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One-Pot Synthesis of Hydroxamic Acids from Aldehydes and Hydroxylamine

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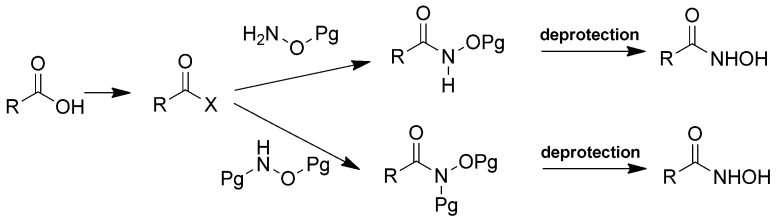
Abstract: A one-pot oxidative transformation of aldehydes into hydroxamic acids by the use of an aqueous solution of hydroxylamine is reported. The methodology gives high yields and makes use of cheap, abundant and easily available reagents.

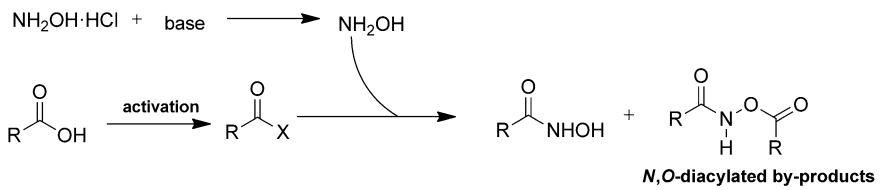
Keywords: acyl derivatives; aldehydes; hydroxamic acids; hydroxylamine

Hydroxamic acids are an important class of compounds with a broad array of biological activities including antibacterial, antifungal, anti-inflammatory and anti-asthmatic properties.[1] They are strong metal ion chelators and, due to this feature, are contained in potent matrix metalloproteinase[2] and histone deacetylase inhibitors.[3] Hydroxamic acids are commonly prepared from previously activated carboxylic acids (active ester,[4] mixed anhydrides,[5] and acyl chloride[6]) and *O*-protected or *N*,*O*-protected hydroxylamine[7] (Scheme 1, pathway 1) and, less frequently, from unprotected hydroxylamine[8] (Scheme 1, pathway 2). The coupling of carboxylic acids with protected hydroxylamines is the preferred method, even though protected hydroxylamines are highly expensive reagents and an additional step (deprotection) is necessary to complete the synthesis. In fact the direct use of unprotected hydroxylamine involves both the formation of *N*,*O*-diacylated by-products (Scheme 1, pathway 2) and difficulties in obtaining the product in a pure form.

These classical syntheses of hydroxamic acids are highly dependent on the structure of the target molecules and product isolation is often extremely difficult.[9]

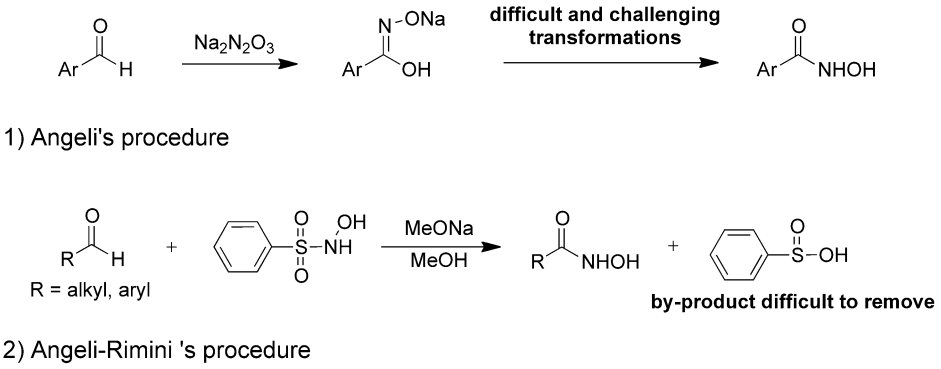


1) Classical approach to hydroxamic acids: the coupling of activated carboxylic acids with O-protected or *N*,*O*-protected hydroxylamine.



2) Direct coupling of activated carboxylic acids with hydroxylamine.

