Development of a Novel Silyl Ether Linker for Solid-Phase Organic Synthesis[1]

Terri L. Boehm[†] and H. D. Hollis Showalter*

Chemistry Department, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

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There is a burgeoning expectation that solution- and solid-phase combinatorial chemistries will markedly accelerate the drug discovery process. This is due in part to the successful generation of large libraries of linear biopolymers (principally peptides and oligonucleotides) using solid-phase techniques. While the experimental protocols for making these biopolymers are now well established,[2] such is not the case for the solid-phase synthesis of small "drug-like" molecules. Early work in the solid-phase synthesis of small molecules has relied heavily on these methods,[3] which have severely restricted the types of chemistries that can be carried out and, hence, the diversity of available compound targets.

Much of the current effort in solid-phase organic synthesis is being focused on the development of new types of linking strategies.[4] This has resulted in the construction of a wider range of compound classes due to improved methods for linking and cleaving substrates on solid-supports. In this vein, one recent development is the introduction of "traceless linkers", which allow for the attachment of a substrate to a solid support at an inert site within the molecule. Upon cleavage from the resin, products are formed that show no trace or "memory" of attachment to the solid support. Examples of this include the preparation of *p*-tolyl derivatives by reductive cleavage of benzyl thioesters[5] and several silicon-based traceless linkers that allow for the preparation of variously substituted aromatic compounds by *ipso*desilylative (via proton or other common electrophiles) or fluoride-mediated cleavage of a resin-bound arylsilane.[6] Herein, we report the development and application of a novel strategy for a silicon-based linker in which the arylsilane is linked to a solid support via a silyl ether bond, in contrast to prior strategies utilizing linkage via an alkylsilane bond. Mild fluoride-mediated desilylation of our resin-bound intermediates produces aromatic compounds in generally excellent yield and purity.

Silyl ethers have found widespread application in organic synthesis because of their increased stability over trialkylsilyl ethers.[7] Recently, Danishefsky has described the use of a silyl ether linker in the solid-phase synthesis of oligosaccharides by reacting a hydroxyl group of a carbohydrate with a chlorosilylated resin.[8] We reasoned that a similar approach could be applied to the reaction of a functionalized arylchlorosilane with a solid support containing a hydroxyl functionality to provide a resin-bound arylsilyl ether. Further functionalization of the aromatic moiety followed by reaction conditions in which either the silicon−carbon or the silicon−oxygen bond could be cleaved selectively would lead to elaborated arenes or arenesilanols, respectively.

In order to determine the feasibility of such a linker, we first wished to establish if an aryl moiety attached to a silane ether could be further derivatized[9] and, if so, if the aromatic silicon−carbon bond could then be cleaved under mild conditions in preference to the silicon−oxygen bond. Toward this end, a solution-phase model study was initiated for the synthesis of the 3-arylbenzofuran **11** (Scheme 1), representative of a venerable ring system in natural products and synthetic chemistry with broad pharmacological activity.[10] Thus, the known MOM-protected *p*-bromophenol **1**[11] was subjected to lithium−halogen exchange to generate the protected *p*-lithiobenzene derivative that was then quenched with dichlorodiisoproplysilane to provide the arylchlorosilane **2**. The bulky diisopropylsilane was chosen to impart added stability to the silyl ether. Benzyl alcohol served as a surrogate for polystyrene hydroxymethyl resin. Formation of the silyl ether **4** was then completed under standard conditions.[7] Functionalization of silyl ether **4** to pivotal intermediate **5** was achieved by an *ortho*-directed metalation.[12] Thus, lithiation of **4** with *n*-BuLi in Et_2O/TMEDA followed by quenching with DMF gave the aromatic aldehyde **5** in 61% yield. As the addition of nucleophiles to aldehyde **5** would create a site of diversity in the molecule, we explored this reaction by the addition of *p*-lithioanisole anion (*p*-bromoanisole, *n*-BuLi, THF, −78 °C) to an ice-cold solution of aldehyde **5** to give the benzhydrol derivative **6** in excellent yield. Alternatively, **6** could be made in high yield by reaction of *ortho*-lithiated **4** with *p*-anisaldehyde. Alcohol **6** was then oxidized to the ketone **7** using the highly versatile Dess−Martin-type reagent, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (IBX),[13] which is easily prepared and tolerant of air and moisture.

