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General methodology for solid-phase synthesis of *N*-alkyl hydroxamic acids

Viktor Krchňák[a,*] and Greg A. Slough[b]

[a]*Department of Chemistry and Biochemistry, 251 Nieuwland Science Center, University of Notre Dame, Notre Dame, IN 46556, USA*
[b]*Chemistry Department, Kalamazoo College, 1200 Academy Street, Kalamazoo, MI 49006, USA*

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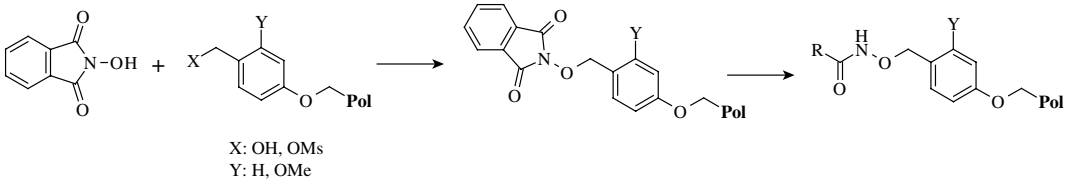
Abstract—Polymer-supported *N*-benzyloxy-2-nitrobenzenesulfonamides **1** were *N*-alkylated using three different routes: via Fukuyama reaction with alcohols, by *N*-alkylation with alkylbromides, and by Michael addition reaction with α,β-unsaturated carbonyl compounds. The *N*-alkylated products prepared on the linker **1b** were obtained in excellent purity and yield. The 2-nitrobenzenesulfonyl (Nos) group was cleaved under mild conditions to yield polymer-supported *N*-alkylated benzyloxyamines. Acylation by carboxylic acids and cleavage with TFA yielded *N*-alkyl hydroxamic acids.

The solid-phase synthesis of hydroxamic acids has been of interest in the recent chemical literature.[1] Typically, hydroxylamine derivatives are tethered to solid supports via the oxygen (Scheme 1), although immobilization through the nitrogen has also been observed. The reaction of *N*-hydroxyphthalimide with Wang or Sasrin resins under Mitsunobu conditions is the common preparative route to *O*-immobilized hydroxylamine,[2–4] while it is also possible for the hydroxyl resin to be converted to a mesylate resin and then reacted with *N*-hydroxyphthalimide.[5] A third preparative route involves the condensation of the trityl chloride resin with either *N*-hydroxyphthalimide,[6–8] or *N*-Fmoc hydroxylamine.[9] The resulting polymer supported hydroxylamine can be acylated by carboxylic acids and cleaved from the resin with TFA to give the target hydroxamic acids. These synthetic routes have been used to prepare combinatorial libraries of hydroxamates.[10,11] For *N*-substituted derivatives of hydroxamic acids, polymer supported hydroxylamine is reductively alkylated and then acylated to yield the desired hydroxamic acid derivative.[12] In this paper, we report an alternative method based on *N*-alkylation of polymer-supported *N*-benzyloxy-2-nitrobenzenesulfonamides **1**—a solid-phase version of Slomczynska's reagent.[13] This procedure has recently been used for the solid-phase synthesis of methyl carboxymycobactins[14] and desferrioxamines.[15]

The synthesis of activated resin **1** was simple and straightforward (Scheme 2). The coupling of Wang resin with *N*-hydroxyphthalimide, removal of the phthalimide group,[2] and *N*-sulfonation with 2-nitrobenzenesulfonyl



Scheme 1. Solid-phase synthesis of hydroxamic acids.

Keywords: Solid-phase synthesis; Linker; Hydroxamic acid; Alkylation.
* Corresponding author. Tel.: +1-574-6315113; fax: +1-574-6316652; e-mail: vkrchnak@nd.edu

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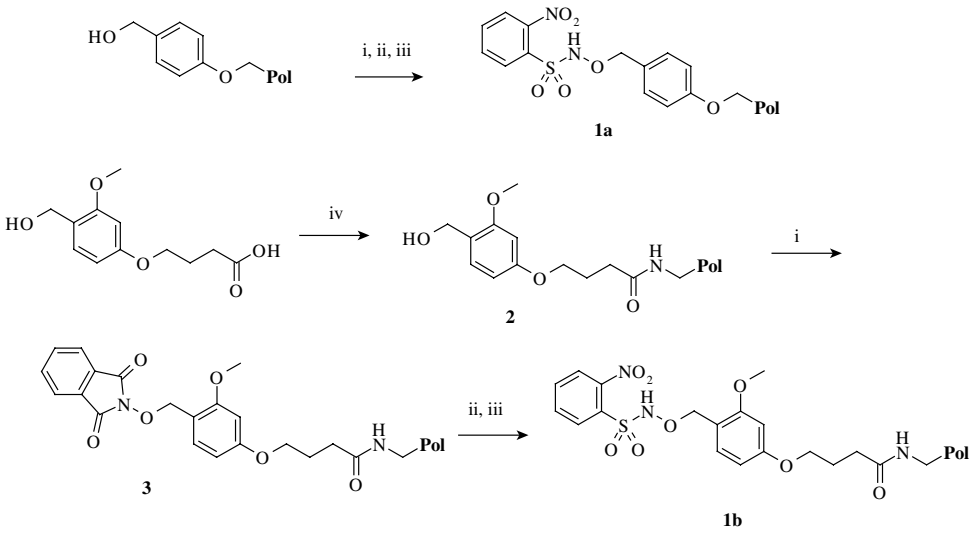


