



Oxidative cleavage of hydroxamic acid promoted by sodium periodate



Changchun Yuan^{a, c}, Biao Du^a, Miao-Miao Xun^c, Bo Liu^{a, b, *}

^a Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China

^b State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, PR China

^c School of Chemical and Environmental Engineering, North University of China, Taiyuan 030051, PR China

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ABSTRACT

A series of hydroxamic acids, involving aliphatic, aromatic and cyclic substrates, were transformed to the corresponding carboxylic acids through NaIO_4 -mediated oxidative cleavage in mild conditions. Esterification of these acids with TMSCHN_2 could result in formation of the corresponding methyl ester. This methodology makes good compensation for the existing methods transforming amides to esters. Our results also pave the way to harness hydroxamic acids as useful synthetic building blocks.

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1. Introduction

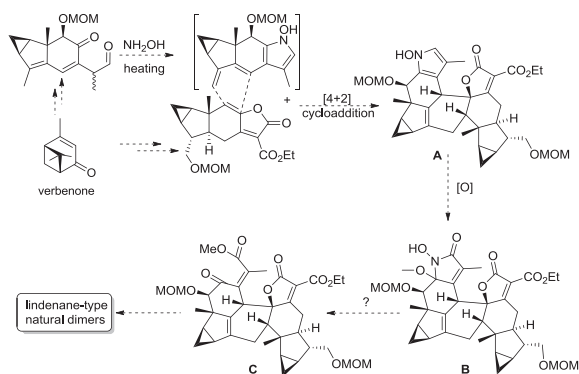
Hydroxamic acids are widely found in natural products with various biological activities,¹ synthetic intermediates,² and chiral ligands.³ Accordingly, numerous synthetic approaches to hydroxamic acids have been developed, involving acylation of hydroxylamines,^{2g,4} oxidation of arylacyl amides,⁵ reaction of aromatic nitroso compounds with oxoacids,⁶ coupling of carboxylic acids or their derivatives (acyl halides, anhydrides, and esters) with hydroxylamine or protected hydroxylamines,⁷ and NHC-catalyzed coupling of aldehydes with *N*-arylnitroso compounds.⁸ However, on the other hand, conversion of hydroxamic acids into other carboxylic acid derivatives through C–N oxidative cleavage has not been systematically studied, although scattered examples were reported though utilizing such oxidants as NaIO_4 ,⁹ NaClO ¹⁰ and $\text{K}_3\text{Fe}(\text{CN})_6$.¹¹ In other words, the potential of hydroxamic acids serving as synthetic building blocks toward carboxylic acid derivatives in organic synthesis need to be well exploited, which arouse our interest during our efforts on total synthesis of lindenane-type sesquiterpene dimers.¹² We actually conceived different strategies to realize the final transformation toward

tetrasubstituted alkenes in the target molecules, one of which are depicted in Scheme 1. Synthetically, a [4 + 2] cycloadduct **A** might be accessed from a diene fragment and a dienophile fragment, both achievable from verbenone. After oxidative elaboration of pyrrole in the intermediate **A**, a lactam could be generated to afford **B**. Oxidative cleavage of cyclic hydroxamic acid and esterification would produce the intermediate **C**, which would be transformed to different lindenane-type natural dimers.

Structurally, hydroxamic acids can be regarded as special amides with one of the amide N–H bond replaced by a N–OH bond. Because of the electron-donating effect of nitrogen to carbonyl, amides are well-known as poor electrophiles.¹³ So transformation of amides to other more labile carboxylic acid derivatives is really challenging. To solve this problem, synthetically useful methods for conversion of amides into esters and carboxylic acids were developed,^{13,14} involving application of a trialkyloxonium tetrafluoroborate salt,¹⁵ electrophilic preactivation of amides with trifluoromethanesulfonic anhydride (TF_2O) and base,¹⁶ copper-mediated methanolysis of bispicolylamine-substituted amides at room temperature,¹⁷ nickel-catalyzed methanolysis of amides,^{14,18} and so on.¹⁹ In addition, *N,N'*-dialkylhydrazides, as analogs of hydroxamic acids, can be efficiently cleaved to generate the corresponding carboxylic acids upon treatment with $\text{PhI}(\text{OH})\text{OTf}$.²⁰ Herein, we present a mild method for conversion of hydroxamic acids to methyl esters or carboxylic acids by treatment with NaIO_4 in mild reaction conditions, which may greatly extend their potential application in organic synthesis.^{17,21}

* Corresponding author. Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China.

