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An efficient synthesis of polymer-supported silyl linkers using a di-Grignard reagent

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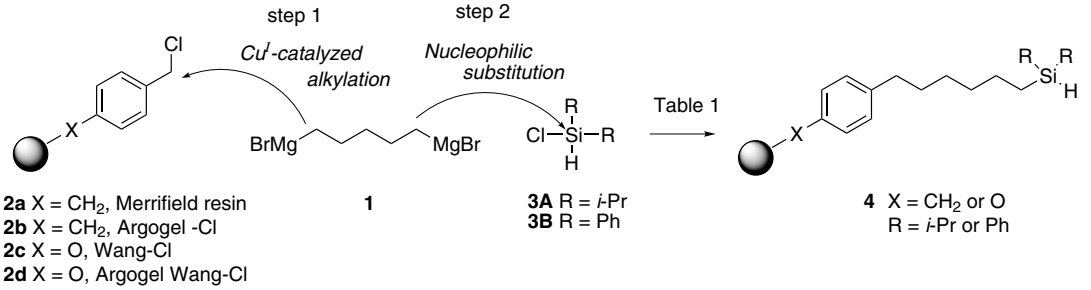
Abstract—Various trialkylsilyl linked polymer supports have been prepared by reacting benzyl chloride resin and a di-Grignard reagent with $CuBr{\cdot}Me_2S$, followed by dialkylchlorosilanes. 4-Alkoxybenzyl type resin, Wang-Cl **2c** and Argogel Wang-Cl **2d** provided **4c** and **4d** at ambient temperature, whereas nonactivated resin, Merrifield **2a** and Argogel-Cl **2b** afforded **4a** and **4b** at 60 °C. Primary and secondary alcohols **6**–**10** were attached to the alkyldiisopropyl-linked Wang type resin **4cA** by a novel dehydrosilation with $B(C_6F_5)_3$ as well as by conventional methods.

Solid-phase synthesis has recently been studied not only in the field of peptides and nucleotides but also for the combinatorial synthesis of small organic molecules.[1] Linkers that join synthetic compounds to the polymer support are particularly important for solid-phase synthesis[2] and their stability should be well tuned, as the linker has to be fully stable during all the reaction processes but should be removed without decomposition of the final products. Trialkylsilyl linkers are very useful in solid-phase synthesis. They can support alcohols, enolates, and aryl functionality, and their cleavage conditions are tunable by different alkyl substituents.[3–12] We have already reported on polymer-supported glycosylation[13] and the efficient solid-phase synthesis of libraries of enediyne–oligosaccharide hybrid compounds[14] and activated vitamin D_3 analogues[15] utilizing an alkyldiethylsilyl linker.[3] Depending on the sensitivities of polymer-supported compounds, the best combination should be selected between the linkers and the reaction conditions, that is, attachment of starting compound, diversity of the solid-phase reactions, and cleavage from the polymer support. To make this strategy successful, we require a range of silyl linkers on the appropriate polymer support. Here we wish to report an efficient synthesis of a variety of trialkylsilyl linkers on various polymer supports using sequential coupling of a di-Grignard reagent.

In order to introduce a variety of silyl linkers onto solid supports, we planned to utilize the di-Grignard reagent **1** as an alkyl spacer to connect the linkers to the polymer support as illustrated in Scheme 1. Since the



Scheme 1. Sequential coupling of di-Grignard reagent **1** to polymer-supported benzyl chlorides **2** and dialkylchlorosilanes **3**.

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polymer support acts like a bulky substituent, selective monoalkylation of the di-Grignard reagent **1** could be achieved using the polymer-bound benzyl halides **2**. Then, the second Grignard site of **1** can be utilized for the attachment of various dialkylchlorosilanes **3** to provide the desired **4**. As alkyldiethylsilane-supported polymer has been used for immobilization of alcohols,[3] the various trialkylsilanes **4** should be useful as linkers.

