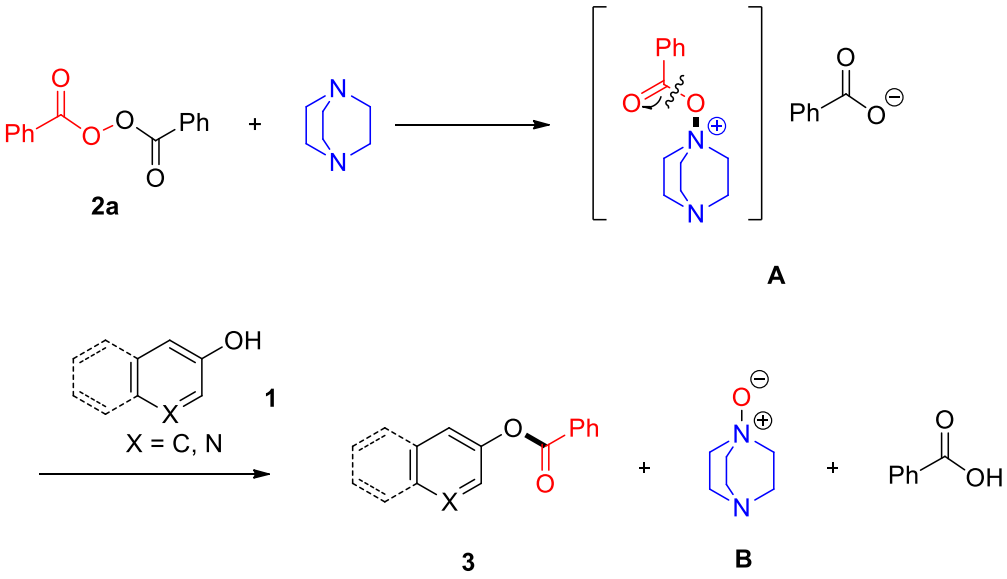
[a] Reaction conditions: **1a** (1.0 mmol), **2** (0.2 mmol), DABCO (0.4 mmol), DCE (2 mL), at room temperature for 6 h. [b] Isolated yields.

The gram-scale reaction was carried out under the optimal reaction conditions to examine the scale-up of this method. The reaction proceeded smoothly with 30 mmol of **1a**, 6 mmol of **2a** and 12 mmol of DABCO, and 0.98 g of the target product **3a** was obtained in 66% yield. The result of the gram-scale reaction reveals the potential for applications of the method.



Scheme 2. Control experiments of esterification reaction.

In order to gain insight into the reaction pathway, we verified the possible mechanism of the reaction through control experiments (Scheme 2). When three equivalents of free radical inhibitor TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction system, the target product **3a** was still obtained in 66% yield (Scheme 2a). Meanwhile, when three equivalents of BHT (2,6-di-*tert*-butyl-4-methylphenol) was added to the reaction under the standard conditions, **3a** was obtained in 85% yield. In addition, 1,1-diphenylethylene was added as a mild radical scavenger, and 81% yield of **3a** could still be obtained. No radical coupling product was detected in the process. These results indicate that the reaction does not involve a free radical process. Signifcantly, the by-product benzoic acid was detected by HRMS in this transformation. When the reaction of benzoic acid with **1a** was performed under optimized conditions, no target product could be detected (Scheme 2b).



Scheme 3. Plausible mechanism.

Based on these experimental results and previous works,[32-34] a possible reaction mechanism is depicted in Scheme 3. First, nucleophilic attack occurs between DABCO and aryl acyl peroxides to generate intermediate **A** as an acyl donor. Subsequently, the esterification reaction proceeds smoothly between the substrate **1** and intermediate **A**. The oxyanion acts as a benzoyl acceptor after deprotonation. The aromatic ester compound **3** is generated, along with the production of DABCO *N*-oxide **B** benzoic acid (detected by HRMS, see supporting information) as by-products.

Conclusions

In summary, we have developed an efficient method for the synthesis of aromatic esters. At room temperature, a series of aromatic esters was prepared in good yields using (hetero)arylphenol and aroyl peroxide as reactants, DABCO as base, and DCE as solvent. The reaction has a good functional group tolerance, especially for pyridine heterocyclic substrates, which can be well compatible. The research is expected to provide a simple, efficient and fast way for the efficient construction of complex aromatic esters.

Experimental Section

General. Unless otherwise noted, all commercially available compounds were used as provided without further purification. For column chromatography, 200–300 mesh silica gel was used. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 500 MHz spectrometers in $CDCl_3$. Melting points were measured with an Electrothermal digital melting point apparatus.

General procedure for the synthesis of aryl acyl peroxide. Hydrogen peroxide (30 wt.% H_2O_2, 4 mmol) was added dropwise to a solution of aryl acyl chloride (8 mmol) in methyl *tert*-butyl ether (3 mL) over 10 min under ice bath conditions, then an aqueous solution of NaOH (0.4 g, 10 mmol, 10 mL) was added drop by drop over 20 min. White precipitate was collected by filtration. After washing with water (3×5 mL) and methyl *tert*-butyl ether (3×5 mL), the solid was recrystallized with cold acetone/water mixture (1:3 V/V).[35]

General procedure for DABCO-mediated synthesis of aromatic esters. In a dry 10 mL reaction tube were added 2-naphthol (1.0 mmol), benzoyl peroxide (0.2 mmol), triethylenediamine (0.4 mmol), and then 1,2-dichloroethane solution (2 mL). The reaction was stirred at room temperature for 6 h, and the reaction was monitored by thin-layer chromatography. After the reaction was completed, the target product was obtained by column chromatography using petroleum ether/ethyl acetate (3:1-20:1 V/V) as the eluent.

Synthesis of naphthalen-2-yl benzoate (3a). Following the general procedure, 2-naphthol (**1a**, 144.2 mg, 1.0 mmol) and benzoyl peroxide (**2a**, 0.2 mmol) were used. Product **3a** (42.3 mg, 85%) was obtained as a white solid. m.p. 104.5-105.1 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.2 Hz, 2H), 7.92–7.82 (m, 3H), 7.71–7.64 (m, 2H), 7.57–7.47 (m, 4H), 7.36 (dd, J = 8.8, 2.3 Hz, ^{1}H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.45, 148.64, 133.87, 133.73, 131.57, 130.28, 129.59, 129.55, 128.68, 127.87, 127.75, 126.65, 125.80, 121.32, 118.78.

Acknowledgements

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Supplementary Material

Full experimental details, spectroscopic data, and ^{1}H and ^{13}C NMR spectra of products can be found via the "Supplementary Content" section of this article's webpage.

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