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Improved Solution- and Solid-Phase Preparation of Hydroxamic Acids from Esters

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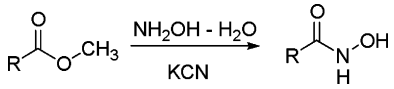
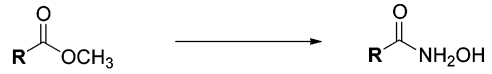


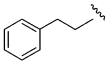
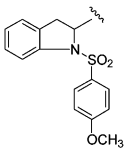
The addition of small amounts of solid KCN to solution and solid-phase esters in THF/MeOH/50% aqueous NH_2OH increases the efficiency of their transformation to the corresponding hydroxamic acids.

Hydroxamic acid analogues are important targets for the medicinal chemist because of the bidentate chelating interaction of this functional group with the Zn^{2+} in the active site of metalloproteinases.[1,2] We required an efficient conversion of esters to hydroxamic acids suitable for the preparation of multigram quantities of compound and a solid-phase method versatile enough to support a variety of syntheses directed toward hydroxamic acid targets. The direct solution-phase hydroxyamination of esters is generally achieved by a two-step preparation of the potassium salt of hydroxylamine followed by the addition of the ester in alcohol solvent[3] or by the stepwise saponification of the ester to the acid followed by activation of the acid as the acyl chloride or mixed anhydride and then quenching with an O-protected hydroxylamine analogue.[4] In special cases, the hydroxyamination of ester substrates has been achieved via enzymatic methods[5] or, for more reactive esters, by treatment with excess hydroxylamine in alcohol solvent.[6] The solid-phase synthesis of hydroxamic acids via the direct transhydroxamination of an ester-linked substrate has been reported.[7] However, this method required exposure of the esterified resin to concentrated aqueous hydroxylamine in THF over 2 days and was regarded as being of limited scope because it often fails to give reproducible results.[8a] Several activated resins have been designed to facilitate the direct transhydroxamination process but have the

TABLE 1. Solution-Phase Hydroxamic Acid Formation from Esters with and without KCN Additive



1a-e **2a-e**

Entry	R	Time (h)	Ester (1): Hydroxamic Acid (2) without KCN	Ester (1): Hydroxamic Acid (2) with KCN
1	 **1a** to **2a**	1	100: 0	86: 14
		2	100: 0	76: 24
		4	99: 1	56: 44
		6	97: 3	43: 57
		24	95: 5	4: 96 [b]
2	 **1b** to **2b**	1	94: 6	21: 79
		2	89: 11	9: 91
		4	78: 22	1: 99
		6	65: 35	0: 100 [c]
		24	48: 52 [c]	-
3	 **1c** to **2c**	1	82: 18	41: 59
		2	73: 27	17: 83
		4	62: 38	4: 96
		6	58: 42	2: 98
		24	38: 62	2: 98 [c]
4	 **1d** to **2d**	1	87: 13	4: 96
		2	82: 18	1: 99
		4	65: 35	0: 100 [d]
		6	57: 43 [d]	-
5	 **1e** to **2e**	2	90: 10	0: 100
		24	60: 40	-

[a] Ratios were calculated from the integrated area for the ester or hydroxamic acid HPLC peaks divided by the total area for the ester and hydroxamic acid multiplied by 100. [b] Final product contains about 15% carboxylic acid. [c] Final product contains trace (<2%) carboxylic acid. [d] Final product contains about 8% carboxylic acid.

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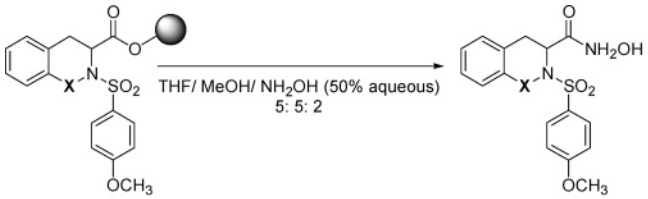
potential to be substantially more reactive than the simple ester linkage.[8] Another approach has been a stepwise method where the ester library was cleaved from the resin to give carboxylic acid intermediates that are subsequently reattached to a hydroxylamine resin by a peptide coupling agent then cleaved to the hydroxamic acids.[9] Alternatively, a variety of specialized hydroxylamine resins can be used.[10] The pitfall of this strategy is the limitation imposed upon subsequent chemistry. Important synthetic transformations such as the Mitsunobu reaction and reactions requiring basic conditions, such as alkylations, become problematic because of the acidic NH group ($pK_a \sim 10$) and are only compatible in the presence of the hydroxylamine-linking group when fully protected.[11]

We believed we could improve upon the existing methods by finding a way of transiently activating an ester toward the N-acylation of hydroxylamine. Hogberg et al.[12] have reported that the conversion of esters with ammonia and simple amines to amides is enhanced by the addition of small amounts of cyanide ion. The authors suggested that this reaction proceeds through an acylcyanide intermediate followed by nucleophilic substitution by the amine. To the best of our knowledge, there is no literature report of a cyanide-mediated N-hydroxyamination of esters to hydroxamic acids. This paper describes our study of the utility of KCN for the synthesis of hydroxamic acids from esters in solution and solid-phase chemistry.

