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One-Pot Synthesis of Esters through a Benzoin Condensation-Oxidative Cleavage-Esterification Triple Cascade Reaction

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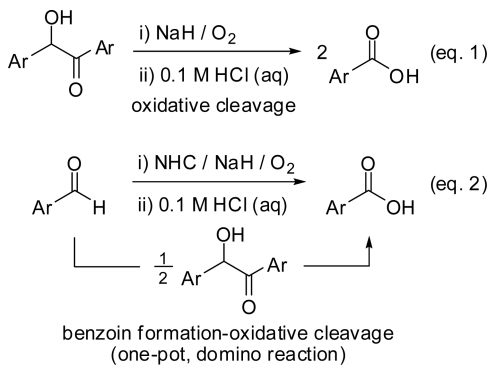
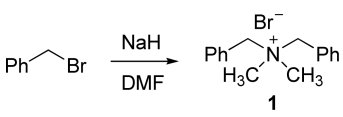
Cascade reactions, in which several bonds are formed in a chain of events without isolating the intermediate, have emerged as a powerful strategy for constructing complex molecules.[1] As part of a wider research program aimed at designing and developing a conceptually new class of one-pot cascade processes, we became interested in the development of an oxidative esterification reaction. Despite the steadily growing interest in the synthesis of esters using diverse oxidative esterification methodologies based on *N*-heterocyclic carbenes (NHCs) catalysis,[2,3] only three examples of oxidative esterification of aldehydes with alkyl halides have been reported.[4] However, stoichiometric amounts of MnO_2[4a] or NHCs,[4b] and elevated reaction temperature[4c] are occasionally required to perform the oxidative esterification reactions. In our search for an alternative method for oxidative esterification of aldehydes, we postulated that esters might be synthesized directly from aldehydes with alkyl halides in the presence of catalytic amount of NHC precatalyst and excess of sodium hydride as a base under oxygen atmosphere. Recently, we demonstrated that the NaH-O_2 system[5] is a powerful promoter of the oxidative cleavage of benzoins to benzoic acids.[6] As an extension, in situ transformation of aldehydes to carboxylic acids[7] was accomplished by the combination of NHC catalysis and NaH-O_2 system *via* NHC-assisted benzoin formation and oxidative cleavage of a carbon-carbon bond (Scheme 1). Herein, we report the NHC-assisted, one-pot, domino oxidative esterification reaction of aldehydes with alkyl halides *via* benzoin condensation-oxidative cleavage-esterification.



Scheme 1. Utility of NaH-O_2 system.

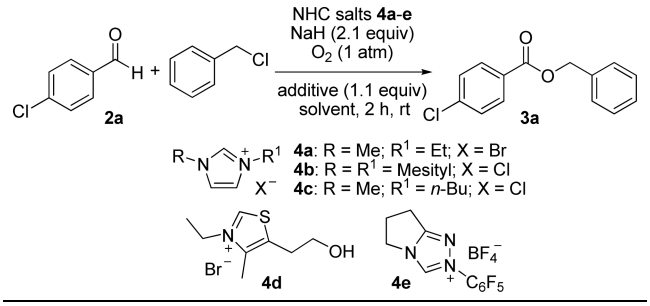
Initially, 4-chlorobenzaldehye **2a** was treated with benzyl chloride in the presence of 10 mol % [Emim][Br] (1-ethyl-3-methylimidazolium bromide, **4a**) as NHC precatalyst, 2.5 equiv of NaH in THF solvent at room temperature under 1 atm O_2. However, no reaction took place in THF. Presumably, THF is less effective at separating ion pairs, such as the sodium carboxylate intermediate that are generated by reacting aldehydes with NaH in the presence of catalytic amount of NHC under 1 atm O_2, than an polar aprotic solvent (DMF). Thus, we decided to switch the solvent from THF to DMF. Surprisingly, the corresponding ester was obtained in only 10% yield (Table 1, entry 2). After searching the literature, we found reports that NaH can also behave as a hydride source. For example, when NaH was treated with benzyl bromide in DMF, quaternary ammonium salt **1** was obtained (Scheme 2).[8] Unexpectedly, low conversion in our system may be due to the formation of insoluble salts during the reaction, that inhibited further oxidative esterification.

In general, quaternary ammonium or phosphonium salts are widely used to enhance the nucleophilicity and solubility of alkali metal salts both in polar aprotic solvents and in nonpolar solvents. With these concepts in mind, we decided to use a phase-transfer reagent. Gratifyingly, we observed that in the presence of a phase-transfer reagent, the oxidative esterification reaction proceeded smoothly in a THF solvent to furnish the desired product within a short period in high yields. Tetrabutyl ammonium chloride showed higher reaction activity than the other quaternary ammonium salts (Table 1, entries 3-5). Next, we examined the catalytic activities of several NHCs **4a-e** for the domino reaction. The NHC precatalysts **4a-c** derived from imidazolium salt performed better than those derived from thiazolium **4d** and triazolium backbone **4e** in terms of chemical yields. Among the imidazolium salts **4a-c**, [Bmim][Cl] (1-butyl-3-methylimidazo-



Scheme 2. Action of NaH as a reducing agent.

