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Aerobic oxidation of aldehydes to acids with *N*-hydroxyphthalimide derivatives

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ABSTRACT

The *N*-hydroxyphthalimide derivative-mediated aerobic oxidation of a selection of aldehydes to the corresponding carboxylic acids in air is described. This reaction proceeds via rearrangement of the Creigee (carboxylic peracid) intermediate and/or by the treatment of H_2O and/or sulfides. Optimization of reaction conditions established NHNPI (**14**) as a mild catalyst for the oxidation reaction in MeCN under an atmosphere of air.

Introduction

N-Hydroxyphthalimide (NHPI, **1**) is an efficient organo-catalyst for free-radical processes and has been used for the aerobic oxidation of a wide range of organic substrates [1–4]. A combination of different co-catalysts, especially transition-metal complexes, have been used to activate the *N*-oxyl radical species. However, metal-free processes are important for environmental reasons, and the development of non-metal co-catalysts has attracted a great deal of attention. Recently, our group reported the use of Fmoc-OPhth, as a non-metal activator, in combination with NHPI (**1**) [5]. Fmoc-OPhth is normally used in the context of Fmoc protection and was designed and synthesized to avoid the formation of Fmoc-βAla-OH by Lossen rearrangement [6–9]. NHPI (**1**) was recently developed as a novel and reversible method of detecting *N*-terminal amino groups during Fmoc-solid phase peptide synthesis as alternative to the Kaiser test [10]. HYPERLINK "SPS:refid::bib10"

Kang recently described the use of the organo-catalyst, NHPI (**1**), for the oxidation of aldehydes (**2**) to acids [11]. Alkylaldehydes were selectivity oxidized into the corresponding carboxylic acids in 3 h at 30 °C under 1 atm of O_2 in the presence of 5 mol% of NHPI (**1**; aromatic aldehydes required forcing conditions (1.5 d, 90 °C, 10 mol% of NHPI (**1**), 1 atm of O_2). In the mechanism for the oxidation proposed by Kang, (i) a phthalimid-*N*-oxyl radical (PINO) acts as a nonterminating chain propagation radical; (ii) a free radical chain reaction proceeds via acyl radical **A** (generated by PINO); (iii) upon reaction with O_2, an acylperoxy radical **B** is formed; and (iv) peracid **C** reacts with remaining aldehyde via nucleophilic addition to form the Criegee intermediate **D**, which yields two molecules of carboxylic acids (**3**) upon its rearrangement (path a). However, Vanoya et al. reported the possibility of another mechanism for the final step [12], wherein peracid **C** is transformed into the corresponding carboxylic acids during the workup procedure (path b) (Fig. 1) [13,14]. In addition, Deng and Zhou reported detailed mechanisms for the conversion from aldehydes to acids based on density functional theory (DFT) [15].

We were interested in this phenomenon, because it is possible that use of NHPI (**1**) by us is limited to protection and detection of amino groups. Moreover, there was no aldehyde functionality in the peptide chemistry. In addition, catalytic activities of NHPI (**1**) are often lower than those of another organo-catalysts. It is important to understand the property of NHPI derivatives from various perspectives. For the reason, we decided to investigate the aerobic organocatalyzed oxidation by specifically investigation of NHPI derivatives, solvent effect and aldehydes. Although aerobic oxidation of aldehydes is reported in the literature [16–18], we herein report this reaction for the development of NHPI chemistry.

Results and discussion

Dodecanal was selected as a model substrate and its oxidation with 5 mol% NHPI (**1**) in MeCN at room temperature and under an air atmosphere proceeded to give a mixture of dodecanoic acid and its peracid, without any workups, Scheme 1. However, concentration of the reaction mixture after 24 h *in vacuo* and ^{1}H NMR

