Tetrahedron 70 (2014) 4191–4196

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Toward the development of solid-supported reagents for separation of alcohol-containing compounds by steric environment

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ARTICLE INFO

Article history:
Received 1 February 2014
Received in revised form 11 March 2014
Accepted 12 March 2014
Available online 18 March 2014

Keywords:
Solid phase
Hydroxyl group
Separations
Steric environment

ABSTRACT

The affinity of silicon for oxygen has long been exploited to preferentially react hydroxyl moieties in the presence of others. Here, we explore the ability of a variety of dialkylsiloxane-functionalized resins to selectively capture and subsequently, release alcohol-containing compounds based on the steric environment about the silicon and hydroxyl moiety. The devised reagents will be applicable to the separation of compound mixtures, especially for the selective enrichment of low abundant molecules such as bioactive natural products.

1. Introduction

Although chemical space is essentially infinite ($>10^{60}$ possibilities of $<$500 Da containing $\leq$30 C, H, O, N, and S atoms),[1,2] it is likely that only a small percentage of these molecules have significant bioactivity.[3,4] Unlike the vast majority of chemical space, natural products have evolved to optimize their interactions with other biomolecules in terms of functional group content, three-dimensional display, physicochemical properties, and chemical reactivity. The resulting structural diversity can be harnessed as chemical probes of biological processes, therapeutic agents, and novel (bio)synthetic targets.[5,6] It is clear that further exploration of natural products will enable the identification of important molecules. However, this process is made difficult by the aforementioned molecular complexity and the number and concentration range of compounds found in the extracts of most source materials.[7]

A significant obstacle in the natural products discovery pipeline is compound purification. Often, molecules of interest are present in exceptionally low quantities making their isolation difficult.[7] We are working to address this challenge by the development of new strategies for the separation of complex natural product mixtures. Most natural product isolation methods function through a restricted set of separation mechanisms, which are dependent upon the physical properties of the molecules such as solubility, charge state, or size. We are generating tools that separate natural products based upon a distinct and orthogonal chemical property: functional group composition.

We have reported reagents to facilitate the chemoselective enrichment of hydroxyl- and carboxylic acid-containing compounds.[8–10] Targeted compounds are captured onto a solid support utilizing controllably reversible reactions that enable subsequent 'traceless' release of the enriched natural products for direct functional and structural characterization. This work demonstrated that functional group-based separation unmasks minor components in an extract.[9,10] We have also shown that functional group targeted purification yields pools of compounds that are not homogeneous in terms of their physicochemical properties, making subsequent chromatographic separations more effective.[9,10] Accordingly, construction of a chemoselective isolation toolkit is advantageous as these reagents will facilitate the discovery of natural products that are unlikely to be identified by traditional strategies due to low isolation yields, poor compound resolution, the presence of interfering compounds, and/or unfavorable molecular properties (e.g., ease of oxidation). In addition, chemoselective enrichment provides information about compound structure prior to characterization efforts.

1.1. Targeting of hydroxyl-containing natural products

Hydroxyl groups are found in many biologically active molecules including ~65% of known natural products and ~40% of drugs.[2,11–13] Our strategy to facilitate the enrichment of alcohol-

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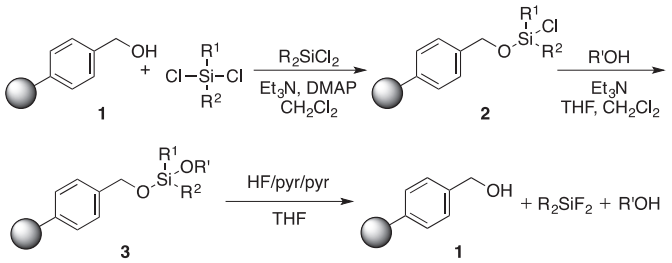
http://dx.doi.org/10.1016/j.tet.2014.03.040

functionalized natural products was inspired by the rich literature describing use of organosilyl groups as a means to protect this moiety.[14,15] We first sought to identify solid supports that could capture a breadth of alcohols and do so in a chemoselective fashion and determined that two dialkylsiloxyl chloride-functionalized resins achieved these goals (Scheme 1, general structure **2**; Table 1, resins **4** and **6**).[8] However, because the hydroxyl is highly prevalent in natural products, we subsequently pursued the development of reagents capable of further parsing this compound pool. Separation of aromatic and aliphatic alcohols was accomplished by generation of selective release conditions that afforded cleavage of phenols from resin **4** at neutral pH (1,1,3,3-tetramethylguanadine/acetic acid) followed by elution of aliphatic compounds with standard HF/pyridine cleavage conditions.[10] Here, we report the synthesis and assessment of a library of dialkylsiloxyl chloride-functionalized resins (Scheme 1, resin **2** and Scheme 2, resin **22**) for the ability to preferentially capture hydroxyl groups that are relatively unhindered, as these reagents would enable separation of the alcohol pool into subfractions based on the local steric environment of this functional group.



Scheme 1. Synthesis of a series of siloxyl resins (**2**) based upon a hydroxylmethyl polystyrene scaffold (**1**).