Scheme 2. Solid-phase synthesis of the sulfonamide linker. Reagents and conditions: (i) *N*-hydroxyphthalimide, PPh_3, DIAD, anhydrous THF, 20 °C, overnight; (ii) 5% hydrazine hydrate, THF/MeOH (1:1), 20 °C, overnight; (iii) Nos-Cl, 2,6-lutidine, DCM, 20 °C, overnight; (iv) aminomethyl PS/DVB resin, DIC, HOBt, DMF, 20 °C, overnight.

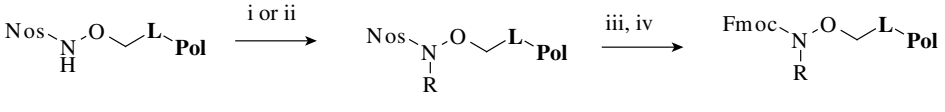
chloride gave a versatile resin, **1a**, in high yield (the Nos group was cleaved, resin-bound hydroxylamine reacted with Fmoc-ONSu, the product cleaved by TFA/methylene chloride mixture and quantified by integration of peak area on analytical HPLC traces at 300 nm). Alternatively, resin **1b** was prepared by acylation of the aminomethyl PS/DVB resin with 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB linker)[16] via DIC/HOBt activation. Acylation of a sample **1b** with Fmoc-Ser(*t*-Bu)-OH (HOBt, DIC, DMAP) and subsequent cleavage with TFA/DCM yielded 91% of the expected product. The HMPB resin **2** reacted with *N*-hydroxyphthalimide under Mitsunobu conditions using the published protocol[17] to yield resin **3**, which was deprotected using hydrazine hydrate and reacted with 2-nitrobenzenesulfonyl chloride to give resin **1b**. Alternatively, the linker was attached to a polymer via an ether bond, that is, the Sasrin resin.[18] The 2-nitrobenzenesulfonamide resins **1** were used as a starting material for the *N*-alkylation.

Fukuyama *N*-alkylation[19] of resin **1a** with model alcohols produced **4a** as a stable resin. Cleavage with TFA did not provide a clean product. Thus the Nos group was cleaved and the polymer-supported benzyloxyamine reacted with Fmoc-Ser(*t*-Bu)-OH. Cleavage of this material with 95% TFA/water[5] revealed the presence of a side-product that included the cleavage of the Wang linker. Previous synthetic work on peptide hydroxamic acids (without *N*-substituent) noted the presence of unspecific impurities.[2]

In order to select a more suitable linker, we used our concept of a double linker with a reference cleavage site to improve the cleavage reaction and ascertain information about undesired side-products. The Sasrin linker increased the acid lability of immobilized hydroxamic acids and products were quantitatively cleaved by 10% TFA in DCM for 30 min. Consequently, we used the more acid labile linker **1b** for evaluation of these *N*-alkylation studies. Fukuyama *N*-alkylation[19] of resin **1b** proceeded smoothly with a range of alcohols and produced resin **4b** in satisfactory yields. The highest purity of products was obtained with the molar ratio alcohol/PPh_3/DIAD adjusted to 1:1:0.8 (Scheme 3).

Alkylation of resin **1b** with alkylbromides in the presence of a base also proved to be an excellent route to *N*-alkyl substituted hydroxamic acids. BEMP provided superior results with respect to product purity.