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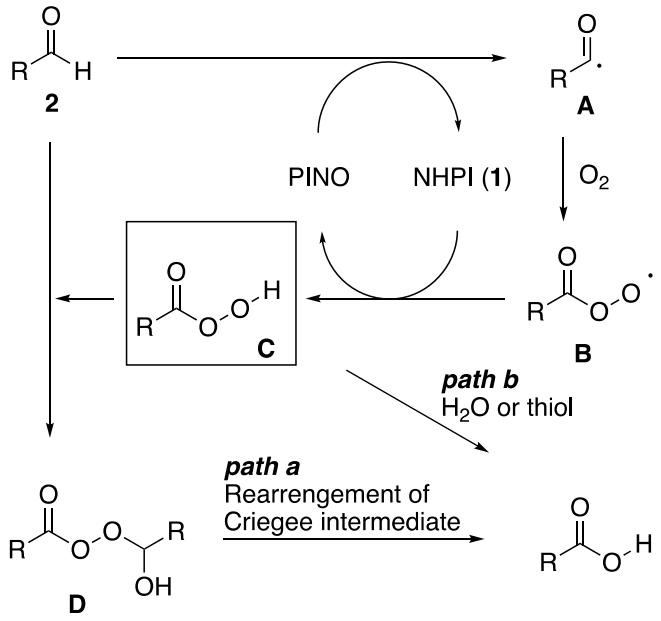
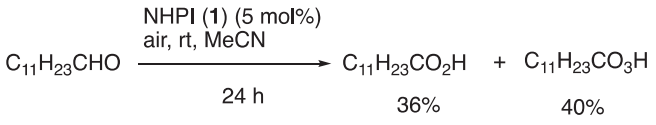


Fig. 1. Plausible mechanism of NHPI (**1**) catalyzed oxidation reaction.



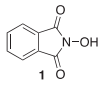
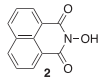
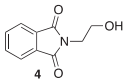
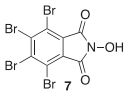
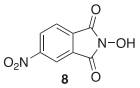
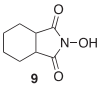
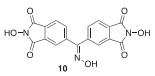
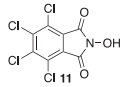
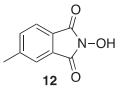
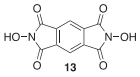
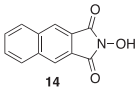
Scheme 1. NHPI (**1**)-catalyzed oxidation of dodecanal. Reaction conditions: NHPI (**1**) (5 mol%), dodecanal (0.5 mmol), air (1 atm), MeCN (2 mL), room temperature, 24 h. Chemical yields were determined by ^{1}H NMR spectra.

analysis of the residue (in $CDCl_3$) suggested that this oxidation is not a straightforward process. For example, in addition to the decrease of the triplet peak corresponding to the H of the aldehyde (9.76 ppm), two new triplet peaks (2.36 ppm and 2.42 ppm for -protons) corresponding to dodecanoic acid and its peracid were observed. Yields of these products were estimated to be 36% and 40%, respectively, using NHPI (**1**) as an internal standard. Neither an atmosphere of pure oxygen nor a co-catalyst was found to be necessary for the reaction to proceed.

A variety of different reaction conditions were investigated. Air oxidation without NHPI (**1**), in the dark, or under an atmosphere of N_2 resulted in very low yield (<5%). However, use of 5 mol% NHPI (**1**) in MeCN gave a mixture of dodecanoic acid and its peracid in satisfactory yields. Increasing the mol% of NHPI (**1**) did not significantly accelerate the reaction, suggesting its kinetics to be controlled by the solubility of O_2 in MeCN.

Next, the catalytic activities of various NHPI (**1**) derivatives were evaluated, previous work having suggested the substituents on the aryl ring of NHPI (**1**) to affect the oxidation outcome [19–21] (Table 1). 1,8-Naphthalimide (**2**), biphenylimide (**3**), and hydroxyethylphtalimide (**4**) were all catalytically inactive (Table 1, entries 2–4). A 3-nitro-substituted NHPI (**5**) and *N*-hydroxybenzamide (**6**) gave dodecanoic acid in moderate yields (entries 5–6). Interestingly, tetrabromo-substituted NHPI (**7**) and 4-nitro-substituted NHPI (**8**) smoothly oxidized dodecanal to give dodecanoic acid in high yields (entries 7–8). The cyclohexyl derivative (**9**) and tetrachloro-NHPI (**11**) were also effective (entries 9, 11). A catalyst bearing an electron-donating methyl group was also effective (entry 12). Catalysts bearing two or three *N*-hydroxy groups (**10** and **13**) were also adequate (entries 10 and 13) However, 2,3-naphthalimide type catalyst NHNPI (**14**) was quickly proceeded

Table 1
Screening of *N*-Oxyl precursors.

