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New Fluoride-Labile Linkers for Solid-Phase Organic Synthesis

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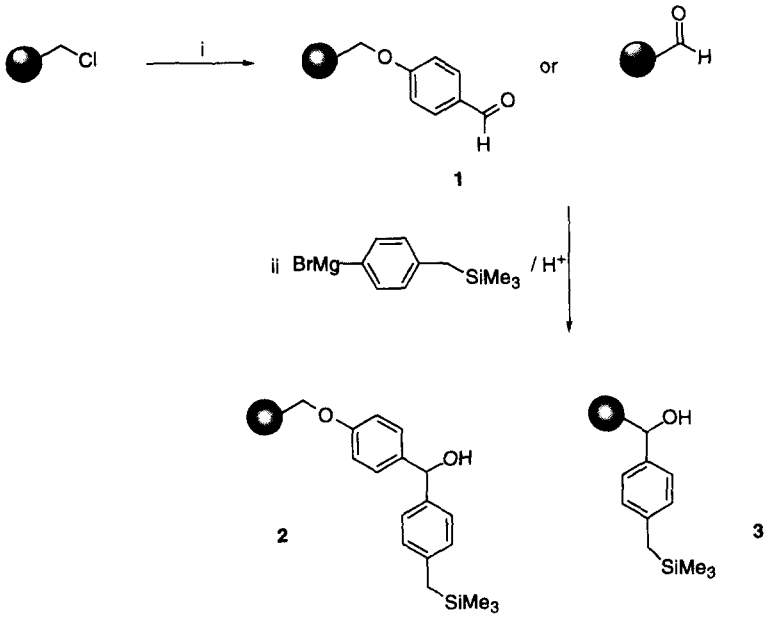
Abstract: Silyl-linkers **2** and **3** are shown to be useful linkers for solid-phase synthesis. They can be cleaved by fluoridolysis under basic (TBAF) or neutral (CsF) conditions. Methods for the synthesis, loading and release are described. © 1997 Elsevier Science Ltd.

Effective linkers[1] are vital tools for solid-phase synthesis[2] and linkers that can be cleaved under neutral conditions are especially valuable. This demand has focused attention on photolabile linkers[3] but many of these have drawbacks such as slow cleavage kinetics[4] and low chemical stability.[1]

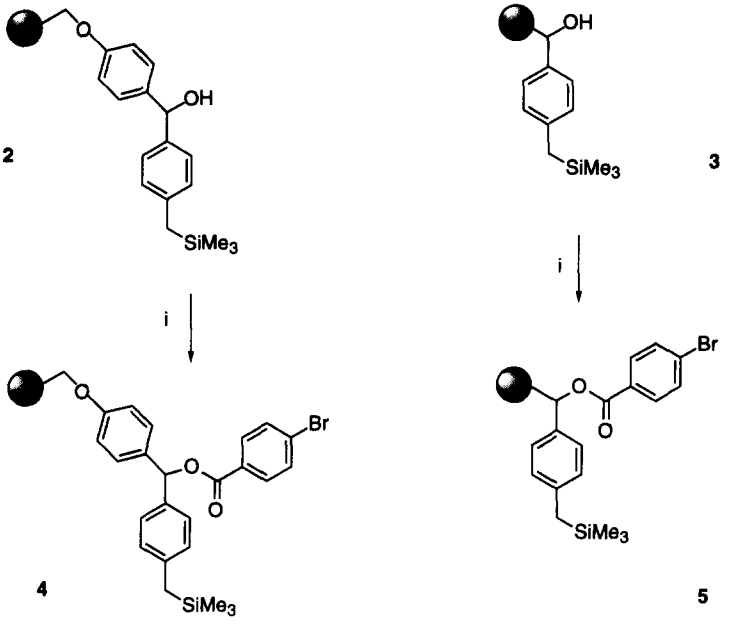
In this Letter we describe the synthesis and evaluation of silyl-linkers that can be cleaved by either basic or neutral fluoridolysis to release a range of functional groups (carboxylates, alcohols and amines). In contrast to similar linkers[5] described in the literature, silyl-linkers **2** and **3** can be easily synthesised and do not require tedious solution chemistry to preform the linker before attachment to resin.



