A Silicon-Based Linker for Traceless Solid-Phase Synthesis[1]

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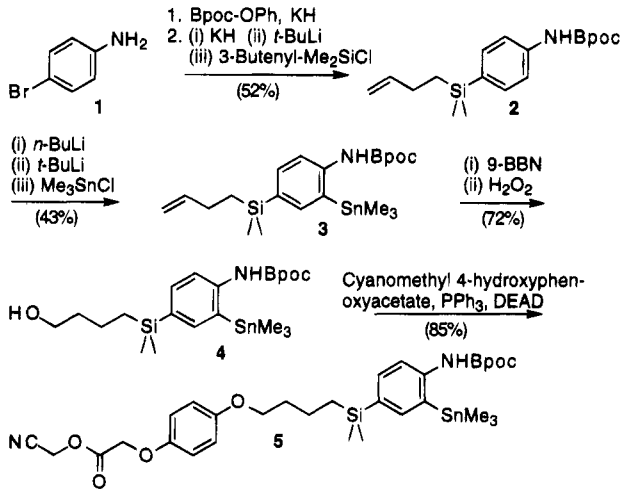
The combinatorial library approach is finding increasing use for the discovery of new molecules with a desired property.[2] Most of the organic chemical libraries synthesized to date have been constructed using solid-phase methods. A key aspect of any solid-phase synthesis strategy is the linkage element, which acts as a tether to the polymeric support material. Ideally, the linker should be stable to all reactions used in a synthesis sequence and should be cleaved quantitatively under conditions that do not degrade the desired target molecule.

Linkage strategies may be roughly grouped into three categories. The first strategy is to link through functionality already present in the desired target molecule, such as in peptide and oligonucleotide synthesis. The second approach is a cyclative cleavage whereby the linking functional group is somehow incorporated into the final molecule.[3] In many cases the previous two methods may not be applicable to a desired compound class or may limit the chemistry that can be performed. Therefore, the third and more general synthesis strategy is the introduction of an auxiliary functional group (such as a phenol, amide, or carboxylate) as a handle for linker attachment. After cleavage from the solid support at the end of a synthesis sequence, this functional group can have a negligible, positive, or negative effect on the biological or chemical activity of the target molecule, depending on where it is situated. An alternate approach is linkage through a functional group that can be excised efficiently and quantitatively when desired, leaving behind no trace or "memory" of the solid-phase synthesis. For aromatic compounds, we envision that linkage through a silicon–aryl bond would fulfill these requirements. This type of bond is often cleaved using acidic conditions, and the effect of aromatic substitution[4] and silicon substituents[5] on reaction rate has been studied extensively. The lability of aryl-silicon bonds to fluoride ion[6] is also well documented.

We have previously developed a method for the solid-phase synthesis of chemically diverse 1,4-benzodiazepine derivatives.[7] The benzodiazepine derivatives are synthesized from a support-bound, protected (aminoaryl)-stannane and three variable components: acid chlorides, Fmoc-amino acids, and alkylating agents. The synthesis sequence includes transition-metal-catalyzed bond formation, an acylation, and acidic and basic reaction conditions. Therefore, we felt that the solid-phase synthesis of this class of pharmaceutically important molecules would be an ideal test of a silicon-based linkage strategy, and adaptation of our solid-phase benzodiazepine synthesis for a silyl-based linkage was undertaken.

Scheme 1



The synthesis of an appropriately functionalized silicon-containing (aminoaryl)stannane is shown in Scheme 1. Synthesis was initiated with protection of 4-bromoaniline (**1**) using the 2-(4-biphenylyl)isopropyloxycarbonyl (Bpoc) group.[8] The reduced basicity of the aniline (compared to an aliphatic amine), and the thermal instability of the Bpoc reagent, required the use of potassium hydride to generate the anilide anion, which then adds rapidly to biphenylylisopropyl phenyl carbonate. Carbamate deprotonation with potassium hydride, lithium–halogen exchange with *tert*-butyl lithium,[9] and quenching with 3-butenylchlorodimethylsilane[10] gave the protected arylsilane **2** in high yield. The stannane was introduced using the directed ortho-metalation reaction followed by addition of trimethyltin chloride.[11] Hydroboration of the resulting arylstannane **3** with 9-BBN and an oxidative workup with basic peroxide[12] provided the primary alcohol **4**. Mitsunobu reaction[13] of this alcohol with the cyanomethyl ester of 4-hydroxyphenoxyacetic acid afforded the preactivated ester derivative **5** in good yield. Use of the cyanomethyl ester eliminates a saponification step from the synthesis sequence and also minimizes exposure of the acid-sensitive arylstannane to the free phenoxyacetic acid and to the acidic coupling additives that are often used for amide bond formation.