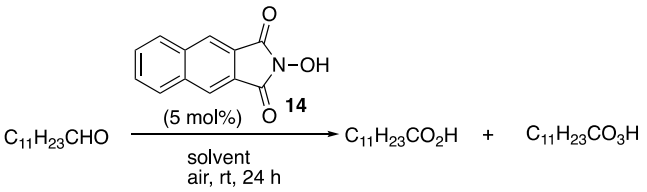
1		0	48	52
2		100	0	0
3		100	0	0
4		99	1	0
5		42	44	14
6		51	37	12
7		7	92	2
8		0	90	10
9		1	34	65
10		0	72	28
11		0	60	38
12		0	62	38
13		0	40	60
14		0	42	58

the oxidation (entry 14). The screening using *N*-oxyl precursors were attempted for 24 h. By the investigation of the reaction for 12 h, dodecanal was detected in all entries except for entry 14. At least, it spends time over 12 h to complete the aerobic oxidation using *N*-oxyl precursors (**1**–**13**). Based on these results, NHNPI (**14**) was selected as the preferred organo-catalyst for this oxidation system.

Reaction conditions: NHPI derivatives (5 mol%), dodecanal (0.5 mmol), air (1 atm), MeCN (2 mL), room temperature, 24 h. Yield of dodecanal and its peracid was determined by ^{1}H NMR analysis.

A selection of solvents was also screened under an atmosphere of air using NHNPI (**14**) as the catalyst with a reaction time of 24 h (Table 2). Ether, PhCl, water, and MeOH were associated with very low yields (entries 1–4). Use of Ph_2O, CH_2Cl_2, EtOH, $CHCl_3$, and hexane with a 24 h reaction time were all more successful, although

Table 2
Screening of solvents for the NHNPI (**14**)-catalyzed oxidation.



entry	solvent	R-CHO	R-CO_2H	R-CO_3H
1	ether	100	0	0
2	PhCl	99	1	0
3	MeOH	99	1	0
4	H_2O	99	1	0
5	Ph_2O	64	12	24
6	CH_2Cl_2	43	7	50
7	EtOH	35	8	57
8	$CHCl_3$	35	31	34
9	hexane	33	11	56
10	toluene	25	52	23
11	benzene	0	30	60
12	MeCN	0	34	66

resulted in the formation of dodecanoic peracid in a higher yield than dodecanoic acid. Reactions in benzene and MeCN proceeded smoothly (entries 11 and 12), consistent with Vanoya's report [12]. It should be noted that the experimental conditions, workup procedures, and analytical method used to ^{1}H NMR all affected the results, with the final product being obtained either by decomposition of the peracid intermediate, or by rearrangement of the Criegee intermediate.

Reaction conditions: NHNPI (**14**) (5 mol%), dodecanal (0.5 mmol), air (1 atm), solvent (2 mL), room temperature, 24 h. Yield of dodecanal and its peracid was determined by ^{1}H NMR analysis.

The oxidation of dodecanal in benzene and MeCN was separately monitored by ^{1}H NMR using MeCN-d_3 and benzene d_6. The reaction was carried out in an NMR tube and a spectrum acquired every 1 h (Fig. 2A). Using MeCN-d_3, the dodecanal was consumed within 8 h and peaks corresponding to dodecanoic acid and its peracid observed in areas corresponding to their moderate yield (Fig. 2B). This is consistent with the aforementioned experiments in MeCN (Table 1, entry 14 and Table 2, entry 12). On the other hand, the NHNPI (**14**)-catalyzed oxidation in benzene d_6 was slower than that in MeCN. After the treatment of reaction mixture for 8 h, the corresponding products yielded and the reaction completed for 18 h (Fig. 2A). It is noted that MeCN sufficiently accelerates the NHNPI (**14**)-catalyzed oxidation and leads aldehyde to the corresponding acid and its peracid (Fig. 2).

