Report

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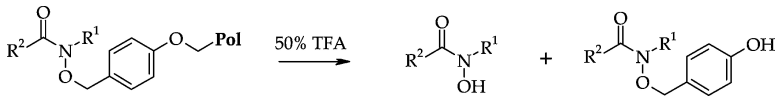

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Incorporation of the Wang Linker upon Cleavage from Polystyrene-based Resin to Form *O*-(4-Hydroxy)benzyl Derivatives

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Introduction. The Wang resin[1] is the most popular acid-cleavable support for the solid-phase synthesis of acids, alcohols, and phenols and the resin of choice for peptide synthesis using the Fmoc/*t*Bu protection strategy.[2] The Wang linker, a 4-(hydroxymethyl)phenoxymethyl, is attached to a polystyrene-based resin, the traditional support for solid-phase synthesis, via an aryl benzyl ether bond (Figure 1).

Aryl benzyl ethers are not completely acid-stable, and the Wang linker can be cleaved from the solid support during treatment with acid-based cleavage cocktails. However, the fate of the cleaved linker is rarely reported. One of the few literature reports is Kobayashi's synthesis of amines.[3] Cleavage of products from the Wang resin by trifluoromethanesulfonic acid, or trifluoroacetic acid (TFA) at 60 °C retained the Wang linker (Scheme 1). The result is not surprising in this case because C(benzyl)−N bonds on the 4-alkoxybenzyl amines are substantially more acid-stable as compared to 4-alkoxybenzyl ethers.

Kobayashi's cleavage conditions are considerably more forcing than those used for cleavage of esters or ethers from a Wang resin. For example, carboxylic acids are completely cleaved from the Wang linker by a 50% solution of TFA in dichloromethane (DCM) within 30 min.[4] However, we observed significant cleavage of the Wang linker from polystyrene-based supports even under these typical conditions. In this Report, we describe the cleavage of the Wang linker from polystyrene-based solid supports documented through the isolation and characterization of *O*-(4-hydroxy)benzyl derivatives, side products originating from cleavage of the Wang linker from the solid support.

Recently, we described a general methodology for solid-phase synthesis of diverse *N*−*H* and *N*-alkyl hydroxamates.[5] The key intermediate is a polymer-supported hydroxylamine, attached via its oxygen atom to the Wang linker. After solid-phase synthesis of compounds **1**, the crude product mixture was analyzed upon cleavage by 50% TFA and found to contain two major components. Exposure of Wang linker-bound hydroxamic acids to TFA results in both the desired compound **2** and cleavage of the Wang linker from the polystyrene support to form a side-product **3** containing an *O*-(4-hydroxy)benzyl group (Scheme 2). The ratio of compounds **2** and **3** depends on the concentration of TFA, length of exposure, structure of the attached substrate, and commercial source of the Wang resin. After 1 h of 50% TFA, the yield of target hydroxamate **2** varied from 45 to 80%, but overall purity of the combined hydroxamates **2** and **3** was >90%. Table 1 lists the ratio of compounds **2** and **3** as a function of structure, cleavage conditions, and Wang resin supplier.

The NB resin and resin Plugs provided comparable amounts of the side products **3**; however, the amount of the O-alkylated derivative **3** synthesized on the ACT resin was substantially lower. According to the data from Advanced ChemTech, this Wang resin typically has a 70:30 mixture of para and meta substituents. We speculate that the lower amount of the side product present on the ACT resin can be attributed to the presence of the meta isomer, which is more stable toward TFA cleavage when compared to the para isomer. The NB resin and resin Plugs have the Wang linker predominantly attached in the para position.

