A Silicon Linker for Direct Loading of Aromatic Compounds to Supports. Traceless Synthesis of Pyridine-Based Tricyclics

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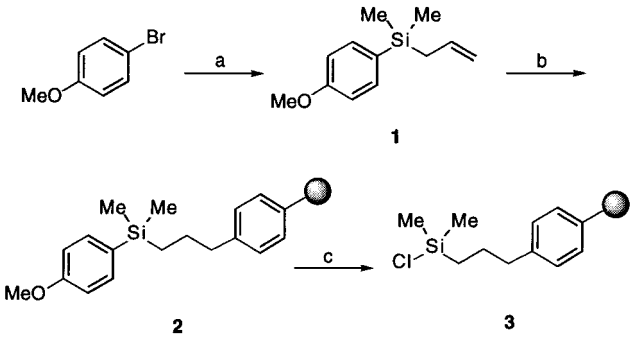
Two years ago we reported a silicon-based linkage strategy to attach aromatic and heteroaromatic compounds to solid supports.[1] Cleavage of synthesis products from the support by protodesilylation leaves no residual functionality on the product, i.e., leaves no trace that synthesis was performed on a solid support. Subsequently, several additional reports appeared describing the application of silicon-based linkers for the traceless synthesis of aromatic compounds.[2,3] A serious limitation of all of the published approaches is the use of preformed handle strategies, whereby the starting material is first attached to the silicon linker, and then the linker is attached to the solid support. Herein, we report the first general method for the *direct* loading of aromatic compounds onto a silyl-substituted support. The utility of the approach is demonstrated by the solid-phase synthesis of pyridine-based tricyclics. Members of this important class of heterocycles have diverse therapeutic activities. For example, nevirapine is an HIV-1 reverse transcriptase inhibitor[4] and pirenzepine is the prototypical M_1-selective antimuscarinic for ulcer treatment.[5]

Frechet first reported the preparation of silyl chloride substituted polystyrene−divinylbenzene resins by lithiation of the phenyl rings followed by reaction with dialkyldichlorosilanes.[6] These silyl-substituted resins have since been employed by a number of researchers for the preparation of silyl ether based linkages.[7] Unfortunately, these resins generally cannot be used to link aromatic or heteroaromatic compounds to supports because protodesilylation will result in cleavage of the silyl group not only from the aromatic compound, but also from the phenyl ring of the support. We have therefore developed a linkage strategy in which the silyl group is attached to the support through a stable aliphatic tether (Scheme 1).

Silane **1** is isolated in quantitative yield by generation of (4-methoxyphenyl)lithium followed by addition to allyldimethylsilyl chloride. Hydroboration of silane **1** followed by in situ Suzuki coupling[8] with bromophenyl-substituted resin[6] directly provides silyl-derivatized resin **2**. Activation to provide silyl chloride resin **3** is accomplished prior to use simply by brief exposure to an HCl solution in CH_2Cl_2. Use of masked silyl resin **2** has two important advantages over methods for the direct preparation of silyl chloride resins. First, silyl resin **2** is stable and can be stored indefinitely. We and others have observed that support-bound silyl chlorides, particularly support-bound dimethylsilyl chlorides, are highly water sensitive and cannot be stored for prolonged periods.[7a] Second, the loading level of the resin **2** can rapidly be

Scheme 1[a]



[a] *n*-Butyllithium, THF, then allyldimethylsilyl chloride; (b) 9-BBN, THF, then bromo-substituted polystyrene−1% divinylbenzene, $Pd(PPh_3)_4$, Na_2CO_3; (c) HCl, CH_2Cl_2.