Scheme 1. Hydroxamic acids from carboxylic acids.



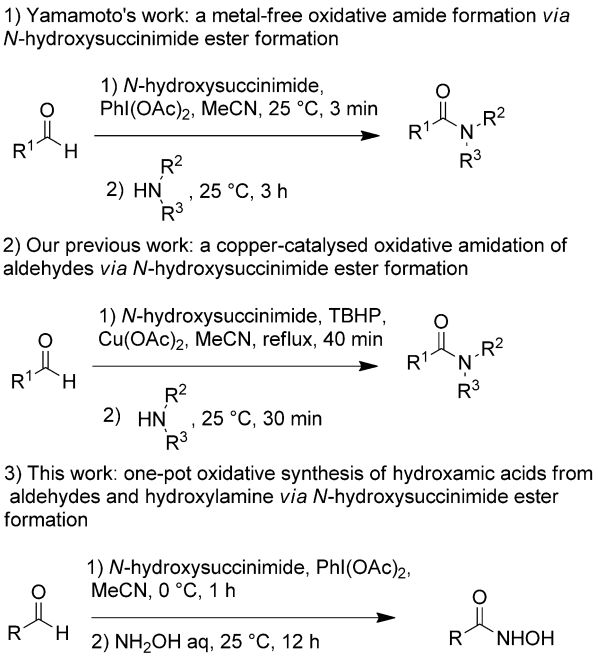
Scheme 2. Hydroxamic acids from aldehydes.

Many natural products contain aldehydes that could be directly transformed into hydroxamic acids to greatly enhance their pharmacological activity.

An organic chemist needing to transform an aldehyde directly into a hydroxamic acid, has only two methods available. The first method was developed by Angeli.[10] It consists of the treatment, in aqueous solution at reflux, of aromatic aldehydes with sodium nitrohydroxamate, $Na_2N_2O_3$ (Angeli's salt)[11] to yield the corresponding sodium salt of hydroxamic acid (Scheme 2, pathway1). Many aldehydes do not react, and the methodology is simply not applicable to aliphatic aldehydes due to the tedious purification of the corresponding hydroxamic acids.[12] A second methodology to prepare hydroxamic acids from aldehydes was later proposed by Angeli and Rimini.[13] The procedure consists of the treatment of an aldehyde with *N*-hydroxybenzenesulfonamide in the presence of a strong base (Scheme 2, pathway 2). Unfortunately the acidic work-up results in the desired hydroxamic acid with the benzenesulfinic acid as a by-product. The latter is not easy to remove from the main product. Due to the difficulties associated with the purification, the Angeli–Rimini reaction has seldom been used in organic synthesis.

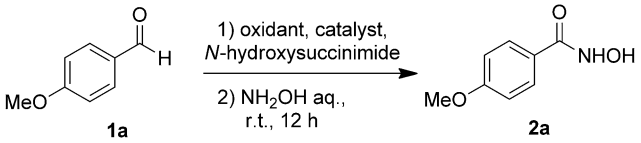
In relation to the pioneering example of an oxidative amidation of aldehydes *via N*-hydroxysuccinimide ester formation using a hypervalent iodine reagent (Scheme 3, pathway 1) reported by Yamamoto and co-workers[15] and to our recently reported copper-catalysed oxidative amidation of aldehydes *via N*-hydroxysuccinimide ester formation[16d] (Scheme 3, pathway 2), we tested the possibility to transform directly an aldehyde into a hydroxamic acid *via N*-hydroxysuccinimide ester formation employing an aqueous solution of hydroxylamine (Scheme 3, pathway 3).

