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A mild method for synthesizing carboxylic acids by oxidation of aldoximes using hypervalent iodine reagents

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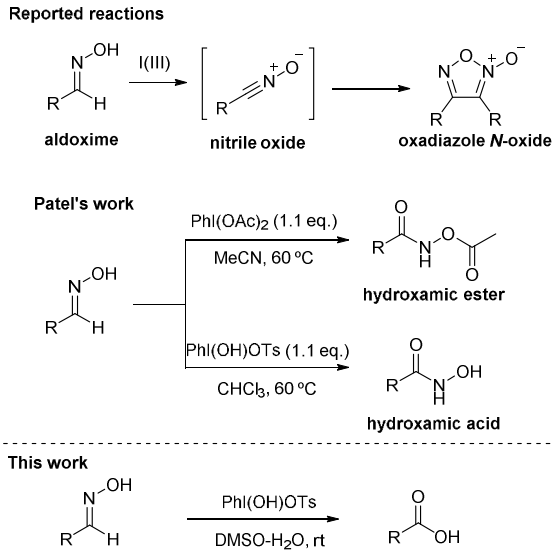
A mild oxidation method for the conversion of aldoximes to carboxylic acids was developed mediated by hypervalent iodine reagents. This method covers a wide range of functionalized aldoximes and proceeds under mild conditions, utilizing PhI(OH)OTs as an oxidant.

Oxidation is one of the fundamental reactions in organic synthesis, particularly the oxidative synthesis of carboxylic acids. Pinnick oxidation is a well-known and widely utilized method for the preparation of carboxylic acids from aldehydes.[1] However, aldoximes, which act as protecting groups to certain aldehydes,[2] are less reactive than the parent aldehyde and few methods have been reported for their oxidation to carboxylic acids. The oxidation of aldoximes with sodium hypochlorite is a cheap and simple method but suffers from substrate limitation.[3] Another method for the oxidation of aldoximes utilizes transition metals as catalysts; however, these reactions require elevated thermal conditions.[4-6] Therefore, the development of a mild oxidation method for the conversion of aldoximes to carboxylic acids is desirable.

Hypervalent iodine reagents are readily available, environmentally benign, and have unique reactivity.[7] Several oxidation reaction methods for the conversion of aldoximes mediated by hypervalent iodine reagents are reported herein (Scheme 1).[8a] The reaction of aldoximes using $PhICl_2$[8b] or $PhI(OAc)_2$[8c] generated nitrile oxides in situ and oxadiazole *N*-oxides were formed by dimerization of nitrile oxides. Patel and co-workers reported that both aromatic and aliphatic aldoximes, with the hypervalent iodine reagents $PhI(OAc)_2$ or PhI(OH)OTs (Koser's reagent), yielded the corresponding hydroxamic esters and hydroxamic acids, respectively, and nitrile oxides were proposed as reactive intermediates.[9] We are interested in hypervalent iodine-mediated reactions, and as such have developed new synthetic methods.[10] During the course of our recent research on the utilization of nitrile oxide, we reacted aldoximes with $PhI(OAc)_2$. Surprisingly, the major product was the corresponding carboxylic acid, and not oxadiazole *N*-oxide or hydroxamic acid. We investigated the reaction in detail and report herein the novel transformation of aldoximes to their carboxylic acids using hypervalent iodine reagents under mild conditions.



Scheme 1 Previous reported conversion of aldoximes and this work.

We employed 4-methoxybenzaldehyde oxime **1a** as a substrate, and conducted the reaction using two equivalents of $PhI(OAc)_2$ at room temperature. The carboxylic acid **2a** was isolated in 47% yield and the aldehyde in 25% yield (entry 1). Other hypervalent iodine reagents were also examined and two equivalents of PhI(OH)OTs gave acid **2a** in 63% yield, slightly better than that with use of $PhI(OCOCF_3)_2$ (entries 2 and 3). Next, various solvents were studied and reactions in tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidone (NMP) gave moderate yields (entries 4–6).

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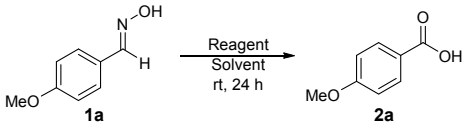
Table 1 Optimization of reaction conditions.[a]