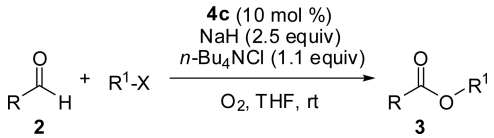
Table 1. Optimization of the reaction conditions[a]



Entry	NHC precatalyst (mol %)	Solvent (M)	Additive	Yield (%)[b]
1	**4a** (10)	THF (0.1)	-	ND
2	**4a** (10)	DMF (0.1)	-	10
3	**4a** (10)	THF (0.1)	*n*-Bu_4NCl	46
4	**4a** (10)	THF (0.1)	*n*-Bu_4NBr	23
5	**4a** (10)	THF (0.1)	*n*-Bu_4NI	19
6	**4b** (10)	THF (0.1)	*n*-Bu_4NCl	62
7	**4c** (10)	THF (0.1)	*n*-Bu_4NCl	81
8	**4d** (10)	THF (0.1)	*n*-Bu_4NCl	29
9	**4e** (10)	THF (0.1)	*n*-Bu_4NCl	21

[a]Reaction conditions: aldehyde **2a** (0.7 mmol), benzyl chloride (1.05 mmol), NHCs precatalyst **4a-e** (10 mol%), tetrabutyl ammonium salts (0.77 mmol), NaH (60% dispersion in mineral oil; 1.47 mmol), O_2 (1 atm), solvents (0.1 M). [b]Isolated yields.

Table 2. Substrate scope for the oxidative esterification[a]



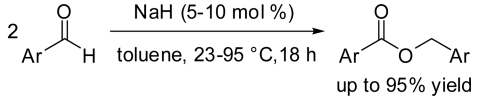
Entry	R	R^1-X	Product	Time (h)	Yield (%)[b]
1	4-Cl-C_6H_4	BnCl	**3a**	2	86
2	3-Cl-C_6H_4	BnCl	**3b**	2	81
3	4-Br-C_6H_4	BnCl	**3c**	2	97
4	4-CF_3-C_6H_4	BnCl	**3d**	2	75
5	4-CN-C_6H_4	BnCl	**3e**	2	77
6	4-NO_2-C_6H_4	BnCl	**3f**	2	65
7	3-NO_2-C_6H_4	BnCl	**3g**	2	57
8	Ph	BnCl	**3h**	2	72
9	2-Naphthyl	BnCl	**3i**	2	82
10	2-Biphenyl	BnCl	**3j**	2	59
11	4-MeO-C_6H_4	BnCl	**3k**	2	43
12	Furyl	BnCl	**3l**	2	56
13	Cyclohexyl	BnCl	**3m**	2	37
14	(*E*)-Cinnamyl	BnCl	**3n**	2	75
15	4-Cl-C_6H_4	*n*-C_3H_7Cl	**3o**	20	53
16	4-Cl-C_6H_4	*n*-$C_8H_{17}Cl$	**3p**	56	22

[a]Reaction conditions: aldehyde **2** (0.7 mmol), benzyl chloride (1.05 mmol), NHCs precatalyst **4c** (10 mol %), tetrabutyl ammonium chloride (0.77 mmol), NaH (60% dispersion in mineral oil; 1.75 mmol), O_2 (1 atm), THF (0.1 M). [b]Isolated yields.

lium chloride, **4c**) was capable of catalysing the reaction in THF to give **3a** in 81% yield.

In a related study, Werner *et al.* reported the Tishchenko reaction with two molecules of (hetero) aromatic aldehydes in the presence of 5-10 mol % of NaH to give the corresponding Tishchenko esters in high yields (Scheme 3).[9] Our approach may result in a competitive pathway such as the Tishchenko reaction. However, the Tishchenko reaction is significantly suppressed by the addition of a NHC precatalyst, alkyl halide, and O_2 under similar reaction conditions.

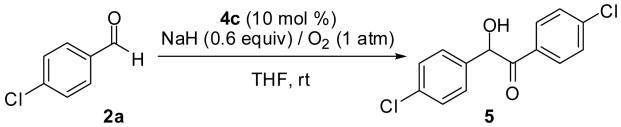
With the optimum reaction conditions in hand, we extended our protocol to different aldehydes and alkyl halides. In general, aromatic aldehydes with electron-withdrawing substituents showed enhanced reactivity over aromatic aldehydes with electron-donating groups. In particular, aldehydes bearing weakly deactivating groups (*i.e.* halogens) were readily converted to esters in high yields (Table 2, entries 1-3). Conversely, aldehydes bearing relatively stronger electron-withdrawing groups such as cyano, or nitro groups gave lower yields under optimal conditions (Table 2, entries 5-7). A heteroatom-containing aldehyde gave the desired product in moderate yield. *trans*-Cinnamaldehyde was also a suitable candidate for oxidative esterification (Table 2, entry 14). We utilized *n*-propyl chloride and *n*-octyl chloride as alkylating reagents. The long-chain alkyl halide exhibited lower conversion than the short-chain alkyl halide.