Solid-phase synthesis (Scheme 2) is initiated with acylation of **5** onto (aminomethyl)polystyrene resin using DMAP and *i*-Pr_2EtN.[14] Stille coupling reactions of stannane **6** (the linker has been omitted for clarity) with both aromatic and aliphatic acid chlorides are performed using

(1) A preliminary account was presented at the 209th American Chemical Society National Meeting, Anaheim, CA, April, 1995; Abstract ORGN 267.

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(5) Bott, R. W.; Eaborn, C.; Jackson, P. M. *J. Organomet. Chem.* **1967**, *7*, 79–83.

(6) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372–4385.

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(9) KH is necessary because lithium–halogen exchange competes with proton transfer: Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110.

(10) Steinmetz, M. G.; Yu, C. *J. Org. Chem.* **1992**, *57*, 3107–3120.

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(13) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *42*, 335–656.

(14) The active ester derived from 4-hydroxyphenylacetic acid acylates at least 10-fold more slowly under these conditions, perhaps due to reduced electrophilicity of the carbonyl carbon.

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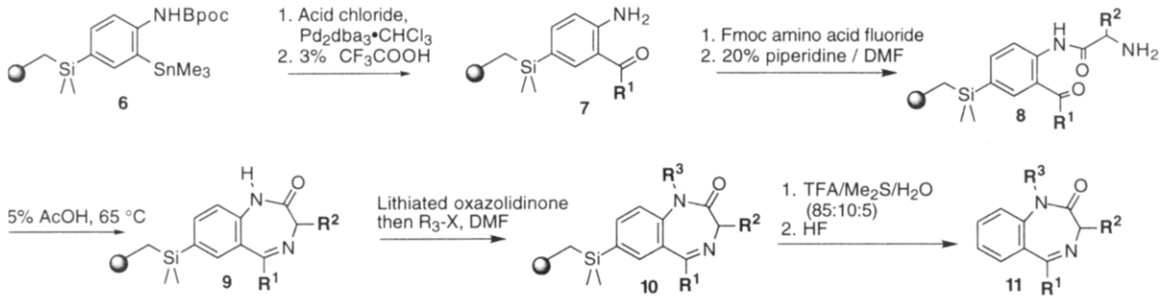
Scheme 2



the ligandless catalyst Pd_2dba_3·$CHCl_3$. The Bpoc protecting group is removed by brief treatment with 3% trifluoroacetic acid in CH_2Cl_2 to give 2-aminoaryl ketone **7**. This compound is acylated with an α-*N*-Fmoc-amino acid fluoride,[15] and the protecting group is removed with 20% piperidine in DMF to give **8**. This intermediate is cyclized with mild acidic catalysis at 65 °C to afford support-bound benzodiazepine derivative **9**. Deprotonation and alkylation gives the fully functionalized derivative **10**. Any amino acid side chain protecting groups are then removed by treatment of **10** with trifluoroacetic acid/dimethyl sulfide/water. The silicon−aryl bond is stable to these conditions because of the extremely electron-poor nature of the protonated benzodiazepine. The aryl−silicon bond is cleaved with anhydrous HF to give the product benzodiazepines **11**.[16]

Using this general route we have synthesized several derivatives **11a**−**d**, shown in Table 1. These compounds incorporate amide, phenol, ether, aromatic, and alkyl functionality. Cleavage with HF will present problems with certain functional groups, such as the debenzylation side product seen with compound **11c**. However, the commonly used cleavage reagent trifluoroacetic acid should suffice for most classes of aromatic compounds.[17]

In conclusion, we have developed a novel linker for solid-phase organic synthesis of aromatic compounds and have successfully demonstrated its application in the synthesis of several members of a class of functionalized heterocyclic structures. Currently, we are investigating other electrophile-induced desilations and are exploring different metal-based linkage strategies for increased lability of electron-poor aromatic compounds.[18]

Table 1. Structures and Yields of 1,4-Benzodiazepine Derivatives[a]

compd	R^1	R^2	R^3	% yield
11a	3-MeO-C_6H_4	$-CH_2CH(CH_3)_2$	$-CH_2CH_3$	66
11b	1-adamantyl	$-CH_2CH(CH_3)_2$	$-CH_2CH_3$	60
11c	$-C_6H_5$	$-CH_2C_6H_4OH$	$-CH_2C_6H_5$	50[b]
11d[c]	4-MeO-C_6H_4	$-CH_3$	$-H$	68

[a] The yields above are based on the initial aminomethyl substitution level of the polystyrene resin. If based upon the loading level of the protected (aminoaryl)stannane, the yields are higher by approximately 10%, since the loading to give **6** was not quantitative. After acylation of **5**, the unacylated aminomethyl groups were capped using Fmoc-alanine, HOBt, and diisopropylcarbodiimide. Fmoc quantitation then gives the percent unreacted aminomethyl groups. [b] The debenzylated product was also obtained in 11% yield. [c] This compound was prepared from the allyl-derived linker described in ref 16.

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Supporting Information Available: Experimental details for the synthesis and characterization of all compounds (6 pages).

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