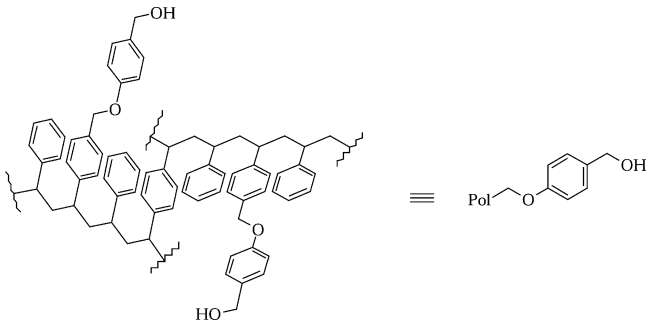
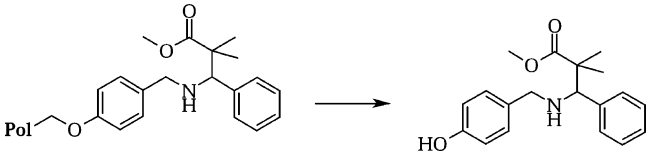
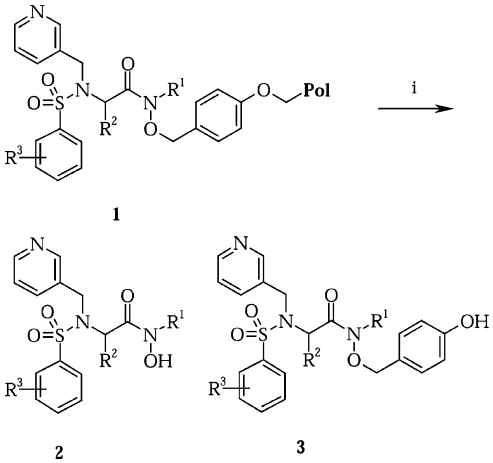


Figure 1. Wang resin, 4-(hydroxymethyl)phenoxymethyl copoly-(styrene−1% divinylbenzene)

Scheme 1. Acidolytic Cleavage of Wang Linker from Solid Support[3]



Scheme 2. Formation of *O*-(4-hydroxy)benzyl Derivatives[a]



[a] Reagents: (i) 50% TFA in DCM; for reaction time, see Table 1.

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Table 1. Relative Ratio of Hydroxamate **2** and Its *O*-Alkyl Derivatives **3**[a]

entry	resin[b]	R^1	R^2	R^3	time	**2**	**3**
1	NB	*n*-propyl	hydrogen	2-nitro	30 min	60	40
2	NB	*n*-propyl	methyl	2-nitro	30 min	42	58
3	NB	benzyl	methyl	2-nitro	30 min	39	61
4	NB	*n*-propyl	*i*-propyl	2-nitro	1 h	80	20
5	NB	*n*-propyl	*i*-propyl	4-methoxy	1 h	45	55
6	NB	methyl	*i*-propyl	2-nitro	1 h	80	20
7	Plug	methyl	*i*-propyl	2-nitro	1 h	82	18
8	ACT	methyl	*i*-propyl	2-nitro	1 h	>95	<1
9	NB	3-pyridylmethyl	*i*-propyl	2-nitro	1 h	47	53
10	Plug	3-pyridylmethyl	*i*-propyl	2-nitro	1 h	45	55
11	ACT	3-pyridylmethyl	*i*-propyl	2-nitro	1 h	>95	<1
12	NB	methyl	*i*-propyl	4-methoxy	1 h	73	27
13	NB	methyl	*i*-propyl	4-methoxy	2 h	84	16
14	NB	3-pyridylmethyl	*i*-propyl	4-methoxy	1 h	21	79
15	NB	3-pyridylmethyl	*i*-propyl	4-methoxy	2 h	63	37
16	NB	*n*-butyl	hydrogen	2-nitro	1 h	80	20
17	NB	*n*-butyl	*i*-propyl	2-nitro	1 h	71	29
18	ACT	ethyl	methyl	2-nitro	15 min	94	6
19	ACT	ethyl	methyl	2-nitro	30 min	>95	<1
20	ACT[c]	ethyl	methyl	2-nitro	30 min	88	12
21	ACT[c]	ethyl	methyl	2-nitro	1 h	>95	<1
22	NB	*n*-propyl	*i*-propyl	2-nitro	1 h	>95	<1
23	NB	methyl	*i*-propyl	2-nitro	1 h	>95	<1
24	NB	3-pyridylmethyl	*i*-propyl	2-nitro	1 h	>95	<1