E-mail address: chembliu@scu.edu.cn (B. Liu).



Scheme 1. A plausible application of oxidative cleavage of hydroxamic acid.

2. Results and discussion

Initial studies were focused on the cleavage of a model substrate, *N*-hydroxy-*N*-methyl-2-naphthamide (**1a**), with various oxidants (Table 1, entries 1–9). Lead (IV) acetate was employed to promote the reaction in benzene, whereas formation of 2-naphthoic acid was not observed even though full conversion of **1a** (Table 1, entry 1). So was the case in which NaClO₂ was attempted in mixed THF/H₂O as solvents (Table 1, entry 2). Interestingly, treating **1a** with NaClO₂ in aqueous methanol afforded 2-naphthoic acid smoothly,¹⁰ which was subsequently transformed to **2a** in 66% yield over two steps through esterification with

Table 1
Optimization of the reaction Conditions.^a

Entry	Oxidant	Solvent 1	t (h)	Solvent 2	Yield ^b (%)
1 ^c	Pb(OAc) ₄	benzene	0.5	–	–
2 ^c	NaClO ₂	THF/H ₂ O	0.5	–	–
3 ^d	NaClO ₂	MeOH/H ₂ O	15	THF/MeOH	66
4 ^e	K ₃ Fe(CN) ₆	THF/H ₂ O	4	THF/MeOH	57
5	DMP	THF/H ₂ O	0.5	THF/MeOH	38 ^f
6	IBX	THF/H ₂ O	0.5	THF/MeOH	65
7	PhI(OCOCF ₃) ₂	THF/H ₂ O	0.5	THF/MeOH	61
8	PhI(OAc) ₂	THF/H ₂ O	0.5	THF/MeOH	72
9	NaIO ₄	THF/H ₂ O	0.5	THF/MeOH	94
10	NaIO ₄	acetone/H ₂ O	0.5	THF/MeOH	94
11	NaIO ₄	MeOH/H ₂ O	0.5	THF/MeOH	90
12	NaIO ₄	MeCN/H ₂ O	0.5	THF/MeOH	80
13	NaIO ₄	THF/H ₂ O	0.5	Et ₂ O/MeOH	98
14 ^g	NaIO ₄	THF/H ₂ O	0.5	DCM/MeOH	98
15 ^h	NaIO ₄	THF/H ₂ O	0.5	MeOH	98

^a Unless otherwise specified, the reaction was carried out with **1a** (1.0 mmol) and the oxidant (2.0 mmol) in solvent 1 (10 mL, v/v = 4/1) and was monitored by TLC. After complete conversion, 0.5 mL of 2 N HCl solution was added to quench the reaction. After workup and concentration, esterification of the resultant acid with TMSCHN₂ (2.0 mmol) in solvent 2 (9 mL, v/v = 2/1) afforded methyl 2-naphthoate (**2a**).

^b Isolated yield.

^c 2-Naphthoic acid could not be obtained in this entry.

^d This reaction was performed with NaClO₂ (3.0 mmol) in MeOH (7.5 mL) and H₂O (2.5 mL).

^e K₃Fe(CN)₆ (4.0 mmol) and NaOH (4.0 mmol) was added.

^f The yield was determined by ¹H NMR with 4-bromoacetophenone as internal standard.

^g TMSCHN₂ (3.5 mmol) was added to ensure complete esterification.

^h TMSCHN₂ (7.0 mmol) was added to ensure complete esterification.