Transformation of the carboxylic peracid to carboxylic acid was accomplished with a large excess of phenylmethylsulfide [22] at room temperature. This step could also be accomplished using water, especially on large scale, although the reaction was much slower using water compared with phenylmethylsulfide. For example, a full week was required for the hydrolysis of dodecanoic peracid derivatives to the corresponding benzoic acids using water (Scheme 2, Fig. S2).

In contrast, treatment of dodecanoic acid from dodecanal proceeded via rearrangement of the Criegee intermediate. It is obvious that dodecanoic peracid was generally isolated on the NHNPI (**14**)-oxidation of dodecanal. In other words, dodecanal is used to trap mainly by PINO and to react with peracids as the side reaction. As the dodecanoic peracid after the purification was treated with dodecanal, the reaction with dodecanoic peracid could smoothly proceed and give dodecanoic acid solely in satisfactory yields. *m*-Cyanobenzaldehyde was not oxidized under the optimized condition (5 mol% NHNPI (**14**), MeCN, air, room temperature, 12 h), but could be oxidized to *m*-cyanobenzoic acid in 90% yield (see supporting information Fig. S3). It means that dodecanoic peracid is the substrate for the rearrangement of Criegee intermediate in the presence of dodecanal. Scheme 3 depicts a mechanism for the oxidation of *m*-cyanobenzaldehyde that accounts for this result. This reaction proceeds by reaction of m-cyanobenzaldehyde with dodecanoic peracid, which decomposes to give product carboxylic acids, i.e. dodecanoic peracid is the substrate for the rearrangement of Criegee intermediate. Lehtinen reported that there are two routes, Baeyer-Villiger (BV) and Anti-BV types, by the rearrangement of Creigee intermediate to give formates and carboxylic acids. In this case, the corresponding formate adducts have not been detected and therefore, anti-BV type reaction proceeded to yield *m*-cyanobenzoic acid and dodecanoic acid (Scheme 3) [13].

With optimized reaction conditions in hand, the scope of this method was investigated using a variety of alkyl, branched chain, and aromatic aldehydes. In all cases, the corresponding acids were

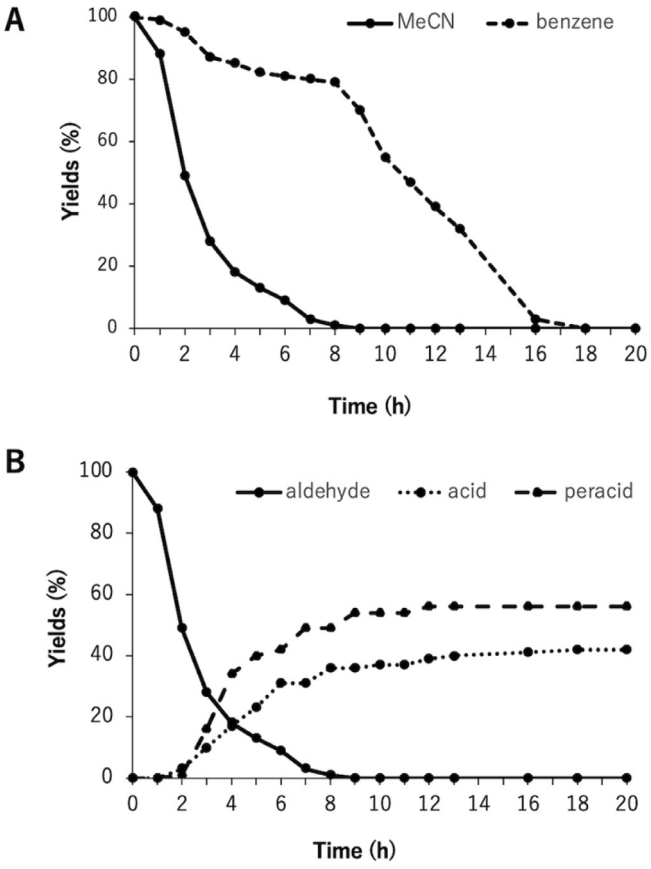
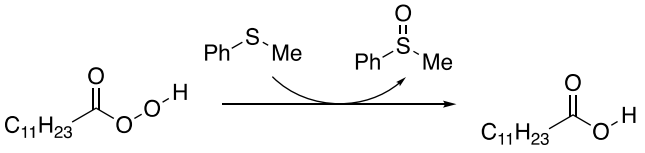
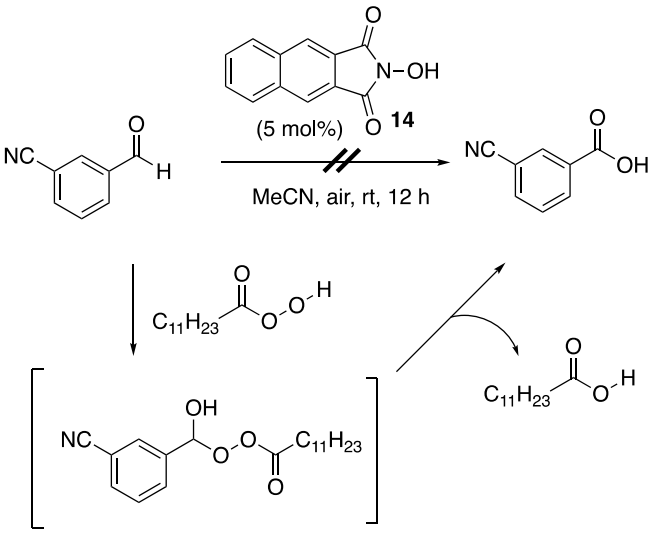