[a] Cleavage by 50% TFA/DCM. [b] NB: Wang resin 100−200 mesh, 1% DVB, 1.0 mmol/g from NovaBiochem (San Diego, CA, www.novabiochem.com); ACT: Wang resin SS, 100−200 mesh, 1% DVB, 1.0 mmol/g from Advanced ChemTech (Louisville, KY, www.advancedchemtech.com); Plug: PL-Wang Plug, a generous gift from Polymer Laboratories (Amherst, MA, www.polymerlabs.com). [c] 25% TFA/DCM

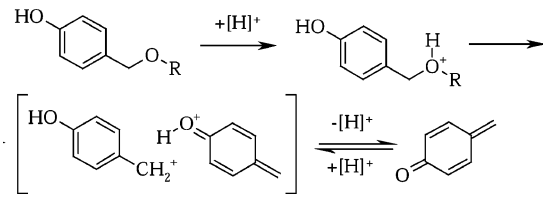
To confirm that the *O*-(4-hydroxy)benzyl side-products resulted from cleavage of the Wang linker off the resin, we examined more acid-labile linkers, such as the 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid (HMPB) linker.[6] The presence of an additional methoxy group on the linker, as compared to the Wang linker, labilizes the hydroxamates toward acid-mediated cleavage under milder conditions. Three compounds (entries 22 − 24, identical to entries 4, 6, and 9 in Table 1) were synthesized on aminomethyl-derivatized VersaMatrix beads acylated with the HMPB linker. Crude purity of the hydroxamate upon cleavage from the supports by 50% TFA for 1 h was determined by analytical HPLC and compared to synthesis on the Wang resin. With the HMPB linker, the purity of all three compounds was >95%, and no evidence of a *O*-(4-hydroxy)-benzyl group containing side-products was observed.

On the Wang resin, cleavage of resin-bound hydroxamates **1** with 90% TFA/DCM for 1 h eliminated the O-alkyl side product **3** for all the substrates and supports examined. Under these conditions, all of the Wang linker was cleaved from the target compounds. However, the crude product was contaminated with a substantial amount of cleaved Wang linker.

Upon acid-mediated cleavage, a carbocation, the protonated *p*-quinone methide, is formed from the Wang linker (Scheme 3). *p*-Quinone methides have attracted significant attention because of their interesting biological activities (cf., e.g., ref 7 and references cited therein). This very reactive species can undergo transformations such as self-polymerization, alkylation of the polystyrene resin, or alkylation of any soluble products.

