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Protodetachable Arylsilane Polymer Linkages for Use in Solid Phase Organic Synthesis

Balan Chenera, Joseph A. Finkelstein, and Daniel F. Veber*

Department of Medicinal Chemistry
SmithKline Beecham Pharmaceuticals, 709 Swedeland Road
King of Prussia, Pennsylvania 19406

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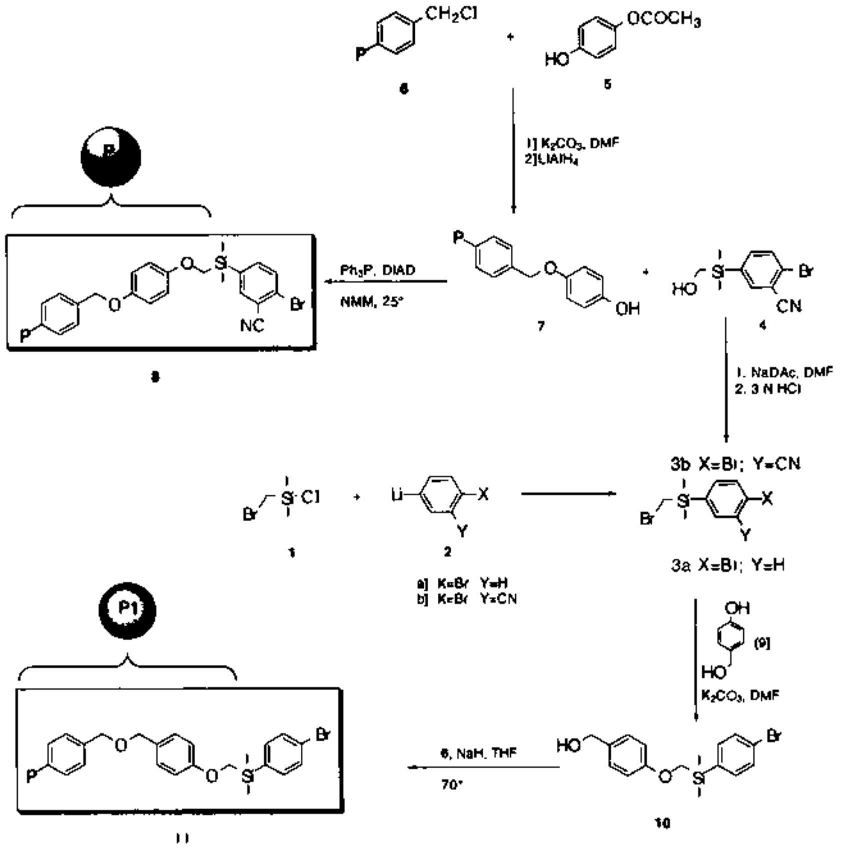
The synthesis of peptides attached to a polymeric support by a detachable covalent linkage has significantly improved both efficiency and speed of preparation for even the most complex members of this compound class.[1] Aside from varied forms of repetitive oligomer synthesis, little use has been made of this powerful technique as a general approach for organic synthesis. The development of combinatorial approaches for the synthesis of compound "libraries" bound to polymer beads[2] has raised interest in broader applications.

Detachable polymer linkages are widely available which release the diversity of functional groups common to biopolymers. Normally, release results in a hydrogen attached to a heteroatom such as nitrogen, oxygen, or sulfur to produce amines, amides, alcohols, acids, mercaptans, and the like. A highly desirable alternative linker would be capable of product release with formation of a carbon−hydrogen bond in place of the resin attachment. Reductive cleavage of a benzyl ether linkage in one or two steps has been applied to produce *p*-tolyl derivatives on release from resin.[3] We report here novel arylsilane resin linkers which generate an unsubstituted aryl ring on cleavage with either trifluoroacetic acid[4] or CsF[5] in DMF or with liquid HF. The cleavage conditions are mild enough to allow synthesis of diverse chemically sensitive molecules, while the linkage is sufficiently robust to withstand a broad range of complex synthetic methodology. Although an alternate silane resin linker has been reported, its use has been directed at protection and release of a hydroxy group in carbohydrate synthesis.[6]

