

NHC-Assisted One-Pot Domino Oxidation of Aldehydes into Carboxylic Acids using Sodium Hydride under Oxygen Atmosphere

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Domino reactions are powerful tools in synthetic chemistry for the formation of target molecules in a single flask without the isolation of intermediates, and hence the number of reaction steps is reduced and waste may be minimized.¹ As part of a wider research program aimed at exploring new domino reactions, we became interested in developing a new strategy for the oxidation of aldehydes to the corresponding carboxylic acids.² Surprisingly, despite impressive advances in the area of oxidation, domino reactions have not been applied to the oxidation of aldehydes to carboxylic acids.³ Very recently, we began to explore the utility of sodium hydride-molecular oxygen (NaH-O₂) system and successfully applied to the oxidation of benzoin to benzils,⁴ and the oxidative cleavage of benzoin to benzoic acids.⁵ Based on these results, we envisioned that the combination of the self-benzoin condensation of aldehyde and the oxidative cleavage of benzoin using NaH-O₂ could provide a conceptually new domino oxidation reaction. Herein we report our preliminary results on NHC-assisted one-pot domino oxidation.

To identify the feasibility of our approach, we first carried out domino benzoin condensation/NaH-O₂ oxidation with *p*-chlorobenzaldehyde **1a**. Thus, self-benzoin condensation reaction of **1a** in the presence of 50 mol % *N*-heterocyclic carbene (NHC) precatalyst **3c** with K₂CO₃ as a base in CH₂Cl₂ for 24 h yielded the intermediate **I**.⁶ The successive addition of 1 equivalent of NaH in a mixed solvent of THF and CH₂Cl₂ under oxygen atmosphere, provided the desired *p*-chlorobenzoic acid **2a** in a 77% yield after 10 min (Scheme 1).

We next attempted to develop one-pot domino reactions by employing NHC precatalyst/NaH-O₂ together. Our studies began with an initial examination of the catalytic activities of several NHCs⁷ **3a-e** for the domino oxidation of **1a**. The results are summarized in Table 1. The NHC precatalysts **3a**,

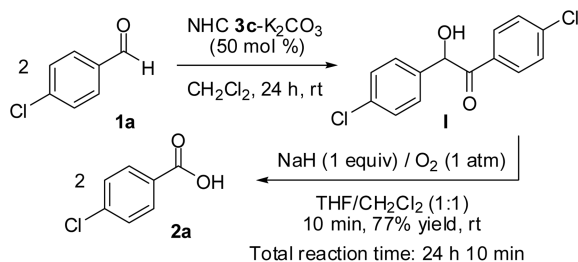
3b derived from imidazolium salt produced the desired product **2a** in 58% and 78% yields after 30 min and 2 h, respectively (Table 1, entries 1-2). Among the imidazolium salts **3a-c**, **3c** is capable of catalyzing the reaction in undegassed dry THF to give **2a** in a 72% yield after only 10 min under NaH-O₂ system (Table 1, entry 3). Noteworthy is that the current one-pot, domino oxidation methodology is superior to the sequencing reaction in terms of reaction rate. Even if the turnover frequency in the benzoin formation step is much lower than that in the oxidative cleavage step, presumably, **1a** was quickly consumed in relatively large quantities by NaH/O₂, thereby producing the desired product **2a** within 10 min. In contrast, the reaction was sluggish and gave lower yield (32%) without oxygen atmosphere (Table 1, entry 4), which was attributed to the remaining self-benzoin product **I**. We also investigated the effects of solvent and NaH loading. Replacing the solvent THF with EtOAc or toluene led to lower chemical yields (Table 1, entries 7-8). With the use of precatalyst **3c** (10 mol %) and NaH (0.6 equiv) under oxygen atmosphere, the desired product was formed in poor yield (32%) due to the major portion of unreacted aldehyde **1a**, the formation of the 4,4'-chloro-

Table 1. Optimization of the reaction conditions^a

Entry	Catalysts	Solvent	NaH (equiv)	Time	Yield (%) ^b
1	3a	THF	1.1	30 min	58
2	3b	THF	1.1	2 h	78
3	3c	THF	1.1	10 min	72
4 ^c	3c	THF	1.1	10 min	32
5	3d	THF	1.1	12 h	60
6	3e	THF	1.1	12 h	47
7	3c	EtOAc	1.1	2 h	42
8	3c	Toluene	1.1	2 h	25
9	3c	THF	0.6	2 h	32

^aReaction conditions: **1a** (0.7 mmol), NHC precatalyst **3a-e** (0.07 mmol), NaH (60% dispersion in mineral oil, 0.6 or 1.1 equiv), O₂ (1 atm), rt.

