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An expeditious hydroxyamidation of carboxylic acids

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Abstract—Capitalizing on in situ activation with the cyclic phosphonic anhydride PPAA (**1**), the conversion of carboxylic acids into hydroxamic acids has been reduced to an experimentally simple one-pot operation that addresses the issue of polyacylation without resorting to a large excess of hydroxylamine or to protection. Scope and selectivity were satisfactory with a wide range of substrates, including α,β-unsaturated acids and hydroxyacids.
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The past decade has seen the resurrection of interest for hydroxamic acids, spurred by the occurrence of a key *N*-hydroxyamide motif in an array of bioactive compounds that includes zinc-protease inhibitors of oncological and anti-inflammatory relevance,[1] microbial siderophores,[2] and the antibiotic phosphidomycin, a powerful antimalarial agent that inhibits the non-mevalonate biosynthesis of isoprenoids.[3]

Despite continuous progress in amide bond formation, the synthesis of hydroxamic acid and their derivatives has not significantly advanced over the past years, and still relies on protocols that offer potential for improvement, especially when applied to the parent compounds.

Acylation of hydroxylamine under carbodiimide promotion is plagued by *N*,*O*-diacylation even with sub-stoichiometric amounts of acids.[4] To overcome this problem, ex situ activation of carboxylic acids (chlorides,[5] mixed anhydrides,[6] esters,[7] oxazolidinones[8]), *O*-protection of hydroxylamine[9], and a large excess of it have been employed alone, or more often, in combination. Faced with the problem of preparing a library of fatty acid hydroxamates to assay against various proteins of the endocannabinoid system,[10] we have developed a practical solution to the problem. Our hydroxyamidation protocol provided an expeditious entry into the *N*-hydroxyamides of acids difficult to handle for their lability (arachidonic, ximeninic, retinoic), and, by avoiding an excess hydroxylamine, turned out to be of general applicability also to polyfunctionalized and α,β-unsaturated substrates.

We reasoned that the chemoselectivity issue in the acylation of hydroxylamine is somewhat similar to that plaguing the acylation of phenolic amines, the underlying common problem being the presence of an acidic oxygen function that can be activated in terms of nucleophilicity by deprotonation. In a previous study, we discovered that mixed phosphoric anhydrides show very low reactivity toward oxygen functions, and identified the cheap cyclic anhydride PPAA (=T3P, **1**)[11] as a superior, traceless, and environmentally benign promoter for the *N*-acylation of phenolic amines.[12] Given the similar chemoselectivity problem, we wondered if this acylation protocol could be extended also to hydroxylamine.

The reaction was investigated with oleic acid, whose hydroxamate can inhibit the degradation of the endogenous sleep factor oleamide.[13] The reported synthetic protocol[13] involves ex situ activation to oleyl chloride and ex situ deprotonation of an excess hydroxylamine hydrochloride, and its overall yield (45%) served as a yardstick for our investigations.

Attempts to translate the original conditions for the acylation of phenolic amines to hydroxylamine (1.2 equiv PPAA, stoichiometric acid-to-amine ratio, in situ de-salification of the amine hydrochloride with triethylamine (TEA), and dichloromethane as the solvent)[12] gave excellent results in terms of chemoselectivity, but only a modest yield (25%), essentially due to a

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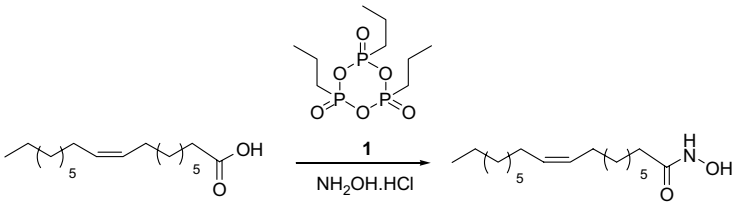
Table 1. Hydroxyamidation of oleic acid under various conditions



Entry	$NH_2OH{\cdot}HCl$ (equiv)	Solvent	Yield (%)[a]
1	1	CH_2Cl_2	35
2	2	CH_2Cl_2	41
3	2	EtOAc	53
4	1	CH_3CN	76
5	2	CH_3CN	85

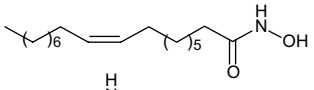
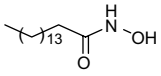
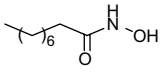
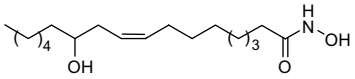
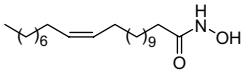
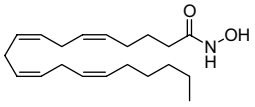
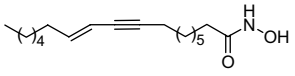
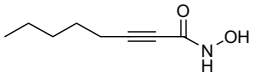
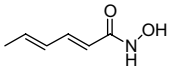
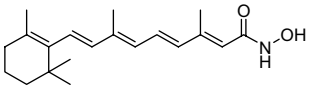
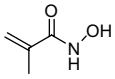
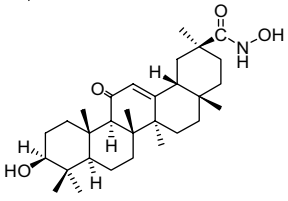
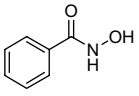
[a] All reaction were carried out at room temperature with 1.2 mol equiv PPAA, and were quenched after stirring overnight. Yields were calculated after gravity column chromatography purification of the reaction mixture. Differences in yield essentially reflect differences in conversion, the remaining mass balance being starting oleic acid.