Commercially available (bromomethyl)chlorodimethylsilane (**1**) has served as a key common reagent for producing arylsilane resin attachments as outlined in Scheme 1. *p*-Lithiobromobenzene (**2a**) (generated by reacting *p*-dibromobenzene at low temperature with *n*-butyllithium)[7] cleanly reacts with **1** to give *p*-[(bromomethyl)dimethylsilyl]bromobenzene (**3a**), which is then used to alkylate *p*-hydroxybenzyl alcohol **9**. The resulting benzyl alcohol **10** is then attached to 1% cross-linked chloromethylated polystyrene[8] mediated by sodium hydride in DMF. This pathway was found to give the highest silane incorporation as inferred from bromine analysis of resin products compared to several other linkage pathways that were tried. In contrast to the use of **3a**, the chemical instability of **3b** results in poor silane incorporation when the same pathway is followed. A high-yield alternative is shown in Scheme 1 (upper sequence). Mitsunobu chemistry[9] using alcohol **4** proceeds cleanly when applied to the novel catechol-derived polymer **7**. The two silane-linked phenyl bromides, **8** and **11** have served as the basis for further model chemistry.

Scheme 1



Lithium−halogen exchange with excess butyllithium in THF at −78 °C is complete after 5 h with resin **8**. At shorter times residual bromine can be detected by elemental analysis and the Beilstein test. At higher temperatures (−30 °C and above) lower yields have been observed for subsequent steps. The polymer-bound organolithiums have proven to be highly versatile intermediates, undergoing much of the known chemistry for this type of compound. Acylation and carbonylation are facile and proceed in high yield. Release of benzophenone derivatives and benzaldehyde after acidolysis also proceeds in high yield (details to be reported elsewhere). The Suzuki coupling has been reported to proceed cleanly on solid support for other aryl bromides.[10] We have found both **8** and **11** to be useful substrates in this reaction and have used the reaction to initiate the four- and five-step sequences of Scheme 2. Both resin bromides (**8** and **11**) undergo facile palladium-catalyzed coupling with (*p*-formylphenyl)boronic acid to give the resin-bound biphenyl aldehydes (**13a** and **13b**). The reaction proceeds to completion in 16 h and can be followed using FT-IR to monitor aldehyde incorporation to the resin. PMR of the resin-bound products using the technique of "magic angle spinning" (MAS)[11] confirms the conversion to resin-bound biphenyl aldehyde. Further elaboration of the aldehydes (**13a, 13b**) is exemplified by Schiff base formation[12] with benzylamine (reaction monitored by FT-IR; formation of C=N absorption at 1640 cm^{-1} with the disappearance of C=O absorption at 1700 cm^{-1}). Both Schiff bases are fully reduced by sodium triacetoxyborohydride in dichloromethane to give **14**a and **14b**. Again the reaction can be monitored by FT-IR and the products analyzed by PMR (magic angle). It was also found that the Schiff base produced from **13a** underwent smooth addition of allylmagnesium bromide in 1:1 toluene/diethyl ether to yield the adduct **16**.

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(8) Commercially available 100−200 mesh chloromethyl polystyrene with a loading of 1.24 mequiv/g (Advanced ChemTech) has been further size separated using a continuous flow flotation technique in toluene to obtain beads of average size between 90 and 105 μm. The low contamination with small resin beads facilitates single-bead analysis of any given active component when used in the preparation of combinatorial libraries.

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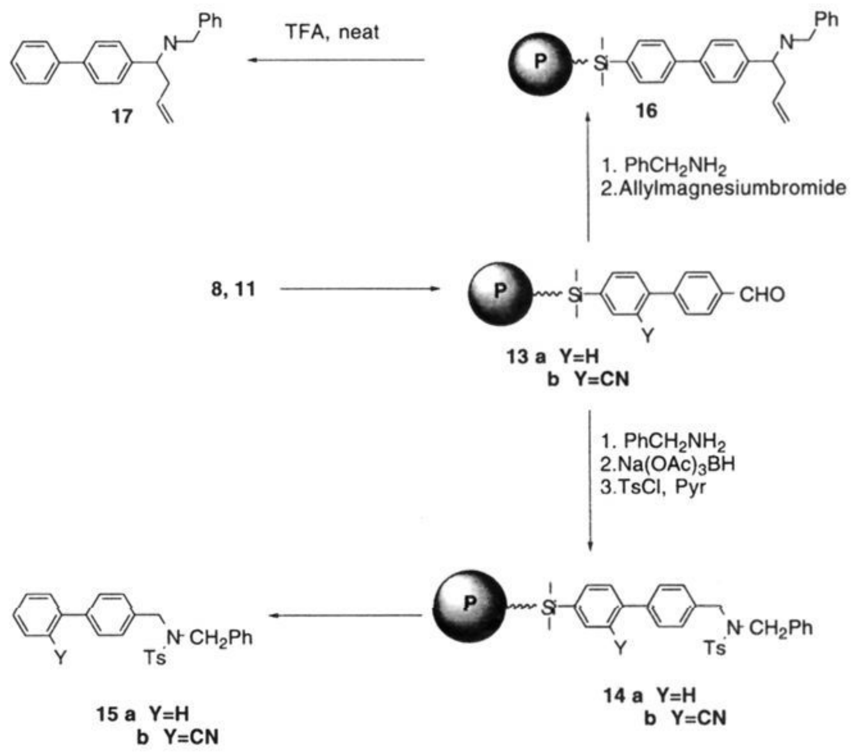
Table 1