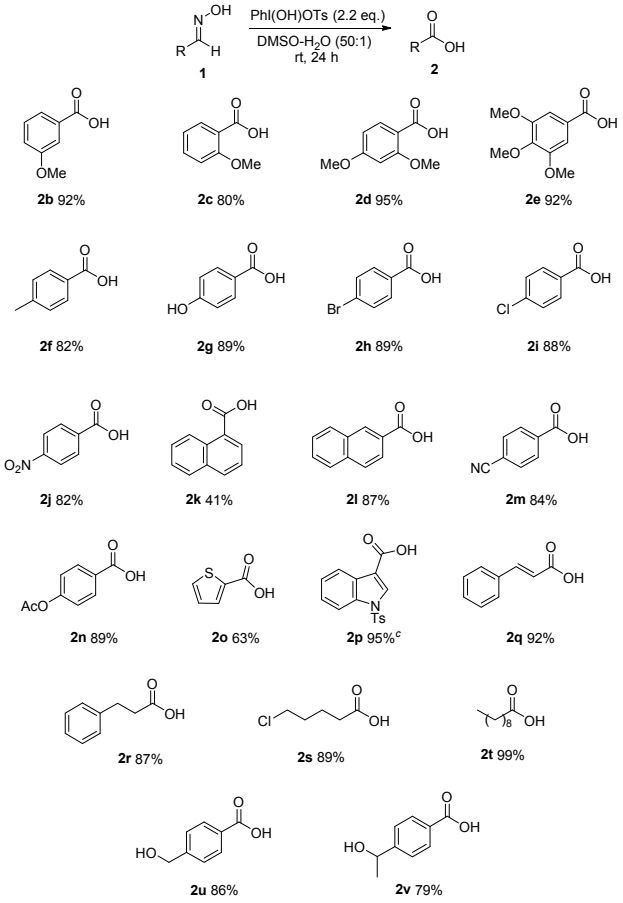
Entry	Reagent	Eq.	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$	2	MeCN	47 (25)[c]
2	$PhI(OCOCF_3)_2$	2	MeCN	60
3	PhI(OH)OTs	2	MeCN	63
4	PhI(OH)OTs	2	THF	43
5	PhI(OH)OTs	2	DMF	57
6	PhI(OH)OTs	2	NMP	18
7	PhI(OH)OTs	2	CH_2Cl_2	72
8	PhI(OH)OTs	2	DMSO	75
9	PhI(OH)OTs	1	DMSO	23
10	PhI(OH)OTs	2	DMSO-H_2O (50:1)	85
11	PhI(OH)OTs	2.2	DMSO-H_2O (50:1)	94
12	PhI(OH)OTs	2.2	DMSO-H_2O (1:1)	74 (10)[c]

[a] All reactions were carried out at rt with 0.1 M concentration. [b] Isolated yield. [c] The yield of aldehyde

The yield was increased in CH_2Cl_2 and the best result was obtained in dimethyl sulfoxide (DMSO) (entries 7 and 8). One equivalent of PhI(OH)OTs resulted in a decrease in yield (23%) (entry 9). It was found that the addition of water had a significant effect, and the reaction with a 50:1 ratio of DMSO-H_2O improved the yield to 85% (entry 10). Finally, the acid **2a** was obtained at 94% yield by the use of 2.2 equivalents of PhI(OH)OTs (entry 11).[11] When the reaction was performed in a 1:1 ratio of DMSO-H_2O, the yield of **2a** was decreased to 74% and the aldehyde was isolated at 10% (entry 12).

After optimizing the reaction conditions, the substrate scope was explored (Table 2). Electron-rich benzaldehyde oximes were successfully converted to the corresponding carboxylic acids in good yields (**2b**–**2f**). In the presence of the phenolic hydroxy group, the reaction provided the acid **2g** in 89% yield without dearomatization of the phenol moiety.[12] The reaction of the substrate with electron-withdrawing substituents at the para-position proceeded well and the corresponding acids were obtained in good yields (**2h**–**2j**). The different reactivities of 1-naphthaldehyde oxime and 2-naphthaldehyde oxime were observed under these conditions, and 1-naphthoic acid **2k** was isolated at 41% yield, whereas 2-naphthoic acid **2l** was obtained at 87% yield. The aldoximes with the nitrile group (**1m**) and ester group (**1n**) successfully converted to acids **2m** and **2n** in yields of 84% and 89%, respectively. The yield of 2-thiophenecarboxylic acid (**2o**) was decreased to 63% due to the partial decomposition. The Ts-protected indole moiety endured these conditions and the acid **2p** was obtained in 95% yield. The oxidation proceeded in the presence of conjugated double bonds and produced cinnamic acid **2q** in 92% yield. Aliphatic aldoximes were also oxidized to carboxylic acids in high yields (**2r**–**2t**). We next examined selective oxidation in the presence of benzyl

Table 2 Scope of substrates.[a,b]



[a] All reactions were carried out at rt by using 2.2 equivalents of PhI(OH)OTs with 0.1 M concentration of DMOS-H_2O (50:1). [b] Isolated yield. [c] 2 equivalents of PhI(OH)OTs was used.

alcohols. The oxidation of aldoximes proceeded in the presence of primary and secondary benzylic alcohols, which remained intact, and the acids **2u** and **2v** were obtained in 86% and 79% yields, respectively.