A second site of diversity was generated by treating ketone **7** with 5% TFA in CH_2Cl_2 at 0 °C to provide phenol **8**. This was then alkylated with *tert*-butyl α-bromo ketone at 80 °C in NMP catalyzed by Hunig's base to give the diketone **9**. Cyclization to the benzofuran **10** was carried out with DBU in NMP at 80 °C. When benzofuran **10** was subjected to standard proto-*ipso*desilylation conditions (TFA),[14] the corresponding silanol was isolated resulting from cleavage of the silicon−oxygen bond, indicating that these conditions were not suitable to cleave the aryl silicon−carbon bond. However, the ap-

[†] Present address: G.D. Searle-Monsanto, St. Louis, MO.

* To whom correspondence should be addressed. Phone: (313)996-7028. Fax: (313)996-7879. E-mail: Showalh@aa.wl.com.

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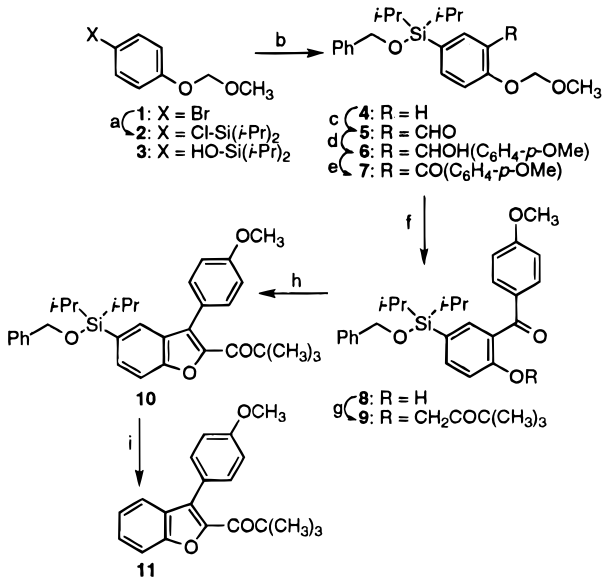
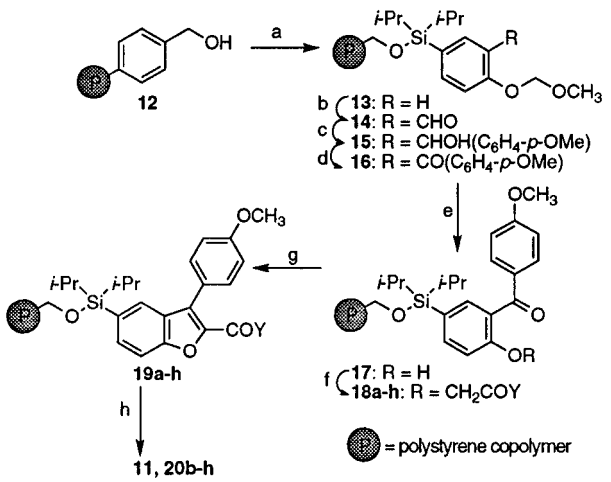
Scheme 1[a]



[a] Key: (a) (i) *n*-BuLi, THF, −78 °C, (ii) $(Cl)_2Si(i\text{-}Pr)_2$, −78 °C to rt, 71%; (b) benzyl alcohol, imidazole, DMF, rt, 91%; (c) (i) *n*-BuLi, TMEDA, Et_2O, 0 °C, (ii) anhydrous DMF, 0 °C, 61%; (d) 4-bromoanisole, *n*-BuLi, THF, −78 °C, 90%; (e) 1-hydroxy-1,2-benziodoxol-3(1*H*)-one, DMSO/THF, rt, 93%; (f) 5% TFA in CH_2Cl_2, 0 °C, 88%; (g) $BrCH_2COC(CH_3)_3$, $(i\text{-}Pr)_2NEt$, NMP, 80 °C, 88%; (h) DBU, NMP, 80 °C, 90%; (i) TBAF, DMF, 65 °C, 92%.

Scheme 2[a]



[a] Key: (a) **2**, imidazole, DMF, rt; (b) (i) *n*-BuLi, TMEDA, Et_2O, 0 °C, (ii) anhydrous DMF, 0 °C; (c) 4-bromoanisole, *n*-BuLi, THF, −78 °C; (d) 1-hydroxy-1,2-benziodoxol-3(1*H*)-one, DMSO/THF, rt; (e) 5% TFA in CH_2Cl_2, 0 °C; (f) $BrCH_2COY$, $(i\text{-}Pr)_2NEt$, NMP, 80 °C; (g) DBU, NMP, 80 °C; (h) TBAF, DMF, 65 °C.

plication of Stork's method[15] of fluoride-induced hydrodesilylation of a siloxane (TBAF in DMF at 60 °C) to silyl ether **10** provided the desired derivative **11** in excellent yield.

