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Solution and solid-phase synthesis of hydroxamic acids via palladium catalysed cascade reactions

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Abstract

The elaboration of a series of aryl iodides into heterocyclic hydroxamates proceeds in good to excellent yield in a palladium catalysed termolecular cascade reaction involving carbon monoxide and protected hydroxylamines. Deprotection affords a range of novel heterocyclic hydroxamic acids. In a related process, *N*-benzyloxyimides were synthesised in a pentamolecular cascade. The hydroxamic acids were also synthesised using resin-bound hydroxylamine derivatives in a solid-phase cascade process. © 1999 Elsevier Science Ltd. All rights reserved.

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Hydroxamic acids have been extensively studied as metalloenzyme inhibitors and, in particular, they have been shown to be potent inhibitors of matrix metalloproteinases,¹ a family of zinc-dependent enzymes associated with diseases such as cancer, arthritis and multiple sclerosis. Although available from nitro-compounds² and other miscellaneous methods,³ hydroxamic acids are almost exclusively synthesised via the acylation of hydroxylamine and its derivatives. Alternative methods of synthesising this class of compounds are desirable.

We now report a novel and flexible route to hydroxamic acids⁴ employing a catalytic cascade reaction in which the hydroxamic acid functionality is introduced via the palladium catalysed carbonylation of aryl iodides and subsequent trapping of the acylpalladium(II) intermediate with a hydroxylamine derivative. The aryl iodides 1 were selected for their ability to form a range of heterocycles.⁵ Thus, 5-*exo*-trig cyclisation and carbonylation of **1a** generated intermediate **2** which was trapped in situ with O-benzylhydroxylamine to afford a mixture of the desired benzyl hydroxamate **3a** and N-benzyloxyimide **4a** (Scheme 1). Studies confirmed that the latter compound resulted from the trapping of intermediate **2** with **3a**.

When an excess (2-3 equiv.) of O-benzylhydroxylamine was employed, **3a** was produced in good yield (63%) in a termolecular cascade reaction in which three new bonds are formed (shown in bold).

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Scheme 1.

Several analogues were synthesised in this manner (Table 1). Using two equivalents of the aryl iodide to one equivalent of *O*-benzylhydroxylamine furnished **4a** in 57% yield as a 1:1 mixture of the racemic and *meso* compounds (¹H NMR). Formation of **4a** involves a pentamolecular cascade in which six new bonds are formed (shown in bold). Likewise, analogues **4b**,**c** could be synthesised by appropriate choice of aryl iodide (Table 1).

N-Protection was investigated as an alternative to using an excess of *O*-benzylhydroxylamine. The reaction of **1a** with *N*-Boc-*O*-benzylhydroxylamine under standard conditions⁶ afforded the bis-protected hydroxamic acid **5a** in 96% yield. Using *N*-Boc-*O*-benzylhydroxylamine as a nucleophile, analogues **5b–e** were synthesised in 85–92% yield (Table 1). Deprotection by standard methods (i. TFA; ii. H₂/Pd-C or HCO₂NH₄/Pd-C) afforded the free hydroxamic acids **7a–e** in 60–70% yield.

The synthesis of resin-bound hydroxylamines (and their subsequent acylation to generate hydroxamic acids) is established,^{7,8} and we have utilised these resins in our cascades. Thus, the resin-bound hydroxylamine **6** was synthesised from Wang resin⁷ and used in the cascade reaction as before (Scheme 2). Simultaneous deprotection and cleavage afforded the free hydroxamic acids **7a–e** in 20–40% yield. We believe this to be the first reported palladium catalysed carbonylation using a resin-bound capture reagent.



Scheme 2.

We have illustrated, in this instance using a series of aryl iodides, novel methods for the synthesis of hydroxamic acids in solution and on solid-phase. In a related process, N-benzyloxyimides were also synthesised. This method is applicable to other aryl or vinyl halides, triflates and other species susceptible to oxidative addition with palladium(0).

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Table	1
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Aryl Iodide	Hydroxylamine	Product		Yield	(%) [*]
	3eq NH₂OBn	R N.o ^{-R'}	R=H, R'=Bn	3a	65
	leq NHBocOBn		R=Boc, R'=Bn	5a	96
la		✓ 0	$\mathbf{R} = \mathbf{R}' = \mathbf{H}$	7a	70 ^c
	0.5eq NH ₂ OBn			42	57
1	3eq NH ₂ OBn	Ŗ	R=H, R'=Bn	3Ь	51
	leq NHBocOBn		R=Boc, R'=Bn	5b	92
			$\mathbf{R} = \mathbf{R'} = \mathbf{H}$	7Ь	64 ^c
16	0.5eq NH2OBn	OBn N N N N N N N N N N N N N N N N N N N		4b	68
	3eq NH₂OBn	N A N B'	R=H, R'=Bn	3c	70
Ľ _ N	leq NHBocOBn		R=Boc, R'=Bn	5c	85
CO ₂ Me		CO,Me	$\mathbf{R} = \mathbf{R'} = \mathbf{H}$	7c	67 ^c
ĸ	0.5eq NH2OBn			4 c	58
	: 3eq NH₂OBn		R=H, R′=Bn	3d	21 ^b
Ľ_∕_Ņ∕	leq NHBocOBn		R=Boc, R'=Bn	5d	89
ŚO₂Ph 1d		SO ₂ Ph	$\mathbf{R} = \mathbf{R}' = \mathbf{H}$	7d	60°
	ieq NHBocOBn	R' NO ⁻ R' CH ₂ Ph	R=Boc, R'=Bn R = R' = H	5e 7e	85 65°

^a Isolated yields ^b Formed as a mixture with the corresponding imide. ^c Two steps from 5.

- 6. Representative procedure for the cascade process (not necessarily optimised): Aryl iodide 1 (1 mmol), K₂CO₃ (1 mmol), Pd(OAc)₂ (0.05 mmol), PPh₃ (0.1 mmol) and the appropriate hydroxylamine (0.5–3.0 mmol) were combined in toluene and stirred at 100°C for 16 h under CO (1 atm). The mixture was then filtered, concentrated and purified as necessary by column chromatography.
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