We started our investigation by treating *para*-methoxybenzaldeyde **1a** (2 equiv.) with *N*-hydroxysuccinimide (NHS) (1.1 equiv.), $Cu(OAc)_2$ (15 mol%) as a catalyst, an aqueous solution of 70% *tert*-butyl hydrogen peroxide (TBHP) (2 equiv.) in acetonitrile as solvent at reflux. After 1 h (the reaction was monitored by TLC until the disappearance of *N*-hydroxysuccinimide) the reaction mixture was cooled to room temperature and an aqueous solution of 50% NH_2OH (5 equiv.) was added. After 12 h at room temperature the desired hydroxamic acid **2a** was obtained with a 79% yield (Table 1, entry 1). Even if the product was obtained with a very good yield, the method did not appear advantageous due to the large excess of aldehyde, oxidising reagent and hydroxylamine employed. We repeated the same reaction using stoichiometric amounts of aldehyde, TBHP and *N*-hydroxysuccinimide, but very poor results in terms of yield (31%) were obtained (Table 1, entry 2). We achieved the same reaction with the use of $FeCl_3 \cdot 6H_2O$, obtaining the product **2a** with a 27% yield (Table 1, entry 3). The reaction was carried out without the use of any catalyst, but the aldehyde did not react even after 8 h of reflux. In order to maintain a stoichiometric ratio



Scheme 3. Oxidative amidation of aldehydes.

Table 1. Screening of reaction conditions.



Entry	Oxidant	Catalyst	Yield
1	TBHP	$Cu(OAc)_2 \cdot H_2O$	79%[a]
2	TBHP	$Cu(OAc)_2 \cdot H_2O$	31%[b]
3	TBHP	$FeCl_3 \cdot 6H_2O$	27%[c]
4	TBHP	–	–[d]
5	H_2O_2	$Cu(OAc)_2 \cdot H_2O$	–[e]
6	H_2O_2	–	–[f]
7	Oxone	–	–[g]
8	IBX	–	24%[h]
9	$PhI(OAc)_2$	–	82%[i]

[a] *Reaction conditions: para*-methoxybenzaldeyde **1a** (2 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), $Cu(OAc)_2$ (15 mol%), TBHP (aq. sol. 70%) (2 equiv.), in acetonitrile at reflux for 1 h. NH_2OH (aq. sol. 50%) (5 equiv.) was then added.

[b] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), $Cu(OAc)_2$ (15 mol%), TBHP (aq. sol. 70%) (1.1 equiv.), in acetonitrile at reflux for 1 h. NH_2OH (aq. sol. 50%) (5 equiv.) was then added.

[c] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), $FeCl_3$ (15 mol%), TBHP (aq. sol. 70%) (1.1 equiv.), in acetonitrile at reflux for 1 h. NH_2OH (aq. sol. 50%) (5 equiv.) was then added.

[d] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), TBHP (aq. sol. 70%) (1.1 equiv.), in acetonitrile at reflux for 8 h.

[e] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), H_2O_2 (1.1 equiv.), $Cu(OAc)_2$ (15 mol%), in acetonitrile at reflux for 8 h.

[f] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), H_2O_2 (1.1 equiv.), in acetonitrile at reflux for 8 h.

[g] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), Oxone (1.1 equiv.), in acetonitrile at reflux for 8 h.

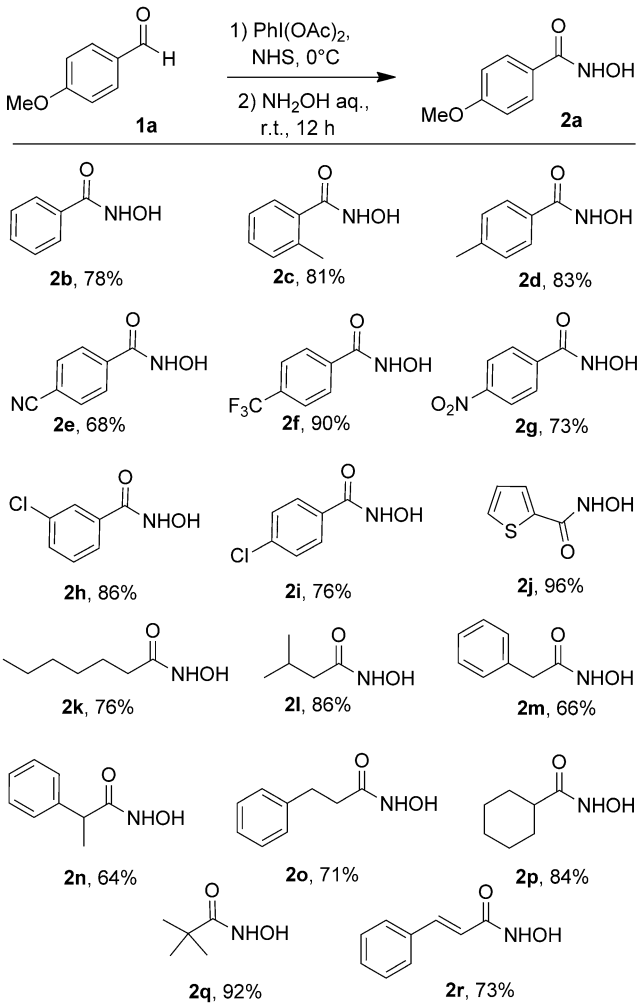
[h] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), IBX (1.1 equiv.), in acetonitrile at room temperature for 1 h. NH_2OH (aq. sol. 50%) (2 equiv.) was then added.