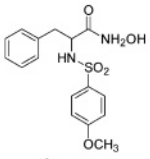
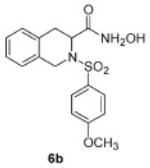
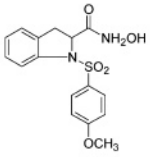
We followed the time-dependence of the solution-phase N-hydroxyamination of a series of esters **1** with and without catalytic amounts (~0.2 equiv) of KCN additive in THF/MeOH with 50% aqueous hydroxylamine at room temperature (Table 1). In all cases, addition of the KCN accelerates the formation of the desired *N*-acylhydroxamic acid product **2a**−**e**. For methyl benzoate (**1a**, entry 1) with KCN added the reaction is essentially complete after 24 h, while little of the corresponding hydroxamic acid **2a** is formed in that same time without KCN. For entries 2−4, almost all of the ester **1b**−**d** is converted to the corresponding hydroxamic acid **2b**−**d** within 6 h with added KCN, while considerable amounts of **1b**−**d** remain for the controls. In the case of the dihydroindole **1e** (entry 5), reaction is complete after 2 h with KCN while 60% of **1e** is unchanged after 24 h without KCN. Trace amounts of the corresponding carboxylic acid are formed as a byproduct in entries 2 and 3 (≤2%) with more substantial amounts of carboxylic acid formed for methyl benzoate (entry 1, 15%) and methyl mandelate (entry 4, 8%). No carboxylic acid was detected for the dihydroindole in entry 5. To apply this methodology to synthetic-scale

TABLE 2. Solid-Phase Reaction of Hydroxylamine with Esters of HMBA-AM Resin 5a−c with and without KCN Additive



5a: N-(4-methoxyphenyl)sulphonyl-DL-phenylalanine
5b: X = -CH_2-
5c: X = bond

6a-c

Entry	Products 6a-c	Time, h	% Conversion [a] to 6 without KCN	% Conversion [a] to 6 with KCN [b]
1	 **6a**	0.5	1.5	58
		1	3	83
		2	5.8	100
		4	11.9	-
		6	16	-
		20	28	-
2	 **6b**	0.5	6.5	68
		1	12	100
		2	16	-
		4	45	-
		20	100	-
3	 **6c**	0.5	18	85
		1	34	85
		2	56	100
		4	100	-
		20	-	-

[a] Determination of % conversion: The HPLC peak areas of products **6a**−**c** were normalized to the peak area of an internal standard (1-indanol). Complete cleavage of the product was apparent when the normalized peak areas for **6a**−**c** were observed to increase no further at subsequent time points. Percentages of conversion were all calculated relative to time point at which complete cleavage was observed. [b] In these experiments, 5 mg of KCN was used for 100 mg of resin.

reactions, we prepared the hydroxamic acids of methyl phenylacetate **1b** and methyl 3-phenylpropionate **1c** on a 2 mmol scale. Using a mixture of THF/MeOH/50% aqueous NH_2OH (1:1:0.5, 2.5 mL) with KCN (5 mg), a 77% yield of the *N*-acylhydroxamic acid **2b** was obtained from **1b** after 2 h at ambient temperature and a 67% yield of the hydroxamic acid **2c** from **1c** after 3 h at ambient temperature.

To explore the effectiveness of cyanide in the assistance of hydroxylamine mediated cleavage for solid-phase library synthesis, we selected the hydroxymethylbenzamide (HMBA-AM) resin because of the well-established compatibility of the ester linkage with Fmoc and Boc chemistry as well as stability toward Mitsunobu and reductive amination conditions.[13] A solid-phase library of DL-phenylalanine and several constrained analogues (**3a**−**c**, Scheme 1) was prepared on the HMBA resin by the esterification of the Fmoc-protected DL-amino acids using standard DCC coupling conditions at room temperature overnight. The resin-bound Fmoc amino acids **4a**−**c** were deprotected with piperidine/DMF (1:4) and

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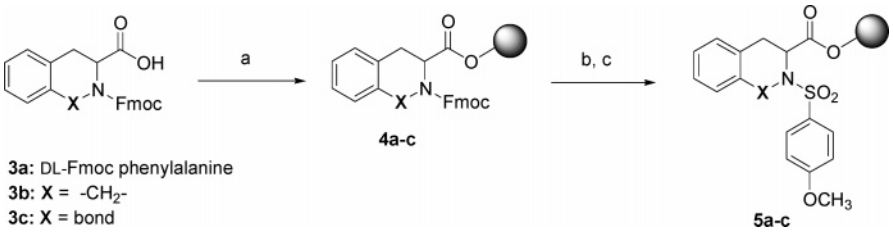
SCHEME 1. Preparation of Solid-Phase Library[a]