^bIsolated yield. ^cWithout oxygen atmosphere.



Scheme 1. Sequencing reaction for oxidation of aldehyde to carboxylic acid.

benzoin **1**, and the trace amounts of remaining 4,4'-chlorobenzil, all of which were isolable and confirmed *via* ^1H and ^{13}C NMR spectroscopies (Table 1, entry 9).

The above results indicated that this protocol involved 4,4'-chlorobenzoin **1** as a key intermediate for the subsequent oxidation mediated by NaH-O₂ system, which is solid evidence that aldehyde **1a** is not directly oxidized to carboxylic acid **2a** under this reaction condition. In a related study, Lewis reported a single example of oxidation of *p*-nitrobenzaldehyde using a NaH-O₂ system, and proposed that the reaction occurred by Cannizzaro reaction, thereby producing *p*-nitrobenzoic acid with accomplishing of *p*-nitrobenzyl alcohol.⁸ In contrast, under our newly designed system, the corresponding benzyl alcohols were not observed in any cases, indicating that the oxidation was not related to the Cannizzaro reaction pathway. To demonstrate the differentiation between our current protocol and Lewis' method, we carried out the reactions of 4-methylbenzaldehyde **1h** and *p*-chlorobenzaldehyde **1a** with NaH either in the presence or absence of the NHC precatalyst **3c** under oxygen atmosphere (Table 2). Quite surprisingly, the trace amount of the desired product **2h** (< 5% yield) was observed (Table 2, entry 1) during the reaction of **1h** bearing an electron-donating group in the absence of the NHC precatalyst **3c** under NaH-O₂ system, whereas with the use of precatalyst **3c** under NaH-O₂ system resulted in a large amount of the product **2h** (82% yield; Table 2, entry 2). A similar pattern was observed when **1a**

possessing an electron-withdrawing group was employed (Table 2, entries 3-4). It turned out that the reaction was significantly accelerated by the addition of NHC precatalyst **3c**.

To explore the scope of substrate of our domino oxidation, various aldehydes were examined (Table 3). In general, the aromatic aldehydes **1a-d**, which possesses electron withdrawing substituents, resulted in higher performance compared to those of electron donating substituents, and the reactions were completed within 20 min and produced the desired products in high yields (72-90%).

In summary, we achieved one-pot, domino oxidations of aldehydes to their corresponding carboxylic acids using a combination of NHC catalyst and a NaH-O₂ system. Moreover, the dramatic acceleration effect was observed upon addition of NHC catalyst.

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Table 2. Comparison of concept for the oxidation of aldehydes

$\text{Ar}-\text{CHO} \xrightarrow[\text{THF [0.5 M], rt}]{\text{NaH (1.1 equiv) / O}_2 \text{ (1 atm)}} \text{Ar}-\text{COOH}$				
Entry	Ar	Conditions	Time	Yield (%) ^a
1	4-Me-C ₆ H ₄	without precatalyst 3c	8 h	< 5
2	4-Me-C ₆ H ₄	with precatalyst 3c	8 h	82
3	4-Cl-C ₆ H ₄	without precatalyst 3c	10 min	22
4	4-Cl-C ₆ H ₄	with precatalyst 3c	10 min	72

^aIsolated yield.

Table 3. Substrate scope for the domino oxidation of aldehydes^a

$\text{Ar}-\text{CHO} \xrightarrow[\text{THF [0.5 M], rt}]{\text{NHC } \mathbf{3c} \text{ (10 mol \%)} \text{ NaH (1.1 equiv) / O}_2 \text{ (1 atm)}} \text{Ar}-\text{COOH}$			
Entry	Ar	Time	Yield (%) ^b
1	4-Cl-C ₆ H ₄ (a)	10 min	72
2	3-Cl-C ₆ H ₄ (b)	10 min	83
3	4-CF ₃ -C ₆ H ₄ (c)	20 min	77
4	4-NC-C ₆ H ₄ (d)	10 min	90
5	4-NO ₂ -C ₆ H ₄ (e)	10 min (8 h) ^c	51 (90) ^c
6	Ph (f)	2 h	72
7	2-Naphthyl (g)	8 h	83
8	4-Me-C ₆ H ₄ (h)	8 h	82
9	3-Me-C ₆ H ₄ (i)	8 h	85
10	4-MeO-C ₆ H ₄ (j)	8 h	33

^aReaction conditions: **1** (0.7 mmol), NHC precatalyst **3c** (0.07 mmol), NaH (60% dispersion in mineral oil, 1.1 equiv), O₂ (1 atm), THF [0.5 M], rt. ^bIsolated yield. ^cUsing NHC precatalyst **3b**.