In a similar fashion, the Michael addition reaction could also be used to install the *N*-substituent (product **6b**). This third route greatly extended the range of carbon

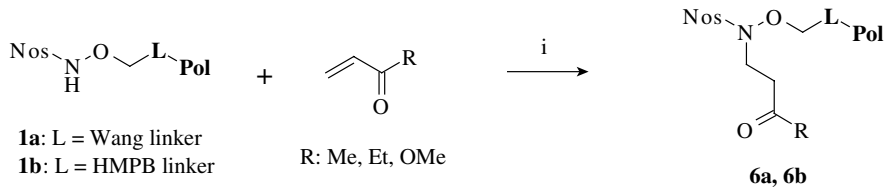


1a: L = Wang linker
1b: L = HMPB linker

4a, 4b

5a, 5b

Scheme 3. Alkylation of 2-nitrobenzenesulfonamide of polymer-supported benzyloxyamines. Reagents and conditions: (i) PPh_3, R-OH, DIAD, anhydrous THF, 20 °C, 3 h; (ii) R-Br, BEMP, anhydrous THF, 20 °C, overnight; (iii) 2-mercaptoethanol, DBU, DMF, 20 °C, 30 min; (iv) Fmoc-ONSu, DCM, overnight.



Scheme 4. Michael addition reaction with 2-nitrobenzenesulfonamide of benzyloxyamines. Reagents and conditions: (i) BEMP (cat.), anhydrous THF, 20 °C, overnight.

Table 1. *N*-Alkylation of polymer-supported *N*-benzyloxy-2-nitro-benzenesulfonamide **1b**[a]

Entry	Reagent	t_R[b]	Purity (%)[c]	t_R[d]	Yield (%)[e]
1	Methyl alcohol	2.90	98	6.07	83
2	Benzyl alcohol	5.98	91	7.77	89
3	Methoxyethanol	3.33	89	6.15	83
4	2-(Phenylthio)ethanol	6.92	81	8.48	59
5	3-Hydroxymethylpyridine	2.62	85	4.60	72
6	4-(*tert*-Butyl)benzylbromide	8.22	95	9.48	76
7	Vinyl methyl ketone	3.37	90	6.00	87
8	Vinyl ethyl ketone	4.18	83	6.62	74
9	Methyl acrylate	3.82	89	6.33	85

[a] All products afforded the expected diagnostic ion in mass spectra.
[b] Retention time of the Nos-derivatives (C18 X-terra 30 × 3 mm column, 1.4 mL/min, gradient 0–60% from water with 0.1% TFA to MeCN in 10 min).
[c] Peak area on analytical HPLC traces of the Nos derivative at 220 nm.
[d] Retention time of the Fmoc derivatives.
[e] Yield of cleaved Fmoc derivative (seven reaction steps), calculated from the integrated peak area on analytical HPLC traces at 300 nm.

substituents that could be attached to the hydroxamate. Each Michael reaction was carried out in anhydrous THF with a catalytic amount of the BEMP as a base (Scheme 4).

A sample of the *N*-alkylated product, formed from each of the alkylation methods, was cleaved from the resin **1b** by 10% TFA in methylene chloride for 30 min. Analytical data are summarized in Table 1. The Nos protecting group was then cleaved with 2-mercaptoethanol in DMF in the presence of DBU and the resin-bound *N*-alkyl benzyloxyamines were derivatized with Fmoc-ONSu. Finally, these FMOC-*N*-alkylhydroxamic acids were cleaved from each respective resin (**5** or **6**) with 10% TFA in DCM for 30 min. Analytical results from these derivatives are also summarized in Table 1.

In summary, the polymer-supported *N*-benzyloxy-2-nitrobenzenesulfonamide linker **1b** is a versatile substrate for *N*-alkylation using three different types of carbon-based building blocks: alcohols, alkylbromides, and α,β-unsaturated carbonyl compounds. *N*-Alkylation reactions proceeded under mild conditions, were amenable to manual parallel synthesis, and gave *N*-alkylhydroxamic acids in high yield and excellent purity after convenient cleavage conditions.

General procedure

Resin **1b** (100 mg) in a 3 mL polypropylene disposable reaction vessel (www.torviq.com) was washed three times with anhydrous THF.

Reaction with alcohols: The reaction vessel was charged with 2 mL of 0.25 M PPh_3 (131 mg) and 0.25 M alcohol in anhydrous THF. DIAD (0.4 mmol, 77 μL) was added and the resin slurry was shaken at ambient temperature for 3 h.

Alkylation with alkylbromides: The reaction vessel was charged with 2 mL of 0.25 M alkylbromide solution in anhydrous THF. BEMP (0.5 mmol, 144 μL) was added and the resin slurry was shaken at ambient temperature overnight.

Michael addition reaction: The reaction vessel was charged with 2 mL of 0.25 M α,β-unsaturated carbonyl compound solution in anhydrous THF. BEMP (0.05 mmol, 14 μL) was added and the resin slurry was shaken at ambient temperature overnight.

The resin was washed five times with THF and DCM.

Acknowledgements

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