[a] Reagents and conditions: (a) **3a**−**c** (3 equiv), HMBA-AM resin, DCC (3 equiv), DMAP (3 equiv) DMF, rt, 15 h; (b) piperidine−DMF 1:4; (c) 4-MeOPhSO$_2$Cl (3 equiv), Et$_3$N (3 equiv), DCM, rt, 3 h.

sulfonated with 4-methoxybenzenesulfonyl chloride to give **5a**−**c**. After several attempts, we found that the sulfonamide esters are efficiently cleaved from the resin as the free hydroxamic acids (**6a**−**c**, Table 2) with a mixture of 5:5:2 THF/MeOH/50% aqueous NH_2OH and 5 mg of KCN for 100−200 mg of loaded resin. The importance of KCN additive using these conditions was assessed with this series of analogues by following the time-dependent cleavage of the substrates from the solid support by hydroxylamine in parallel experiments with and without KCN (Table 2). In the case of entries 1 and 2, KCN-assisted cleavage to the hydroxamic acid is complete after 2 h, while in the unassisted parallel experiments, up to 20 h or more for entries 1 and 2 is required. For entry 3, the KCN assisted experiment is complete after 2 h while the unassisted cleavage from the resin to the hydroxamic acid is complete in 4 h. It was important to follow these reactions carefully and work them up upon completion. Extended exposure to the hydroxylamine solution appeared to result in decomposition of the product.

To demonstrate the utility of this procedure on a synthetic scale, 200 mg of the resin **5a** (0.2 mmol of compound based on a loading capacity of 1 mmol of compound per 1 g of HMBA-AM resin) was treated with a mixture of THF/MeOH/50% aqueous NH_2OH (1:1:0.4, 2.4 mL) and KCN (5 mg) to give a 57% yield of hydroxamic acid **6a**, based upon the presumed resin loading.

In this work, we have shown that the addition of small amounts of solid KCN can effectively accelerate the formation of hydroxamic acids from simple esters of alkyl, aryl, and amino acids. The use and advantage of this methodology has been demonstrated for both solution-phase and solid-phase applications.

(13) The resin used in these experiments was the 4-hydroxymethylbenzoic acid AM (HMBA-AM) resin supplied by Calbiochem-Novabiochem Corp., product no. 01-64-0122.

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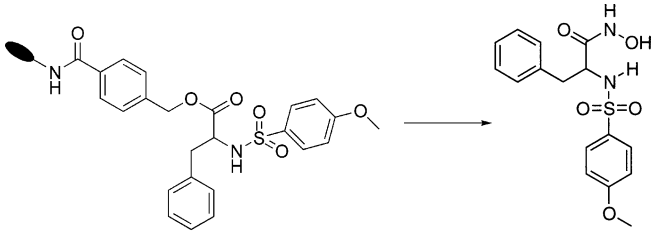
Experimental Section

Standard Procedure for Solution-Phase Time Course Experiments. Entry 3, Methyl 3-Phenylpropionate (1c) to *N*-Hydroxy-3-phenylpropionamide (2c). Two batches of methyl 3-phenylpropionoate (0.10 g, 0.38 mmol) in 1:1 THF/MeOH (1 mL) were prepared. Then 50% aqueous NH_2OH (0.25 mL) was added to each batch followed by the immediate addition of KCN (5 mg) to one reaction while the other was maintained as a control. The parallel reactions were stirred at ambient temperature, and 0.025 mL aliquots of each reaction mixture were withdrawn and diluted with 0.2 mL of MeOH at time points of 1, 2, 4, 6, and 24 h. The aliquots were analyzed by reversed-phase HPLC within 10 min of being diluted. For details on product peak identification and the data used to estimate of the ratio of starting ester **1c** to product hydroxamic acid **2c** formed see the Supporting Information.

Standard Procedure for Solid-Phase Resin Cleavage Time Course Experiments. Entry 1, Cleavage of *N*-(4-Methoxyphenylsulfonyl)-DL-phenylalanine-Modified HMBA-AM Resin (5a) to the Hydroxamic Acid (6a).



Stock Solution Preparation. Indan-1-ol (33 mg) was dissolved with a mixture of THF (5 mL)/MeOH (5 mL)/NH_4OH (1 mL, 50% aqueous solution).

Resin Cleavage. THF (0.3 mL) and the stock solution (1 mL) prepared above were added to resin **5a** (100 mg), and the reaction was shaken. For the reaction with KCN, 5 mg of KCN was added immediately while, for the control, no KCN was added. At time points of 0.5, 1, 2, 4, 6, and 24 h an aliquot (0.05 mL) of the reaction was removed by syringe and immediately diluted with MeOH (0.20 mL). These samples were analyzed by HPLC within 10 min of sampling. The absorbance of the 1-indanol peak and the product **6a** was recorded for each time point. For details on product peak identification and the data used to estimate the percent conversion to product, see the Supporting Information.

Supporting Information Available: Typical experimental procedures, analytical data, and time course experimental data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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