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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.

Keywords: palladium; palladium compounds; hydroxamic acids; hydroxamic acid derivatives; carbonylation; solid-phase synthesis.

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-compounds[2] 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 acids[4] 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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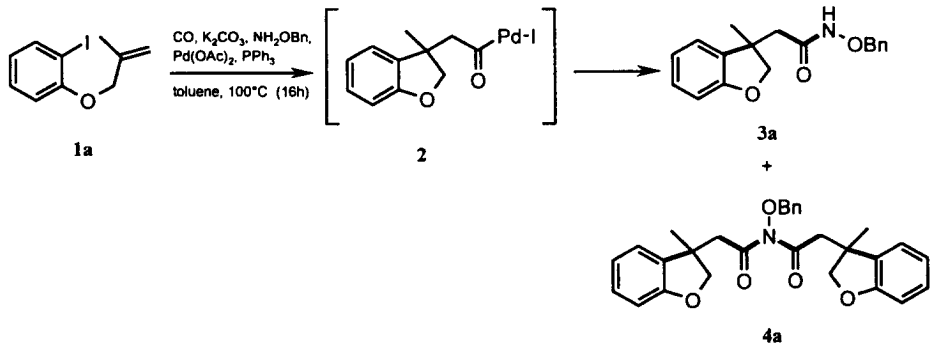
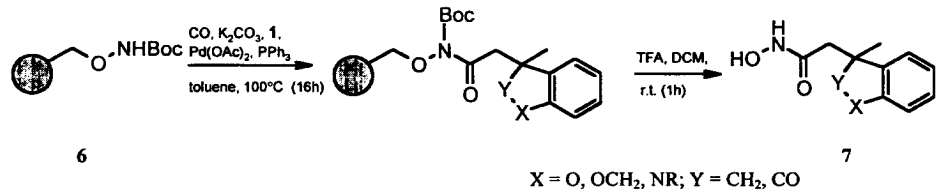


Scheme 1.

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 (^{1}H 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 conditions[6] 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. H_2/Pd-C or HCO_2NH_4/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 resin[7] 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).

References

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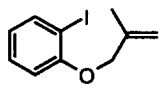
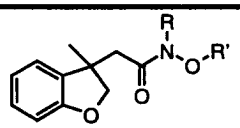
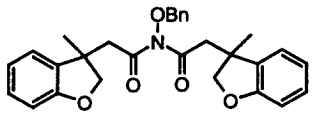
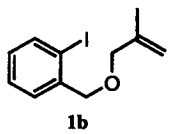
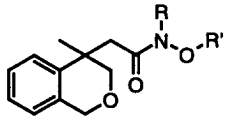
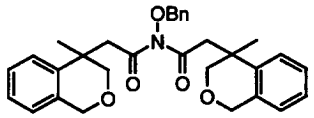
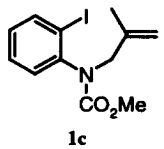
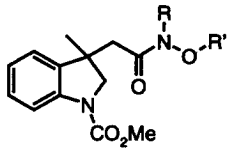
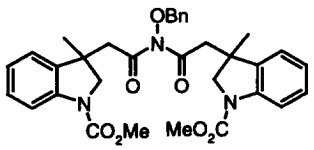
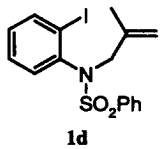
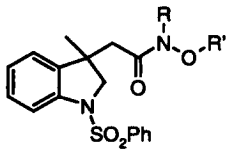
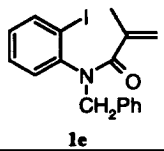
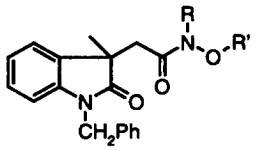
Table 1

Aryl Iodide	Hydroxylamine	Product		Yield (%)[a]
 **1a**	3eq NH_2OBn		R=H, R'=Bn	**3a** 65
	1eq NHBocOBn		R=Boc, R'=Bn	**5a** 96
			R = R' = H	**7a** 70[c]
	0.5eq NH_2OBn			**4a** 57
 **1b**	3eq NH_2OBn		R=H, R'=Bn	**3b** 51
	1eq NHBocOBn		R=Boc, R'=Bn	**5b** 92
			R = R' = H	**7b** 64[c]
	0.5eq NH_2OBn			**4b** 68
 **1c**	3eq NH_2OBn		R=H, R'=Bn	**3c** 70
	1eq NHBocOBn		R=Boc, R'=Bn	**5c** 85
			R = R' = H	**7c** 67[c]
	0.5eq NH_2OBn			**4c** 58
 **1d**	3eq NH_2OBn		R=H, R'=Bn	**3d** 21[b]
	1eq NHBocOBn		R=Boc, R'=Bn	**5d** 89
			R = R' = H	**7d** 60[c]
 **1e**	1eq NHBocOBn		R=Boc, R'=Bn	**5e** 85
			R = R' = H	**7e** 65[c]

[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), K_2CO_3 (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (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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