The established solution-phase protocols were then applied to the solid phase (Scheme 2). Polystyrene hydroxymethyl resin **12** was treated with chlorosilane **2** and imidazole in DMF to give resin-bound silyl ether **13**. Resin **13** was resubjected to the above reaction conditions in order to maximize the loading.[16] Resin-bound silyl ether **13** was then subjected to *ortho*-lithiation followed by quenching with DMF to give the resin-bound aldehyde **14**. *p*-Lithioanisole, generated as in the solution studies, was added to a suspension of resin **14** at 0 °C to give resin-bound benzhydrol **15**. Oxidation of this with IBX in DMSO/THF provided resin-bound MOM-ether **16**, which was cleaved with 5% TFA in CH_2Cl_2 to give the resin-bound phenol **17**. A number of resin-bound diketones **18a**−**h** were synthesized by treating this phenol with a variety of α-bromoketones in the presence of Hunig's base in NMP at 80 °C. These were then cyclized to the resin-bound benzofurans **19a**−**h** by reaction with DBU in NMP at 80 °C for 1 h. The resin-bound benzofurans were cleaved from the solid support by reaction with TBAF in DMF at 65 °C for 1 h. Following an aqueous workup and filtration through a plug of basic Al_2O_3, the benzofurans **11** and **20b**−**h** (except **20c** and **g**) were isolated in good yields and high purity (Table 1). The general efficiency of the solid-phase synthesis is attested to by a comparison of the overall yield of **11** (40% and 57%, respectively) derived from a common solution or resin-bound intermediate (**4** and **13**, respectively). Little or no product was isolated when phenol resin **17** was treated with α-bromo *o*-methoxyphenyl ketone or α-bromo *p*-cyanophenyl ketone.

Table 1. Synthesized Benzofurans[a]

compd	**17** (mg)	Y	yield (mg)
11	209	$C(CH_3)_3$	24
20b[b]	100	C_6H_5	4.0
20c[b]	100	C_6H_4(*o*-OMe)	0.0
20d[b]	100	C_6H_4(*m*-OMe)	4.0
20e[b]	100	C_6H_4(*p*-OMe)	6.0
20f[b]	100	C_6H_4(*p*-Cl)	4.0
20g[b]	100	C_6H_4(*p*-CN)	0.0
20h[b]	100	C_6H_4(*p*-CF_3)	8.0

[a] Yields are for unpurified products. [b] Reactions were carried out in a Diversomer 8-pin synthesizer. Phenol **17** was reacted with α-bromo ketones (3.0 mmol) and Hunig's base (3.5 mmol). The resulting diketones **18a**−**h** were cyclized with DBU (3.0 mmol), and the resin-bound benzofurans were cleaved using TBAF (1.0 mmol) in DMF.

In conclusion, we have developed a simple, silicon-based solid-phase traceless linker that is readily formed from commercially available starting materials and that is stable to a variety of reaction conditions. In addition, the silicon−carbon or silicon−oxygen bonds can be selectively cleaved to their respective products under mild reaction conditions. We currently are expanding this chemistry to include the synthesis of heteroarylsilane ether linkers and to cleave the linker silicon−carbon bond with a range of common electrophiles.[17]

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Supporting Information Available: Experimental details and characterization are available for all compounds (34 pages).

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(16) The substitution level was determined by treating the solid support with TBAF in THF at room temperature for 24 h, which resulted in cleavage of the silicon−oxygen bond. On the basis of the mass of the recovered silanol **3**, the resin loading was determined to be 0.72 mmol/g.

(17) Treatment of **10** with excess Br_2 in CH_2Cl_2 at 0 °C provided a 76% yield of a 1:1 mixture of the desired compound, 1-[5-bromo-3-(4-methoxyphenyl)benzofuran-2-yl]-2,2-dimethylpropan-1-one, as well as 1-[5-bromo-3-(3-bromo-4-methoxyphenyl)benzofuran-2-yl]-2,2-dimethylpropan-1-one resulting from a second bromination of the 3-aryl substituent.