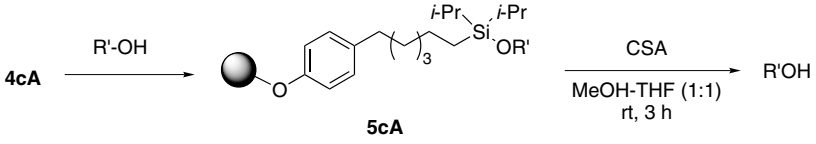
Pentane-1,5-di(magnesium bromide) (**1**) (12 equiv) was coupled to the Merrifield resin **2a**, Argogel-Cl resin **2b**, Wang-Cl resin **2c**, and Argogel Wang-Cl resin **2d** in the presence of $CuBr{\cdot}Me_2S$.[15,16] After simple filtration to remove excess of the di-Grignard reagent, the above resin was, respectively, treated with solutions of chlorodiisopropylsilane (**3A**, R = *i*-Pr) and chlorodiphenylsilane (**3B**, R = Ph) at ambient temperature, to provide **4**.[17] IR spectra of **4** indicated a Si–H absorption (2088–2094 cm^{-1}). The first coupling reactions did not proceed until 60 °C for **2a** and **2b**, whereas those did proceed at room temperature for **2c** and **2d**. It is conceivable that the 4-alkoxyl group employed as an electron donating group to stabilize the benzyl cation also accelerates the substitution of the chloride to achieve the alkylation under milder conditions. The loading amount of **4** was determined by chlorination,[3] attachment of *N*-Fmoc-2-aminoethanol, and Fmoc cleavage test.[18] The overall results are shown in Table 1.

Attachment of various alcohols **6**–**10** to the polymer support **4cA** was investigated by the following four methods: (A) via formation of chlorosilane,[3a] (B) via formation of silyl triflate,[3c] (C) dehydrosilation with Wilkinson catalyst,[3b,5] and (D) dehydrosilation with $B(C_6F_5)_3$.[19] The loading yields were determined by gravimetric analysis after acid cleavage from the corresponding resin **5cA** (Scheme 2 and Table 2). As has been reported, formation of the silyl triflate (method B) is very efficient to attach even hindered alcohols to the

Table 1. Loading of the polymer-supported trialkylsilanes **4**

Resin[a]	R	Temperature, °C	Product	Loading, mmol/g[b]	Yield, %
PS-Cl **2a**	*i*-Pr	60	**4aA**	0.64	54
PS-Cl **2a**	Ph	60	**4aB**	0.62	51
Argogel-Cl **2b**	*i*-Pr	60	**4bA**	0.29	69
Argogel-Cl **2b**	Ph	60	**4bB**	0.27	64
PS-Wang-Cl **2c**	*i*-Pr	25	**4cA**	0.66	79
PS-Wang-Cl **2c**	Ph	25	**4cB**	0.64	77
Argogel-Wang-Cl **2d**	*i*-Pr	25	**4dA**	0.31	74
Argogel-Wang-Cl **2d**	Ph	25	**4dB**	0.3	71

[a] Initial loading **2a** (1.2 mmol/g), **2b** (0.42 mmol/g), **2c** (0.83 mmol/g), **2d** (0.42 mmol/g).
[b] Loading was determined by Fmoc cleavage test after attachment of *N*-Fmoc-2-aminoethanol. Reagents and reaction conditions: (i) 1,3-dichloro-5,5-dimethylhydantoin/CH_2Cl_2/rt/30 min; (ii) *N*-Fmoc-2-aminoethanol/DIEA/DMAP/CH_2Cl_2/rt/12 h; (iii) 20% piperidine in DMF/rt/3 h. DIEA = diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine.



Scheme 2. Attachment of the various alcohols **6**–**10** to the polymer support **4cA**.

Table 2. Attachment of the various alcohols to diisoproylsilyl-bound polymer **4cA** by various methods[a]

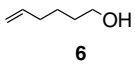
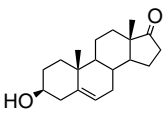
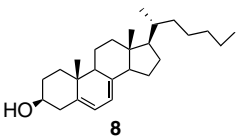
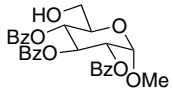
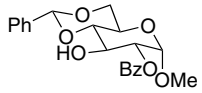
Substrate (R′OH)	Yield, %			
	Method A	Method B	Method C	Method D
 **6**	89	99	29[b]	78
 **7**	76	85	28[b]	61
 **8**	63	75	14[b]	73

Table 2 (*continued*)

Substrate (R′OH)	Yield, %			
	Method A	Method B	Method C	Method D
 **9**	51	73	57	38
 **10**	33	55	49	27

[a] Method A (i) 1,3-dichloro-5,5-dimethylhydantoin/CH_2Cl_2/rt/30 min, (ii) DIEA/DMAP/CH_2Cl_2/rt/12 h; Method B (i) TMSCl/CH_2Cl_2/rt/30 min, (ii) triflic acid/CH_2Cl_2/rt/30 min, (iii) DIEA/DMAP/CH_2Cl_2/rt/1 h; Method C $RhCl(PPh_3)_3$ (4 mol %)/*N*-methylpyrrolidone/65 °C/2 h; Method D $B(C_6F_5)_3$ (30 mol %)/CH_2Cl_2/35 °C/6 h.