[i] *Reaction conditions: para*-methoxybenzaldeyde **1a** (1 equiv.), *N*-hydroxysuccinimide (NHS) (1.1 equiv.), $PhI(OAc)_2$ (1.1 equiv.), in acetonitrile at 0 °C for 1 h. NH_2OH (aq. sol. 50%) (2 equiv.) was then added at room temperature for 12 h.

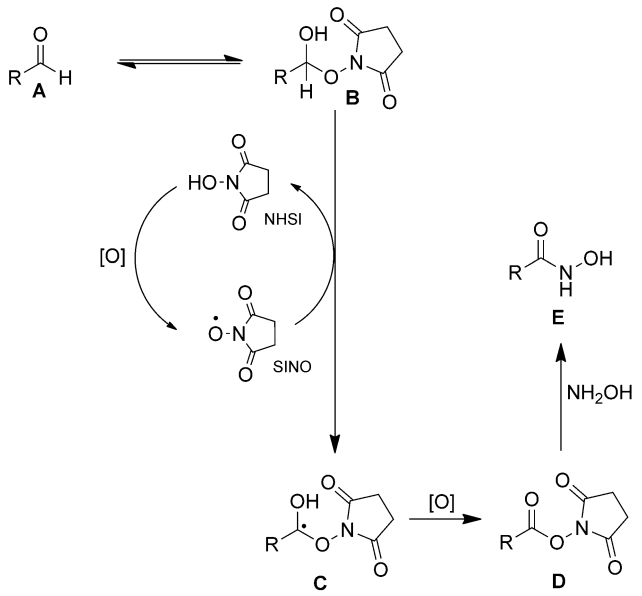
of reactants as much as possible, the reaction was carried out employing different oxidising reagents. Using classical oxidants such as H_2O_2 and Oxone the aldehyde was recovered unreacted (Table 1, entries 5, 6 and 7). When 2-iodoxybenzoic acid (IBX) (Table 1, entry 8) was used the hydroxamic acid **2a** was obtained with a very poor yield. On the contrary (diacetoxyiodo)benzene $PhI(OAc)_2$ displayed high efficiency by providing the product with excellent yield 82% (Table 1, entry 9). This reaction was carried out employing *para*-methoxybenzaldeyde **1a** (1 equiv.) with *N*-hydroxysuccinimide (NHS) (1.1 equiv.), $PhI(OAc)_2$ (1.1 equiv.), in acetonitrile at 0 C° for 1 h. An aqueous solution of 50% NH_2OH (2 equiv.) was then added. After 12 h at room temperature, the desired hydroxamic acid **2a** was obtained with a yield of 82%. It is important to note that the *N*-hydroxysuccinimide used could be recovered unmodified. An overview of the details of the synthesis is provided in Table 1.

After the optimized reaction conditions had been established, the scope of the methodology was investigated.

As depicted in Scheme 4, aromatic aldehydes with a wide range of substituents, both electron-donating, such as OMe (Scheme 4, product **2a**) and benzylic C–



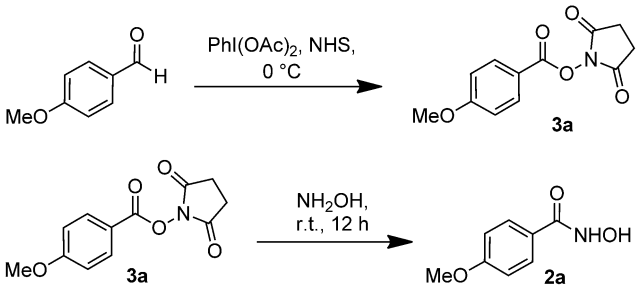
Scheme 4. Aldehyde diversity.



