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Novel silyl linkers for solid-phase synthesis

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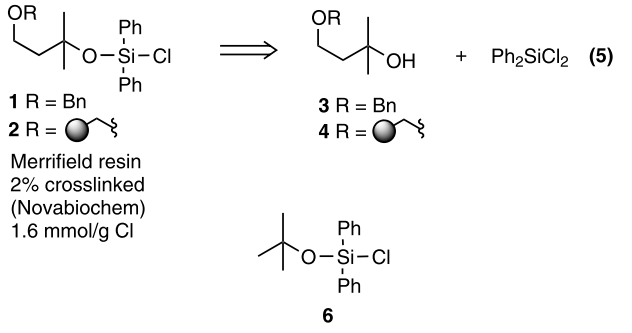
Abstract—The syntheses of two silyl chloride resins, **2** and **10** are described starting from Merrifield resin, 3-methyl-1,3-butanediol and diphenyldichlorosilane or dimethyldichlorosilane, respectively. The silyl chloride resin **2** was used for the attachment of 1° alcohols, 2° alcohols and phenols to the solid phase. A preliminary study of the stability of the diphenylsiloxane linker towards certain reaction conditions was also carried out. A more reactive silyl chloride resin **10** was found to be suitable for the attachment of 3° alcohols to the solid-phase.

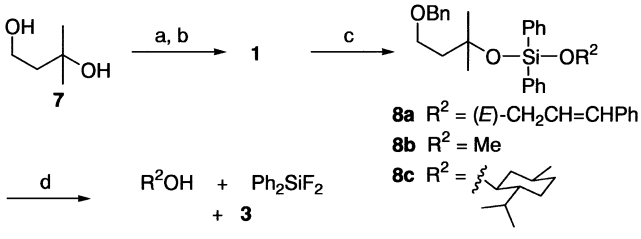
The use of the silicon linkers in solid-phase organic synthesis is well known,[1] both for the immobilisation of alcohols and for the 'traceless' release of unsaturated compounds.[2] We recently began to investigate the development of new silicon linkers, with the objective that their synthesis should be simple and use only cheap, readily available materials (Scheme 1). It was felt that the linker **2** based upon the *tert*-butoxydiphenylsilyl protecting group should satisfy the criteria outlined above, and that the corresponding siloxanes would display a good level of acid and base stability.[3] In addition, *tert*-butoxydiphenylsilyl chloride **6** is known to react readily with a variety of alcohols, including hindered tertiary alcohols, and that the resulting siloxanes are readily cleaved using a source of fluoride anion.[4]

Before attempting to prepare the chlorosilane resin **2**, model studies were carried out in solution to validate the chemistry (Scheme 2).

According to Scheme 2, 3-methyl-1,3-butanediol **7** was selectively benzylated prior to reaction with diphenyldichlorosilane **5**. The resulting chlorosiloxane **1** was quite stable, surviving TLC analysis and an aqueous workup, although **1** was routinely prepared in situ prior to use. Reaction with a number of 1° and 2° alcohols was investigated, leading to the formation of siloxanes **8a–c** in good yield (Table 1). Exposure of siloxanes **8a** and **8c** to TBAF resulted in rapid cleavage, returning the desired alcohols in excellent yields (98 and 94% for *trans*-cinnamyl alcohol and menthol, respectively). After the encouraging results obtained in the solution-phase model, attention was turned to the solid-phase chemistry. Attachment of 3-methyl-1,3-butane



Scheme 1. Approach to the synthesis of chlorosiloxanes **1** and **2**.



Scheme 2. *Reagents and conditions*: (a) NaH, DMF, 0°C, then BnCl; (b) Ph_2SiCl_2, Et_3N, DMAP, CH_2Cl_2, rt; (c) R^2OH, Et_3N, DMAP, CH_2Cl_2, rt; (d) TBAF, THF, rt.