[b] Hydrogenation of the alkene moiety was partially observed.

resin, and better than the formation of the corresponding chloride derivatives (method A). Dehydrosilation using Wilkinson catalyst is also known as a mild method for the one-step attachment of alcohols. However, as anticipated, hydrogenation of the alkene moiety of substrates **6**–**8** also proceeded resulting in low yields (method C). This problem was, however, resolved by utilization of $B(C_6F_5)_3$ (method D).[20] As Piers and co-workers have demonstrated, the dehydrosilation of alkenyl alcohols in solution phase,[19] the efficient coupling of **6**–**8** was accomplished at 35 °C in CH_2Cl_2 without loss of the alkene moieties, whereas the attachment of sugar derivatives **9** and **10** resulted in moderate yields.

In summary, we have demonstrated an efficient and general method for attachment of a variety of trialkylsilyl linkers to a variety of polymer supports. Attachment of various alcohol to the polymer-supported alkyldiisopropylsilane was achieved by a novel dehydrosilation with $B(C_6F_5)_3$ as well as by conventional methods. Utilization of the silyl linker prepared by the present method for selective capture of an activated previtamin D_3 derivative is reported in the subsequent paper.

Acknowledgement

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17. Experimental procedure: To a mixture of resin **2** (500 mg) and copper bromide dimethyl sulfide complex (1.2 equiv) in a 20 mL syringe-shaped vessel (Varian Reservoirs) was added pentane-1,5-di(magnesium bromide) (**1**) (12 equiv, Aldrich, 0.5 M solution in THF) at room temperature under argon. After being shaken for 30 min at room temperature for **2c** and **2d** and 2 h at 60 °C form for **2a** and **2b**, the reaction solution was filtered under argon. A solution of dialkylchlorosilane **3** (12 equiv) in dry THF (10 mL/mmol) was immediately added to the vessel at room temperature. After 3 h, the mixture was filtered. The resin was consecutively washed twice with THF (7 mL), aq

NH_4Cl–H_2O–CH_2Cl_2–EtOH (2:1:1:2, 7 mL), THF–H_2O (3:1, 7 mL), MeOH (7 mL), THF–H_2O (3:1, 7 mL), MeOH (7 mL), and Et_2O (7 mL) and was dried in vacuo for 12 h to afford the silyl-linked resin **4**.

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20. Experimental procedure: In a 5 mL syringe-shaped vessel (Varian Reservoirs) was placed the resin **4cA** (100 mg, 0.08 mmol) and pentafluorophenyl borane (129 mg, 0.24 mmol, 0.3 equiv), which was pre-dried under vacuum for 1 h. A solution of the alcohol (2.0 equiv, 0.16 mmol) in dry CH_2Cl_2 (15 mL/mmol, 1.2 mL) was added to the vessel at room temperature. After 6 h at 35 °C, the reaction solution was filtered and the resin was rinsed three times with CH_2Cl_2 (3 mL, 1 min) to recover the unreacted alcohol. The resin was consecutively washed twice with THF–H_2O (3:1, 3 mL), MeOH (3 mL), THF–H_2O (3:1, 3 mL), MeOH (3 mL), and Et_2O (3 mL) and was dried in vacuo for 12 h to afford the polymer-supported alcohol **5cA**. The polymer-supported alcohol **5cA** was treated with 0.26 mM (+)-camphorsulfonic acid solution in MeOH–THF (1:1, 2.0 mL) at room temperature. After 3 h at the same temperature, the mixture was filtered, and the resin was rinsed twice with ethyl acetate (3 mL, 1 min). The combined filtrate was washed with saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to afford the corresponding alcohol, which was purified through a short pad of silica gel.