Scheme 1 (i) 4-Hydroxybenzaldehyde (3 eq.), NaH (3 eq. 60% dispersion in oil), DMF (anhydrous), ambient temperature, 18h. (ii) **2** >95%[6], **3** >95%.[6]

Commercially available chloromethylpolystyrene[7] was reacted with the sodium salt of 4-hydroxybenzaldehyde to give the resin-bound aldehyde **1**.[8] A Grignard reaction between 4-bromobenzyltrimethylsilane[9] and either the resin-bound aldehyde **1** or commercial formylpolystyrene[10] furnished the resin-bound silyl-linkers **2** and **3** (Scheme 1). Resins **2** and **3** were characterised by gel-phase FTIR and ^{13}C NMR spectroscopy.[11] To study the

utility of silyl-linkers **2** and **3** for solid-phase synthesis they were reacted with 4-bromobenzoic acid using diisopropylcarbodiimide (DIC) in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) and N-hydroxybenzotriazole (HOBt) to afford the resin-bound aryl esters **4** and **5** (Scheme 2).[12]



Scheme 2 (i) Diisopropylcarbodiimide (3 eq.), 4-bromobenzoic acid (3 eq.), pyridine (3 eq.), DMAP (cat.), HOBt (cat.), DMF (anhydrous), ambient temperature, 18 h. **4** 68%[13], 0.455 mmol/g, **5** 66%[13] 0.253 mmol/g.

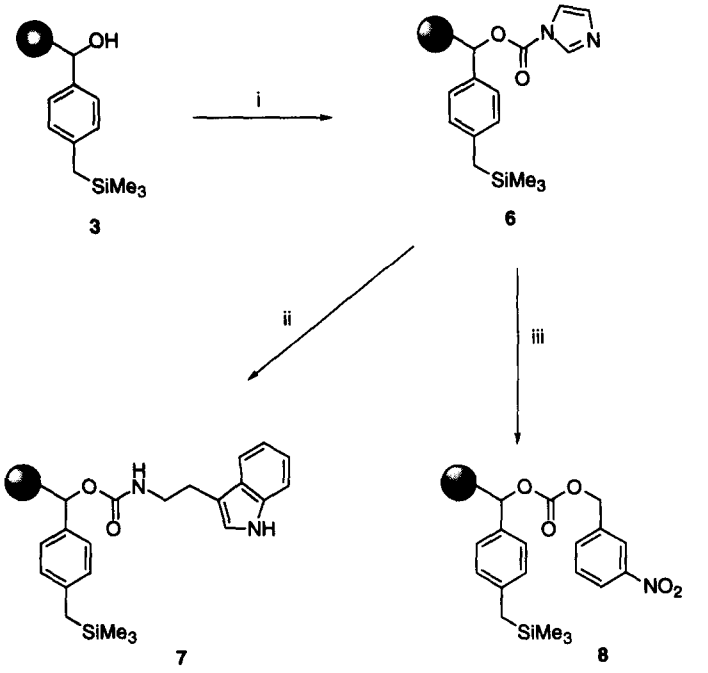
Aliquots of resin **4** and **5** were treated with various cleavage reagents and the results are shown in Table 1.

Table 1

Resin	Cleavage Conditions	Yield %[a]
4	TBAF (3 eq.) in DMF, ambient temperature, 1h.[14]	76
4	CsF (9 eq.) in DMF, ambient temperature, 24h.[15]	75
4	CsF (9 eq.) in DMF, 90°C, 18h.	72
4	1% TFA in CH_2Cl_2, ambient temperature, 0.5h.[16]	76
4	50% TFA in CH_2Cl_2, ambient temperature, 18h.	96[b]
5	TBAF (3 eq.) in DMF, ambient temperature, 1h.	35
5	TBAF (3 eq.) in DMF, 65°C, 1h.	78
5	CsF (9 eq.) in DMF, 90°C, 18h.	77
5	1% TFA in CH_2Cl_2, ambient temperature, 0.5h.	40

[a] Yields determined by UV analysis (240 nm) of the cleavage mixture.
[b] Isolated yield.

Upon fluoridolysis (entries 1-3, 6-8) both linkers gave good release of 4-bromobenzoic acid.[17] On mild acidolysis (entries 5 and 9) linker **2** was shown to be more acid labile than linker **3** thus attention was focused on silyl-linker **3** as a more acid stable linker. In order to explore the application of this linker to the release of other functional groups, carbonyl-1,1-diimidazole was used to activate the secondary alcohol on **3** to give a resin-bound acyl imidazole **6**.[18] Resin **6** was reacted with either tryptamine to give the resin-bound carbamate **7** or 3-nitrobenzyl alcohol to give the resin-bound carbonate **8** (Scheme 3). In both reactions the gel-phase FTIR spectra showed complete loss of the acyl imidazole carbonyl stretch and revealed new carbonyl stretches at 1715 cm^{-1} (for carbamate **7**) and 1750 cm^{-1} (for carbonate **8**).