TMSCHN₂ (Table 1, entry 3). As for K₃Fe(CN)₆, methyl 2-naphthoate was generated in 57% yield, and the presence of NaOH is crucial; otherwise, there is no reaction at all (Table 1, entry 4).¹¹ When we utilized Dess-Martin periodinane as the oxidant, an inferior yield was obtained (Table 1, entry 5). Other oxidants involving IBX, PhI(OCOCF₃)₂ and PhI(OAc)₂ were effective as well and delivered the desired products in moderate yields (Table 1, entries 6–8). To our delight, utilization of NaIO₄ provided **2a** in the highest yield (94%; Table 1, entry 9). Accordingly, NaIO₄ was selected as the optimal oxidant for this reaction.

Subsequently, various solvent system were investigated for conversion of **1a** to 2-naphthoic acid. We noticed that the mixed THF/H₂O system behaved as well as the mixed acetone/H₂O system to afford **2a** in the same yields (Table 1, entries 9 and 10). Lower yields were obtained in the MeOH/H₂O system and the MeCN/H₂O system (Table 1, entries 11–12). Then the solvent effect in esterification of 2-naphthoic acid with TMSCHN₂ was investigated. Among mixed solvent systems, including THF/MeOH, Et₂O/MeOH and DCM/MeOH, and absolute methanol, the Et₂O/MeOH solvent system was determined to be the best (Table 1, entry 13), considering more TMSCHN₂ required to ensure complete transformation of 2-naphthoic acid in mixed DCM/MeOH and absolute methanol (Table 1, entries 14–15). Thus, the optimal reaction conditions for transformation from **1a** to **2a** were established: 1.0 mmol of hydroxamic acid was reacted with 2.0 mmol of NaIO₄ in a mixture of THF and H₂O (8 mL/2 mL) at 0 °C to rt until complete conversion; then the reaction was acidized with 0.5 mL of 2 N HCl solution; after workup and concentration, esterification of the resultant acid with TMSCHN₂ (2.0 mmol) in mixed Et₂O and MeOH (6 mL/3 mL).

With the optimized reaction conditions in hand, we set out to investigate oxidative cleavage of versatile hydroxamic acids. As shown in Table 2, both the aromatic and the aliphatic hydroxamic acids were testified to be applicable into this methodology. Replacing methyl group in **1a** by more bulky aliphatic group such as isopropyl and *tert*-butyl resulted in slower reaction albeit in similar yields (Table 2, entries 1–3). Interestingly, when benzohydroxamic acid **1d** was treated with NaIO₄, an acyl nitroso **4** was firstly generated as known chemistry.²² Compound **4** could be then slowly converted into benzoic acid in MeOH/H₂O at acidic condition at room temperature, and subsequent esterification produced **2d** (Table 2, entry 4). Subsequently, different substituted aromatic hydroxamic acids **1e–1j**, with both electron-donating and electron-withdrawing groups at the para positions, produced the corresponding methyl esters without significant difference (Table 2, entries 5–10), indicating that electronic factor is not pivotal for this reaction. An aliphatic hydroxamic acid **1k** provided **2k** similarly in 96% yield, while compound **1l** with bulky adamantyl group provided **2l** in excellent yield as well albeit after a little bit longer time (Table 2, entries 11–12). Similarly, α,β -unsaturated hydroxamic acid **1m** provided the desired products **2m** in satisfying yield (Table 2, entry 13). However, when cyclic substrates **1n** and **1o** was attempted, only the corresponding carboxylic acids **3n** and **3o** could be achieved respectively (Table 2, entries 14 and 15). Esterification failed to give methyl esters, probably due to lability of nitroso groups in **3n** and **3o**.

Based on the above examples and previous research by other groups,^{11,22} a plausible mechanism for this reaction is shown in Scheme 2. Periodate oxidation of hydroxamic acid **1** in THF/H₂O might yield the oxoammonium **5**, which could be nucleophilically attacked by water to generate the intermediate **6**. After removal of one molecule of nitroso compound, the corresponding carboxylic acid **3** could be produced. Esterification of the resultant acid with TMSCHN₂ accomplishes methyl ester **2**. This mechanism was supported by formation of the stable acyl nitroso species **4** through oxidation of benzohydroxamic acid.²² Compound **4** with less

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