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Table 1. Siloxanes derived from reaction between **1** and various alcohols

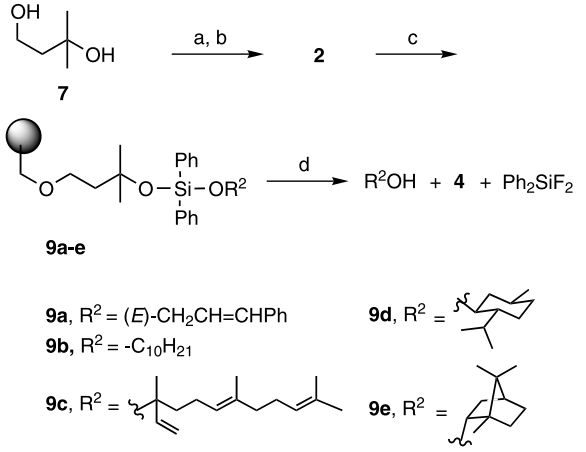
Siloxane	Reaction time (min)	Yield (%)[a]
8a	15	Quantitative
8b	10	90
8c	20	88

[a] Yields refer to siloxanes **8a–c** isolated after purification by flash column chromatography.

diol **7** to Merrifield resin (100–200 mesh, 2% crosslinked, loading 1.6 mmol/g, Novabiochem) with potassium *tert*-butoxide[5,6] under microwave irradiation, using a Personal Chemistry Smith Synthesiser, gave resin **4**. Subsequent reaction with diphenyldichlorosilane **5** afforded resin **2**,[7] which was coupled with a variety of alcohols to afford siloxanes **9a–e** (Scheme 3).[8] As anticipated, subsequent cleavage of siloxanes, with TBAF or KF in THF with 18-crown-6, returned the corresponding alcohols in good to excellent yields, apart from the hindered 3° alcohol nerolidol (Table 2).

To allow attachment of 3° alcohols, a less hindered silyl chloride resin **10** was prepared (Scheme 4). The loading of **10** (0.35 mmol/g) was somewhat lower than that of **2** (0.73 mmol/g), possibly due to crosslinking, although no evidence for this was seen in either ^{13}C or ^{29}Si NMR spectra of resin **11d**. 2° and 3° Alcohols, menthol and nerolidol, were efficiently attached and released from the dimethylchlorosiloxane resin **10** (Table 2).

After the successful reactions with various alcohols, some preliminary stability studies were carried out on the diphenylsiloxane linker. *S*-Methyl lactate was coupled to **2**, and the resulting immobilised ester **12** was treated with phenylmagnesium bromide followed by cleavage with TBAF to afford diol **14** in good yield (60%, based upon the loading of the silyl chloride resin, 0.73 mmol/g),[9] demonstrating the stability of siloxane linker to Grignard reagents (Scheme 5).

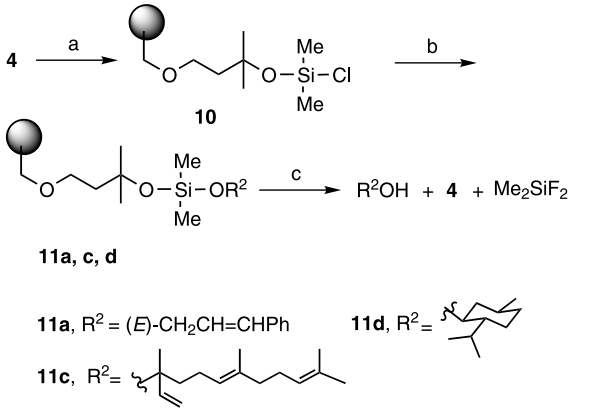


Scheme 3. *Reagents and conditions*: (a) 3-methyl-1,3-butanediol, KO*t*Bu, 18-crown-6, 0°C, then Merrifield resin pre-swollen, THF, microwave irradiation, 120°C, 10 min; (b) Ph_2SiCl_2, Et_3N, DMAP, CH_2Cl_2; (c) R^2OH, Et_3N, DMAP, CH_2Cl_2 rt; (d) TBAF, THF, or KF 18-crown-6, THF, rt.

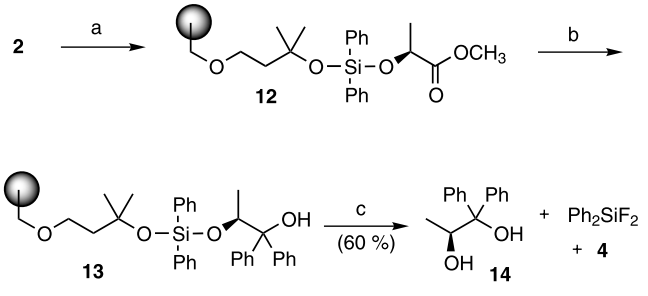
Table 2. Alcohols cleaved from resins **9** and **11**