To elucidate the reaction mechanism, we explored the possible reaction pathways and intermediates (Scheme 2). In accordance with previous reports, the first step would be the formation of nitrile oxide, and then the hydroxamic acid could be formed by the nucleophilic addition of water.[9] The improvement in yield of carboxylic acid in aqueous solvent tends to support this pathway, although there is an excess of water involved in the generation of the aldehyde. Then, the hydroxamic acid seems to react with PhI(OH)OTs to afford the carboxylic acid. The reaction of benzohydroxamic acid with 1 equivalent of PhI(OH)OTs provided benzoic acid in 86% yield (eq. 1), and no reaction occurred with *p*-TsOH (eq. 2). This result is consistent with the previous report about oxidative cleavage of a rhodamine-hydroxamic acid by hypervalent iodine reagents,[13] and the conversion of hydroxamic acid to the corresponding carboxylic acid was confirmed by demonstrating a follow-up experiment using PhI(OH)OTs (see

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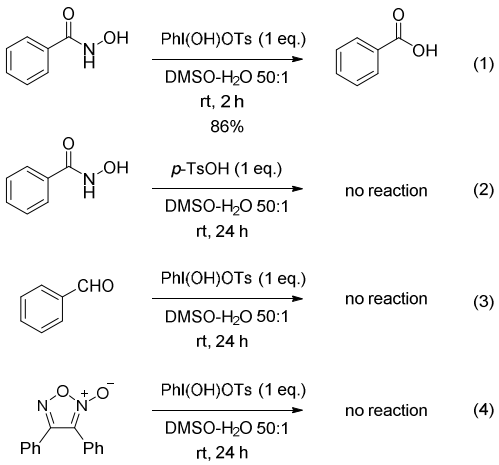
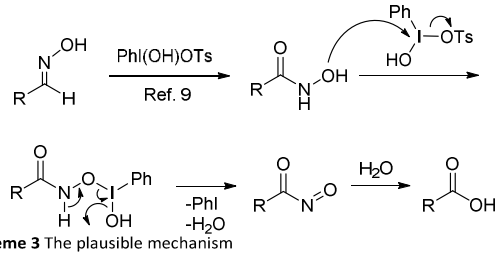


Scheme 2 Investigation of the reaction intermediate.

supporting information). Furthermore, the acid could be obtained by another pathway, via the aldehyde generated by the hydrolysis of the aldoxime. The oxidation of benzaldehyde was examined with one equivalent of PhI(OH)OTs, but no reaction was observed (eq. 3). Hence, this method is a characteristic transformation of aldoximes, not via aldehydes. Another possible intermediate, oxadiazole *N*-oxides generated by dimerization of nitrile oxides, was also applied to the conditions and all of the oxadiazole *N*-oxide was recovered after the reaction (eq. 4). On the basis of control experiments, a possible reaction mechanism was described in Scheme 3. As reported by Patel's work, one equivalent of PhI(OH)OTs was consumed by the transformation of the hydroxamic acid. Then, ligand exchange between hydroxamic acid and tosylate on PhI(OH)OTs was occurred. Elimination of PhI and H_2O from the intermediate afforded the acyl-nitroso compound, which giving the carboxylic acid by hydrolysis.

Conclusions

In conclusion, we have developed a novel method for oxidative conversion of aldoximes to carboxylic acids using the hypervalent iodide reagent, PhI(OH)OTs. The reaction parameters were examined in detail and a variety of aldoximes were successfully transformed into their corresponding carboxylic acids, in good to high yields. This procedure is characterized by its mild reaction conditions and distinctive reactivity. Further investigations concerning the catalytic use of hypervalent iodine reagents with an oxidant are currently under way.



Scheme 3 The plausible mechanism

Acknowledgements

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11 The other solvent systems were also examined (DMSO-H_2O 10:1 and 4:1) and the acid **2a** was obtained in 94% in both cases. Finally, 50:1 ratio was found to be better solvent system as a result of the substrate screening. For example, the yield of **2h** was decreased to 77% when 10:1 ratio of solvent was used.
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14 **General Oxidation Procedure:** To a DMSO-H_2O (50:1, 2 mL) solution of aldoxime **1** (0.2 mmol) was added PhI(OH)OTs (0.21 mmol) at room temperature, and another amount of PhI(OH)OTs (0.21 mmol) was added in 30 min. After completion of the reaction as indicated by TLC monitoring, the reaction mixture was poured into 10% aq. Na_2CO_3 and then EtOAc was added. The organic layer was extracted with 10% aq. Na_2CO_3. The combined aqueous layers were acidified by addition of aq. HCl, and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated *in vacuo* to afford pure carboxylic acid **2** with no need for further purification.