low conversion. A first upgrade to 35% yield was achieved by delaying (ca. 30 min) the addition of hydroxylamine hydrochloride to the acid–PPAA–TEA mixture, thus avoiding partial quenching of PPAA by hydroxylamine (Table 1),[14] while a 1:2 acid to hydroxylamine ratio accelerated the reaction, with, however, only a modest effect in yield. The insolubility of hydroxylamine hydrochloride in dichloromethane was a further point of improvement, since a change to acetonitrile eventually provided a homogeneous reaction mixture and a beneficial effect in yield. After dilution of the reaction mixture with ethyl acetate, washing with brine, and evaporation, the reaction mixture, still containing unreacted acid (ca. 6% by ^1H NMR analysis), was crystallized from hexane, affording *N*-hydroxyoleamide in 72% yield.

Alternatively, unreacted oleic acid could be removed by chromatography on silica gel, affording *N*-hydroxyoleamide in 85% yield. Attempts to drive the reaction to completion failed even with a large excess (10 mol equiv) of hydroxylamine, suggesting that minor amounts of oleyl anhydride might be formed in the activation step. Subsequent anhydride aminolysis would then waste one equivalent of acylating agent as a carboxylate leaving group. The 30-min delay between the addition of hydroxylamine to the PPAA–carboxylic acid mixture seems therefore an optimal time compromise to minimize carboxylic anhydride formation and prevent the partial quench of unreacted PPAA by hydroxylamine.[14]

To investigate the scope and selectivity of the reaction, the optimized protocol[15] was next applied to a variety of carboxylic acids. The range of substrates successfully hydroxyamidated includes (Table 2) polyunsaturated acids, both skipped (arachidonic acid, entry 6) and conjugated (ximeninic acid, entry 7), α,β-unsaturated acids (2-octinoic acid, sorbic acid, retinoic acid, methacrylic acid, entries 8, 9, 10, 11, respectively), and unprotected hydroxyacids (ricinoleic acid, entry 4 and the sterically hindered triterpenoid glycyrrhetic acid, entry 12).[16] Aromatic acids like benzoic acid (entry 13) gave only modest yield, as already noticed with that of oxyamidation protocols (Table 2).[8,17]

Table 2. Hydroxyamidation of various carboxylic acids

Entry	Hydroxamate product	Yield (%)[a]
1		85
2		77
3		85
4		70
5		72
6		52
7		68
8		57
9		72
10		45
11		52
12		64
13		56

The mechanistic rationale for the reluctance of mixed phosphonic anhydrides to react with oxygen nucleophiles is unclear, but it does not seem unreasonable to assume that the negative charge of the intermediate phosphonic anhydride contributes to repel attack from negatively charged oxygen functions, while seemingly having only a minor effect on neutral nitrogen nucleophiles.

In conclusion, by combining the in situ activation of carboxylic acids to mixed phosphoric anhydrides and the generation of hydroxylamine from its corresponding and air stable hydrochloride, the conversion of carboxylic acids to hydroxamic acids has been reduced to an experimentally simple one-pot operation, that avoids ex situ processes (derivatization of the acid, de-salification of hydroxylamine), and addresses the issue of polyacylation without resorting to an excess hydroxylamine or to its protection. The method is especially suitable for labile substrates, whose activation via chloride is not trivial, for α,β-unsaturated acids that do not tolerate large excesses of hydroxylamine, and for hydroxyacids, whose oxyamidation with other protocols would require hydroxyl protection.

Acknowledgements

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References and notes

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4. For instance, treatment of oleic acid with a twofold molar excess of hydroxylamine hydrochloride and triethylamine in dichloromethane gave the *N*,*O*-diacyl derivative as the only reaction product, and even with a very large excess (10-fold) of hydroxylamine hydrochloride, a ca. 3:1 mixture (^{1}H NMR analysis) of mono- and diacyl derivatives was obtained.
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14. Reverse addition of a carboxylic acid to a mixture of PPAA, hydroxylamine, and TEA, gave a lower hydroxamate yield (16% with oleic acid) compared to the direct addition, suggesting a certain competition between carboxylate and hydroxylamine for phosphonylation.
15. Typical experimental procedure: To a stirred solution of PPAA (50% in EtOAc, 1.2 mol. equiv) in acetonitrile (ca. 5 mL/mMol of acid) triethylamine (4 mol equiv) and the carboxylic acid were added. After stirring 30 min at room temp., hydroxylamine hydrochloride (2 mol equiv) was added, and stirring was continued overnight at room temp. The reaction was then worked up by dilution with EtOAc and washing with brine. The organic phase was dried (Na_2SO_4) and evaporated, and the residue was either crystallized from hexane or purified by gravity column chromatography on silica gel. All compounds were characterized by ^{1}H- and ^{13}C NMR, IR and ESI-MS.
16. However, attempts to oxyamidate betulinic acid, an even more encumbered triterpenoid substrate, failed.
17. Since *p*-methoxy- and *p*-nitrobenzoic acids gave yields similar to that of benzoic acid, the origin of this effect is unclear.