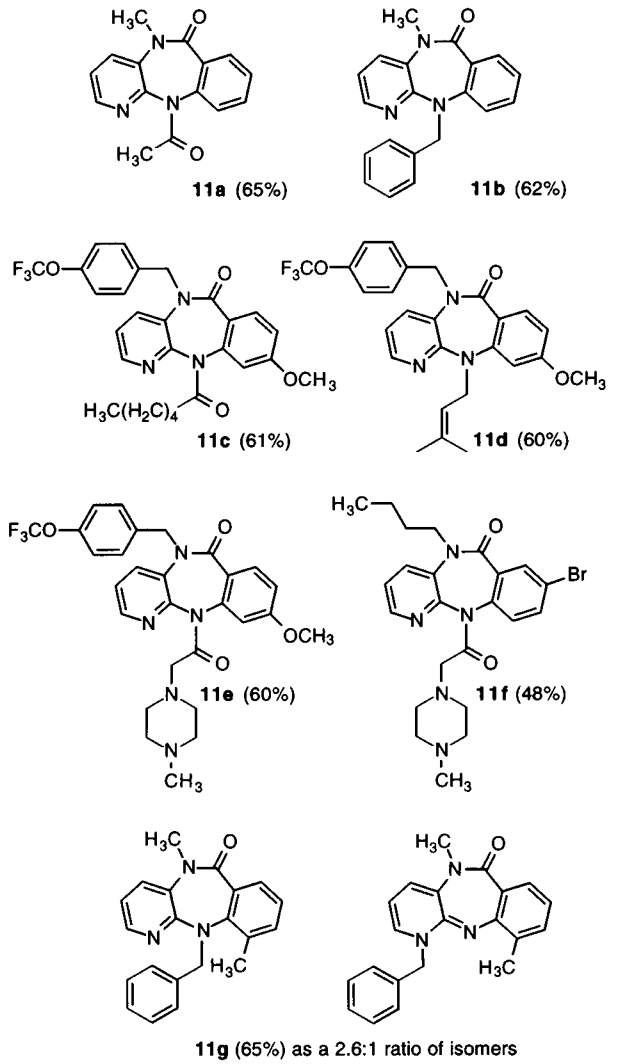


Figure 1.

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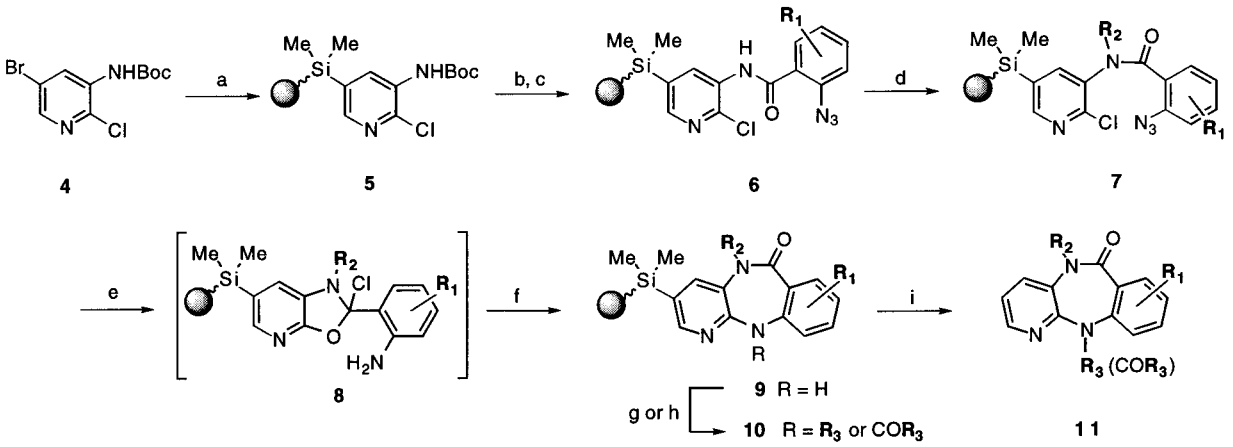
Scheme 2