Fig. 2. NHNPI (**14**)-catalyzed oxidation of dodecanal in MeCN-d_3 and benzene-d_6 monitored as the function of time using ^{1}H-NMR. (A) Consumption of dodecanal in MeCN-d_3 and benzene-d_6. (B) Production of dodecanoic peracid and acid. Reaction conditions NHPI (**1**) (5 mol%), dodecanal (0.1 mmol), air (1 atm), MeCN-d3 or benzene-d6 (0.6 mL), room temperature.

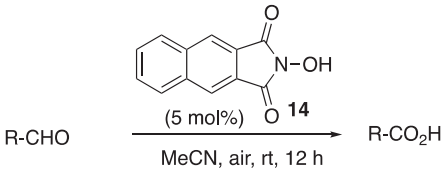


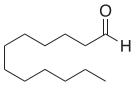
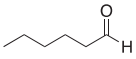
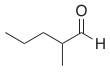
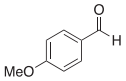
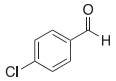
Scheme 2. Trap of dodecanoic peracid by phenylmethylsulfide to dodecanoic acid.



Scheme 3. Oxidation of *m*-cyanobenzaldehyde by dodecanoic peracid.

Table 3
Aerobic oxidation of a variety of aldehyde by NHNPI (**14**).



entry	substrate	R-CHO[a]	$R\text{-}CO_2H$	$R\text{-}CO_3H$	Isolated yield
1		0	34	66	60
2		0	23	77	36
3		0	81	19	37
4		0	78	22	70
5		3	44	53	88
6		0	3	97	92

obtained in moderate or high yields other than low yields observed for entries 1–3, which were attributed to the volatility of substrates (see Supporting information Fig. S4, S5). The NHNPI (**14**)-catalyzed oxidation of benzaldehyde in air was proceeded to give benzoic acid in 70% yield (entry 4). *p*-Methoxybenzaldehyde was oxidized to the corresponding carboxylic acid in 88% yield (entry 5). *p*-Halogenated benzaldehydes were also good substrates (entry 6). There is no obvious relationship between substrates and the ratio of the corresponding carboxylic peracid and carboxylic acid product. However, the structure of the substrate presumably affects the stability of the carbonyl radicals formed by the PINO and the propensity of the carbonyl cation to be oxidized by the peracid (Table 3). Therefore, in principle, this reaction is expected to be usefully chemoselective.

Conclusion

NHNPI (**14**) is an effective catalyst for the oxidation of aliphatic aldehydes and benzaldehydes to the corresponding carboxylic acids at room temperature under an atmosphere of air. For less reactive aldehydes, design and synthesis of new NHNPI derivatives are in progress. NHPI derivatives capable of catalyzing other transformations will also be investigated [23].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153320.

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