Resin	Product cleaved	Conditions	Yield (%)[a]
9a	*trans*-Cinnamyl alcohol	TBAF	100[b]
9a	*trans*-Cinnamyl alcohol	KF, 18-crown-6	100
9b	*n*-Decanol	TBAF	70
9c	*E*-*E*-Nerolidol	TBAF	0[c]
9d	(1*R*,2*S*,5*R*)-(−)-Menthol	TBAF	96
9e	*endo*-Borneol	TBAF	95
11a	*trans*-Cinnamyl alcohol	TBAF	100[b]
11c	*E*-*E*-Nerolidol	TBAF	98
11d	(1*R*,2*S*,5*R*,)-(−)-Menthol	TBAF	95

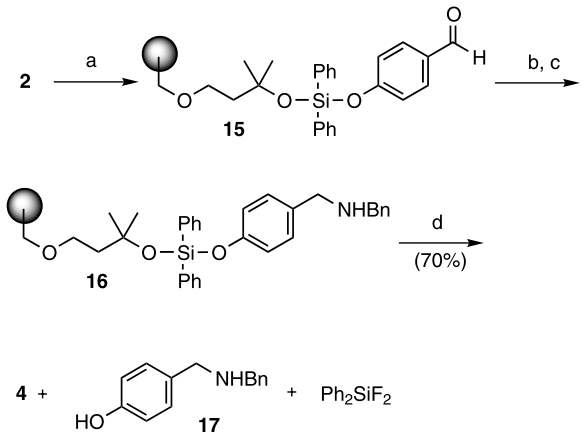
[a] Yields are based on the loading of resin **2**, that was estimated indirectly by coupling of *trans*-cinnamyl alcohol followed by cleavage with TBAF and quantification using GC.
[b] Based on the assumption that *trans*-cinnamyl alcohol reacted completely with **2** and **10**.
[c] Coupling reaction carried out for 24 h at room temperature.



Scheme 4. *Reagents and conditions*: (a) Me_2SiCl_2, Et_3N, DMAP, CH_2Cl_2; (b) R^2OH, Et_3N, DMAP, CH_2Cl_2 rt; (c) TBAF, THF, or KF 18-crown-6, THF, rt.



Scheme 5. *Reagents and conditions*: (a) *S*-methyl lactate, Et_3N, DMAP, CH_2Cl_2, rt; (b) PhMgBr, THF, 0°C, then rt; (c) TBAF, THF, rt.



Scheme 6. *Reagents and conditions*: (a) 4-hydroxybenzaldehyde, Et_3N, DMAP, CH_2Cl_2 rt; (b) $BnNH_2$, $HC(OCH_3)_3$, rt; (c) $Me_4NHB(OAc)_3$, 1% AcOH in CH_2Cl_2, rt; (d) TBAF, THF, rt.

We also investigated reductive amination of an immobilised aldehyde **15**, which was prepared under the usual conditions.[8] Condensation of **15** with benzylamine, followed by reduction of the intermediate imine and TBAF exposure afforded **17** in good yield (70%, based on the loading of the silyl chloride resin **2**, 0.73 mmol/g, Scheme 6).[10,11]

In conclusion, we have synthesised two new silyl chloride resins. The synthesis is straightforward and starts from inexpensive and readily available reagents. The linkers obtained are reactive towards a range of hydroxyl containing molecules, including hindered ones, and could represent a valuable alternative to other commercially available silyl resins. Further applications of the silyl linkers described are currently under investigation.

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8. General procedure for immobilisation of alcohols: Synthesis of **12**: resin **2** (100 mg, loading 0.65 mmol/g) was suspended in dry CH_2Cl_2 (1 mL) under N_2 flow in a peptide vessel and freshly dried Et_3N (133 μL, 0.96 mmol) was added, followed by *S*-methyl lactate (61 μL, 0.64 mmol) and DMAP (40 mg, 0.32 mmol). After 10 min agitation with N_2 the system was sealed and the suspension shaken 1 h. The resin was washed with dry CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum at

40°C for 24 h. Resin **12**: FTIR (on the bead) ν_{max} cm^{-1}: 3058, 2975, 1758 (C=O), 1125; ^{13}C NMR ($CDCl_3$) δ: 173.9 ((C=O)OCH_3), 75.2 (-$C(CH_3)_2$O-), 72.7 ($PhCH_2$O-), 68.1 ((C=O)OCH_3), 51.6 ((CH_3)CH-$COOCH_3$-O-), 30.1 (-CH_3), 21.1 (CH_3-CH($COOCH_3$)-O-).

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