[a] (a) KH (1 equiv) in THF, then *t*-BuLi (2 equiv), then silyl resin **3**; (b) 85% trifluoroacetic acid in CH_2Cl_2; (c) 2-azidobenzoyl chloride in 9:1 CH_2Cl_2/pyridine; (d) lithiated acetanilide in THF, then R_2X; (e) $SnCl_2$/PhSH/Et_3N (1:4:5) in CH_2Cl_2; (f) 7:2:1 DMF/TFA/HO; (g) lithiated *N*-*tert*-butylbenzamide in THF, then R_3X or $(R_3CO)_2O$; (h) chloroacetyl chloride, Et_3N in dioxane, then *N*-methylpyrazine, CH_2Cl_2; (i) Bu_4NF in THF.

determined simply by treating a sample of the resin with Br_2 in CH_2Cl_2 followed by filtration, concentration, and mass balance of the 4-bromoanisole product.[9] To test the linkage strategy, 6-methoxy-2-naphthyllithium was added to activated silyl resin **3**. Cleavage from support with HCl in CH_2Cl_2 provided the expected 6-methoxynaphthalene product in pure form. The efficiency of loading was 86% based upon the initial bromine substitution level of the resin.

The utility of the silyl linkage strategy was demonstrated by the preparation of pyridine-based tricyclics **11** (Scheme 2). Synthesis is initiated by deprotonation of the *N*-Boc 3-amino-2-chloropyridine **4**[10] with KH followed by halogen metal exchange and addition to silyl resin **3**. Treatment of support-bound pyridine **5** with trifluoroacetic acid results in removal of the Boc group without any protodetachment of the electron deficient pyridine intermediate. Addition of 2-azidobenzoyl chlorides in the presence of pyridine then provides the amide product **6**. Alkylation of the amide is performed using lithiated acetanilide as the base followed by addition of the alkylation agent. As previously reported,[11] lithiated acetanilide is sufficiently mild that esters, secondary amides, and secondary carbamates are not deprotonated and alkylated. We also evaluated DBU and Schwesinger phosphazene bases,[12] but incomplete alkylation was observed.

Reduction of the azide with a cocktail of thiophenol/$SnCl_2$/Et_3N (4:1:5) according to the conditions of Bartra and Vilarrasa[13] provides the 2-chlorooxazolidine intermediate **8**,[14,15] which upon exposure to acid rearranges to the pyridine-based tricyclic **9**. The final element of diversity is then introduced by alkylation or acylation of tricyclic **9**. Use of lithiated acetanilide as base did not result in complete alkylation at this site. We therefore employed the more basic lithiated *N*-*tert*-butylbenzamide. Addition of alkylating agents or symmetric anhydrides then provides the fully derivatized tricyclic **10**. Tricyclic **9** could also be acylated under milder conditions without the use of base by treatment with acid chlorides with heating. For example, acylation with chloroacetyl chloride followed by chloride displacement with *N*-methylpiperazine provides access to derivatives that incorporate the key piperazine pharmacophore of pirenzepine (see **11e** and **11f** in Figure 1). Cleavage from support is accomplished by treatment with Bu_4NF in THF at room temperature for 2 h. The yields for representative compounds prepared according to this synthesis sequence are provided in Figure 1.

In conclusion, a silyl linker for the *direct* loading of aromatic and heteroaromatic compounds onto support has been developed. As demonstrated for the therapeutically important class of pyridine-based tricyclics, the linker should have broad utility for the traceless solid-phase synthesis of many different compound classes.

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Supporting Information Available: Experimental details for the synthesis and characterization of all compounds (7 pages).

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(9) The loading efficiency of **2** ranges from 85−95% based upon the bromine substitution level of the starting resin.

(10) Prepared in three steps from commercially available 2-amino-5-bromo-3-nitropyridine (see Supporting Information).

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(15) The 2-chlorooxazolidine intermediate can be isolated by treatment of **8** with Bu_4NF. The corresponding solution-phase azide reduction also provides 2-chlorooxazolidine intermediates.