substrate	cleavage conditions	product	yield,[a] %
13a	TFA, neat, 25 °C	4-formylbiphenyl	70
13a	CsF, 4:1 DMF−water, 110 °C	4-formylbiphenyl	67
13b	TFA, neat, 25 °C	no reaction	0
13b	CsF, 4:1 DMF−water, 110 °C	*o*-cyano-4-formylbiphenyl	66
16	TFA, neat	**17**	79
14b	TFA, neat, 25 °C	no reaction	0
14b	CsF, DMF, water, 105 °C	**15b**	78
14a	TFA	**15a**	60

[a] Yield based on the weight of isolated product related to the initial loading of the resin-bound silanes **8** and **11** as inferred from elemental analysis.

Scheme 2



Cleavage of the aryl−silicon linkage has been evaluated under various conditions as outlined in Table 1. In the case of **13a**, protodesilylation proceeded smoothly to provide the expected 4-formylbiphenyl in 70% overall yield based on **11**. An isotope effect of 5.2 was observed for the cleavage of the biphenyl derivative **16** in CF_3COOH vs CF_3COOD. This value is in close agreement with the solution phase cleavage of various arylsilanes[13] and indicates that the mechanism of protodesilylation is unaltered by the polymer support. Attempted protodesilylation of **13b** (Y = CN) under similar conditions resulted in full recovery of the resin-bound aldehyde.[14] We attribute desilylation failure to the presence of a strong electron-withdrawing group (nitrile or protonated nitrile) in the phenyl ring that prevents the formation of the ipso-substituted intermediate needed to generate a carbonium ion β to the silicon moiety.

For molecules that possess electron-withdrawing groups, base-catalyzed removal of silicon groups has been suggested for protodesilylation.[15] However, these resin-bound silanes have been found to be inert to the base-catalyzed cleavage reaction. In cases where the removal of silane was unsuccessful with TFA, fluoride has proven to be an effective catalyst. Thus, addition of tetrabutylammonium fluoride to the unsuccessful TFA cleavage of **13b** results in good cleavage. Even under neutral conditions fluoride is an effective agent for protodesilylation. Thus, upon reaction of **13b** with cesium fluoride in DMF−water at 100 °C, *o*-cyanobiphenylcarboxaldehyde was released cleanly. This method of cleavage was found to be very efficient on other substrates also. Liquid hydrogen fluoride has proven to be an effective protodesilylating agent but is not applicable to the products described here because of the other cleavable linkages in the products. It is noteworthy that the five-step sequential syntheses of **15a** and **15b** proceed to isolated yields of 60% and 78%, respectively.

Other reaction sequences have been used to produce phenyl-substituted acrylates and methyl vinyl ketone derivatives as well as *phenyl-substituted furan derivatives. In all cases it has been* possible to cause protodesilylation in high yield using the conditions of Table 1 except that water and dimethyl sulfide are required as scavengers in TFA when furan is present in the product. In summary, a wide range of substituents either meta or para to the silyl resin attachments have been utilized and the desired phenyl derivatives have been released in high yield.

These preliminary studies indicate the potential of arylsilane linkages for the solid phase synthesis of molecules having phenyl rings lacking polar heteroatom substituents. The common occurrence of unsubstituted phenyl rings as a pharmacophore in bioactive molecules suggests a high level of utility for large scale synthesis either of single molecules or of bead-bound combinatorial libraries for high-throughput drug screening.

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Supporting Information Available: Experimental details for the preparation of **3a,b**, **4**, **7**, **8**, **10**, **11**, **13a,b**, **14a,b**, **15a,b**, **16**, and **17** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[14] Normal cleavage from TFA results in a slight red color change in all the cases that produce the expected product probably due to cation formation. No color change was observed during the attempted cleavage of **13b**.

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