1.2. Steric environment as a route to separation

The differences in reactivity of various silyl-protected species are governed by both the steric and electronic nature of the silyl substituents and the local environment of the hydroxyl group.[14–16] Selective silylation or desilylation is most often thought of in terms of the ability to perform such reactions at multiple sites on the same molecule. Instead, we sought to generate a library of siloxyl-functionalized resins to identify reagents with properties tuned to enable capture of compounds containing hydroxyls with differing steric environments, thereby creating an additional dimension of separation. Such reagents could yield alcohol subpools as depicted in Fig. 1. For example, less hindered alcohols could first be removed from the mixture with a sterically selective resin and the remaining hydroxyl-containing compounds could then be enriched with the scaffold that demonstrated a broad capture spectrum in our previous studies (resin **4**).[8,10]

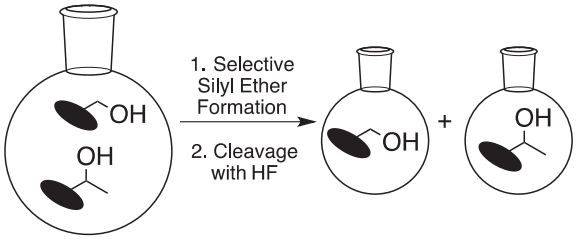


Fig. 1. Separation of sterically differentiated alcohols could be accomplished by identification of a resin(s) that selectively forms silyl ether bonds with a subfraction of the compound pool.

2. Results and discussion

2.1. Benzyl alcohol-derived siloxyl resins

Our previous work led to the identification of benzyl alcohol-derived siloxyl resins (**2**) as appropriate scaffolds for chemoselective enrichment of hydroxyl-containing molecules.[8,10] Synthesis of these solid-supported reagents started from hydroxylmethyl polystyrene (**1**), which was activated with a dialkyldichlorosilane in the presence of triethylamine and dimethylaminopyridine (DMAP) (Scheme 1). Capture of alcohols was readily accomplished with addition of triethylamine, yielding the disiloxyl species (**3**). Enriched alcohols were cleaved with HF·pyr/pyr resulting in concurrent regeneration of the hydroxylmethyl-functionalized resin (**1**; Fig. S1 and Table S2).

Resins **4** and **6** were identified as wide spectrum hydroxyl capture reagents as they facilitated enrichment of compounds with disparate properties (Table 1; yields indicate the amount of compound detected following immobilization and release).[8,10] To explore the possibility of generating a sterically selective scaffold, we synthesized resin derivatives with a range of alkyl groups about the silicon. Resins functionalized with either methyl or ethyl groups demonstrated no preference for primary or secondary hydroxyl groups (resins **4**–**6**). Addition of a bulky substituent (isopropyl; resin **7**) leads to an overall decrease in enrichment yields and did not lead to selectivity for less sterically encumbered substrates, while use of groups larger than this resulted in little to no alcohol capture (resins **8** and **9**; scaffolds that did not show promising results with primary alcohols were not examined with all substrates). It seemed apparent that scaffolds containing this resin linker could not be readily tuned to achieve sterically selective capture. Instead, we turned our attention to another class of siloxyl resins that we had previously found to show striking functional group preference upon alternation of the silyl substituents.[9]

2.2. Tertiary alcohol-derived siloxyl resins

We formerly discerned that solid supports containing a tertiary alcohol linker, first described by Meloni and co-workers,[17,18] enabled capture of alcohols and carboxylic acids (Scheme 2, **22**).[9] Our work demonstrated that resin functionalized with two isopropyl substituents enriched carboxylic acids in high yield.[9] Chemoselectivity for this moiety was achieved by alteration of the leaving group on the silicon, where capture of alcohols was completely eliminated by use of an alkoxyl group instead of the chloride utilized here. We envisioned that returning to the chloride leaving group and further exploration of the silicon substituents could provide a resin that demonstrates preferential enrichment of primary alcohols. These solid support derivatives were generated by reaction of Merrifield resin with a diol linker to yield **21**. A variety of dichlorodialkylsilanes were added in excess in the presence of triethylamine and DMAP to provide the activated reagents (**22**).[17,18] As with the benzyl alcohol-derived scaffolds, capture of alcohols was readily accomplished with addition of triethylamine, yielding the disiloxyl species (**23**). Enriched alcohols were cleaved with HF·pyr/pyr resulting in concurrent regeneration of the tertiary alcohol-functionalized resin (**21**; Fig. S1 and Table S2).

Assessment of the produced resins with a variety of substrates indicated that the bulkiness of the silicon substituents had great influence on the observed alcohol capture profile (Table 2). Comparison of the dimethyl, methylethyl, and diethyl substituted supports, **24**, **25**, and **26**, respectively, indicates that while the enrichment efficiency for primary alcohols remains relatively constant, the yields of secondary hydroxyl-containing molecules dramatically decrease with the addition of steric encumbrance. Addition of exceptionally bulky groups such as *n*-butyl, *s*-butyl, and