Scheme 5. Proposed mechanism of hydroxamic acid formation.

H (Scheme 4, products **2c** and **2d**), and electron-withdrawing, such as CN, CF_3 and NO_2 (Scheme 4, products **2e**, **2f** and 2g) provided the desired hydroxamic acid with moderate to excellent yields. The reaction which took place in the aldehydes with a halide substituent on the aromatic ring provided the corresponding hydroxamic acid, which could be further manipulated by conventional cross-coupling reactions (Scheme 4, products **2h** and **2i**). To prove the synthetic efficacy of the methodology, thiophene-2-carbaldehyde was subjected to the optimised conditions, providing the desired heteroarylhydroxamic acid (Scheme 4, product **2j**) with excellent yield. The methodology was also applied to aliphatic aldehydes, providing very good results (Scheme 4, products **2k**, **2l**, **2m**, **2n** and **2o**). Even with sterically hindered substrates the methodology provided the corresponding hydroxamic acids with satisfactory yields (Scheme 4, products **2p** and **2q**). The reaction was carried out on *trans*-cinnamaldeyde obtaining the corresponding unsaturated hydroxamic acid (Scheme 4, product **2r**) without affecting the double bond. On the basis of previous studies[15] a possible reaction mechanism is depicted in Scheme 5.

The aldehyde **A** reacts with *N*-hydroxysuccinimide (NHSI) giving the corresponding hemiaminal **B**. *N*-hydroxysuccinimide (NHS) is oxidized to the corresponding succinimide *N*-oxy radical (SINO). SINO abstracts a hydrogen atom from the hemiaminal **B** generating the corresponding hemiaminal radical **C**. The presence of the N-oxy (SINO) radical and of the hemiaminal radical **C** was clearly demonstrated by ESR measurements of the reaction mixture.[15] The hemiaminal radical **C** is rapidly subjected to oxidation



Scheme 6. Hydroxylamine displacement step.

providing ester **D**. Finally the ester **D** undergoes a nucleophilic substitution by the hydroxylamine affording the hydroxamic ester **E**. In order to prove the mechanism, we examined the hydroxylamine displacement step (Scheme 6). The *para*-methoxybenzoate ester **3a** was prepared by treating *para*-methoxybenzaldehyde with *N*-hydroxysucinimide and $PhI(OAc)_2$ in acetonitrile at room temperature and then isolated.[16d] The ester **3a** was then reacted with NH_2OH and after 12 h the corresponding hydroxamic acid **2a** was obtained.[17]

In conclusion, a metal- and base-free synthesis of hydroxamic acids has been developed. The starting reagents are aliphatic and aromatic aldehydes, which are cheap, abundant and easily available substances. The procedure is compatible with the presence of water and, as a result, allows the direct use of an aqueous solution of NH_2OH. Hydroxamic acids are normally very difficult to prepare and this procedure offers a way for them to be obtained with great ease, in a pure form, and with high yields.

Experimental Section

General Procedure for the Synthesis of 2a–2r

Aldehyde (4.34 mmol) was added in one portion to a solution of *N*-hydroxysuccinimide (550 mg, 4.77 mmol), iodobenzene diacetate (1.54 g, 4.77 mmol) in MeCN (6 mL) at 0 °C under argon. The reaction mixture was stirred for 1 h at the same temperature (the reaction was monitored by TLC until the disappearance of aldehyde), hydroxylamine solution (50 wt% in H_2O) (0.53 mL, 8.68 mmol) was then added. The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The solvent was removed under vacuum, and the residue purified by flash chromatography (ethyl acetate:petroleum ether).

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[17] The details of the synthesis are provided in the Supporting Information.

6 One-Pot Synthesis of Hydroxamic Acids from Aldehydes and Hydroxylamine

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