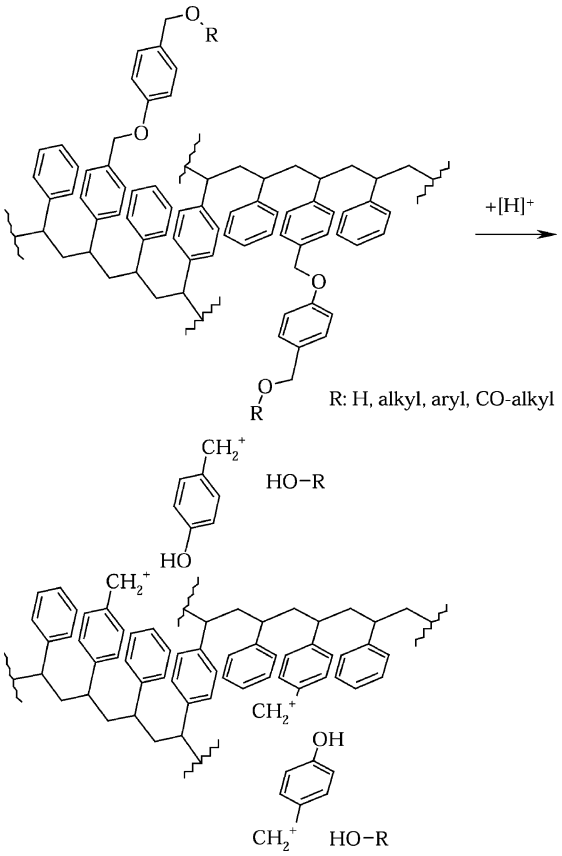
To trace the cleaved Wang linker, we exposed unfunctionalized NB Wang resin (500 mg, 1 mmol/g) to 50% TFA in DCM for 30 min. The cleavage solution yielded 9.8 mg (15%, theor 62 mg) of a white solid upon evaporation. HPLC analysis of the solid did not show distinct peaks; instead, an elevated absorbance was observed that spanned the region from 5 to 8 min (HPLC conditions listed in the Supporting Information), indicating a wide distribution of polymeric entities. Yields of the polymerized Wang linker that are substantially lower than the yields of compound **3** under similar conditions (15 vs 45%) can be attributed to competing alkylation of the aromatic rings of the polystyrene-based support by the TFA-generated carbocations.

Scheme 3. Formation of Protonated *p*-Quinone Methide by TFA Cleavage Cocktail



One must also take into account that exposure of Wang resin and polymer-supported products synthesized on Wang resin to TFA produces two kinds of carbocations, either polymer-supported or "in solution" (Scheme 4). Polymer-supported carbocations alkylate the polystyrene matrix, resulting in additional cross-linking, that can be indirectly documented by reduced swelling capacity of TFA-treated Wang resin. Wang polystyrene resin swells to a volume of 6.0 mL/g of resin in DCM; after TFA treatment, the resin shrinks and swells to a maximum of 3.5 mL/g of resin in DCM. The soluble carbocations can polymerize in solution, alkylate the polystyrene backbone, and benzylate alkylation-prone target compounds. Interestingly, the more acid-labile

Scheme 4. Formation of Two Kinds of Carbocations from Wang Resin



4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric linker[6] forms calyx[4]arene when exposed to TFA.[8]

To quench the carbocations generated from the Wang resin, 5% of triethylsilane (TES), known to effectively scavenge carbocation,[9,10] was added to the cleavage cocktail. This not only eliminates the polymerization side reactions but also prevented product alkylation and, therefore, increased the effective yield of target compounds. The major component of cleavage in the presence of TES was *p*-cresol, as indicated by MS and NMR.

Cleavage of the Wang linker can be avoided altogether by switching the linker system. Use of hydroxymethylphenoxyacetic acid (HMPA)[11] or hydroxymethylphenoxypropionic (HMPP) acid[12] linkers attached by acylation to aminomethyl resin represent alternatives to the Wang linker. These linkers have similar acid labilities; however, a primary amide is introduced into the resin-bound intermediates which may not be compatible with all intended subsequent chemical transformations. Esters of HMPP[12] are cleaved 2−3 times faster than HMPA esters. Another option is to utilize homobenzyl (phenethyl) derivatives as linkers to the resin, replacing the acid-labile linkage to the support.[13−16] Alternative Wang resins such as the Wang TentaGel resin in which the Wang linker is attached to a poly(ethyleneglycol) graft would also avoid Wang carbocation side reactions.

To conclude this report, we documented that substantial cleavage of the Wang linker from polystyrene-based solid-phase support occurs under conditions typically used for cleavage of target compounds (50% TFA in DCM for 30 min). The side-product, *O*-(4-hydroxy)benzyl derivatives of target hydroxamates, has been isolated, purified, and fully characterized. Extended treatment with TFA cleaves the *O*-(4-hydroxy)benzyl group from the target compound; however, the target compound remains contaminated by polymerized Wang linker.

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Supporting Information Available. Details of experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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