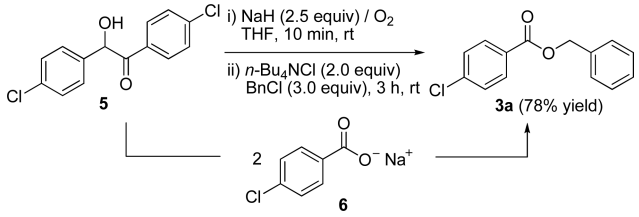
Scheme 3. NaH-catalyzed Tishchenko reaction.

The proposed mechanism for oxidative esterification consists of the following three sequential steps: benzoin formation, oxidative cleavage, and esterification. To study the mechanism, we designed and performed a series of control experiments. To verify the existence of a benzoin compound as a key intermediate in the first step, we reacted aldehyde **2a** with 0.6 equivalent of NaH in the presence of 10 mol % of NHC precatalyst **4c** to give chlorobenzoin **5** in 18% yield. The identity of compound **5** was confirmed by ^1H and ^{13}C NMR spectroscopy (Scheme 4).

The oxidative cleavage of benzoin **5**[10] using the NaH-O_2 system provided the corresponding sodium carboxylate **6**, which attacks another molecule of benzyl chloride to produce the desired ester **3a** in the presence of phase-transfer reagent (Scheme 5). Our observations provide strong evidence that the oxidative esterification of aldehydes to esters proceeds *via* the self-benzoin condensation of aldehyde, then the oxidative cleavage of benzoin, followed by the esterification of carboxylate with the alkyl halide. Our reaction



Scheme 4. NHC-catalyzed benzoin condensation reaction under NaH-O_2 system.



Scheme 5. Oxidative cleavage/esterification in one-pot using NaH-O_2.

pathway is clearly unique from other strategies (Schemes 4 and 5).[4]

In summary, we developed an efficient one-pot, triple cascade oxidative esterification reaction of aldehydes with alkyl halides using the NHC catalyst and NaH-O_2 system. Control experiment delineated the intermediacy of benzoin by NHC catalysis and its conversion to carboxylate salt by NaH-O_2 followed by alkylation.

Experimental Section

Typical Procedure for Oxidative Esterification. To a solution of aldehyde **2a** (0.7 mmol, 98.4 mg), NHC pre-catalyst **4c** (0.07 mol, 17.5 mg), tetrabutyl ammonium chloride (0.7 mmol, 278 mg) and benzyl chloride (1.05 mmol, 173 mL) in anhydrous THF (7 mL), NaH (60% dispersion in mineral oil; 1.75 mmol, 70 mg) was added under oxygen (1 atm) atmosphere and then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with H_2O, and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc:hexanes = 1:20) to afford the desired product **3a**. The physical data of the known compounds **3** were found to be identical to the data reported in the literature: **3a**,[11a] **3b**,[11b] **3c**,[4b] **3d**,[11c] **3f**,[11d] **3g**,[11e] **3h**,[11b] **3i**,[11f] **3k**,[11a] **3l**,[11g] **3m**,[11h] **3n**,[11b] **3o**.[11i]

Benzyl 4-Cyanobenzoate (3e): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, 2H, J = 8.7 Hz), 7.74 (d, 2H, J = 8.7 Hz), 7.44-7.39 (m, 5H), 5.39 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.0, 135.6, 134.1, 132.5, 130.5, 130.0, 128.9, 128.7, 118.2, 116.7, 67.8. HRMS (FAB): calcd for $C_{15}H_{12}O_2N$ $(M+H)^+$: 238.0863, found 238.0868.

Benzyl Biphenyl-4-carboxylate (3j): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, 2H, J = 8.4 Hz), 7.68-7.61 (m, 4H), 7.49-7.38 (m, 8H), 5.39 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 146.0, 140.2, 136.3, 130.5, 129.2, 129.1, 128.9, 128.5, 127.5, 127.3, 70.0. HRMS (FAB): calcd for $C_{20}H_{17}O_2$ $(M+H)^+$: 289.1223, found 289.1229.

Benzyl Cyclohexanecarboxylate (3p): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, 2H, J = 8.7 Hz), 7.4 (d, 2H, J = 9 Hz), 4.31 (t, 2H, J = 13.2 Hz), 1.81-1.71 (m, 2H), 1.42-1.25 (m, 10H), 0.89 (t, 3H, J = 13.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.0, 139.4, 131.2, 129.2, 128.9, 128.8, 65.6, 32.0, 29.5, 29.4, 28.9, 26.3, 22.9, 14.3. HRMS (FAB): calcd for $C_{15}H_{22}O_2Cl$ $(M+H)^+$: 269.1303, found 269.1308.

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