Scheme 3 (i) Carbonyl-1,1-diimidazole (3 eq.), pyridine (3 eq.), dichloromethane (anhydrous), ambient temperature, 1h., >95%.[19] (ii) tryptamine (3 eq.), pyridine (3 eq.), DMF (anhdrous), ambient temperature, 18h., 32%.[18] (iii) 3-nitrobenzylalcohol (3 eq.), DBU (3 eq.), dichloromethane (anhydrous), ambient temperature, 0.25h., 65%.[19]

Carbamate **7** was treated with TBAF in DMF and UV analysis (220 nm) of the cleavage mixture showed 82% of the resin-bound tryptamine had been released. When resin **7** was treated with CsF, 88% of the tryptamine was released. Carbonate **8** was treated with TBAF, under the same conditions that had been successful for **7**, but only 45% of the resin bound benzyl alcohol was released. Aliquots of the resin were exposed to various cleavage conditions (Table 2) in order to optimise the release.

Table 2

Cleavage Conditions	Yield %[a]
TBAF (3 eq.) in DMF, 60°C, 3h.	51
TBAF (3 eq.) in DMF, sonicate, 4A molecular sieves, 60°C, 3h.[20]	53
Benzyltrimethylammonium hydrogen difluoride (3 eq.) in DMF, 65°C, 3h.	32
Triethylamine trihydrofluoride (3 eq.) in DMF, 65°C, 3h.	3
CsF (8 eq.) in DMF, 90°C, 24 h.	62
TBAF (8 eq.) in DMF, 4A molecular sieves, 65°C, 3h.	40
CsF (24 eq.) in DMF, 90°C, 24h.	68

[a] Yields determined by UV analysis (263 nm) of the cleavage mixture.

The highest yield from the resin-bound carbonate **8** was achieved using CsF. Increasing the amount of fluoride ion in the cleavage mixture gave no significant increase in the amount of 3-nitrobenzyl alcohol released. The other sources of fluoride ion explored (entries 3 & 4) gave poorer release.

In summary, in this Letter we have illustrated the use of a versatile fluoride-labile linker which is easy to synthesise and can be used in solid-phase synthesis to release carboxylic acids, amines and alcohols under neutral conditions. Work is currently in progress to use this linker in the synthesis of small molecule libraries.

Acknowledgments

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References and Notes

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6. As judged by the absence of an aldehyde carbonyl stretch in the gel-phase FTIR spectra of both **2** and **3** and by gel-phase ^{13}C NMR spectroscopy. Gel-phase FTIR were performed by swelling approximately 5 mg of dried resin with CH_2Cl_2 and squeezing the swollen resin between two NaCl plates, the spectra was acquired as for a normal thin film FTIR
7. Purchased from Aldrich (1 mmol/g, 2% divinylbenzene).
8. Gel-phase FTIR for **1** (ν cm^{-1}) 1693 (C=O).
9. Bordeau, M.; Villeneuve, P.; Bennetau, B.; Dunogues, J., *J. Organomet. Chem.*, **1987**, *331*, 169-174.
10. Purchased from Novabiochem (0.44 mmol/g, 100-200 mesh, 1% divinylbenzene)
11. Spectroscopic data for **2**; Gel-phase FTIR (ν cm^{-1}) 854 (C-Si). Gel-phase ^{13}C NMR(CD_2Cl_2, δ ppm) -1.97(Si<u>C</u>$(CH_3)_3$), 26.67(<u>C</u>H_2SiC$(CH_3)_3$), 69.99(<u>C</u>H_2O), 75.60(<u>C</u>OH). Spectroscopic data for **3**; Gel-phase FTIR (ν cm^{-1}) 854 (C-Si). Gel-phase ^{13}C NMR(CD_2Cl_2, δ ppm) -2.15(Si<u>C</u>$(CH_3)_3$), 26.56(<u>C</u>H_2SiC$(CH_3)_3$), 75.77(<u>C</u>OH).
12. Gel-phase FTIR for **4** (ν cm^{-1}) 1717 (C=O).
Gel-phase FTIR for **5** (ν cm^{-1}) 1718 (C=O).
13. Determined by elemental analysis for bromine. All elemental analyses were performed by MEDAC LTD, Department of Chemistry, Brunel University, Uxbridge, U.K.
14. ***Procedure for the release of 4-bromobenzoic acid ($\varepsilon_{MEOH/1\%\ TFA}$= 12300) by TBAF and determination of yield by UV spectroscopy.***
Resin **4** (13.1 mg, 0.006 mmol of resin-bound 4-bromobenzoic acid) was swollen in anhydrous DMF (0.1 ml), TBAF (12.0 µl, 0.012 mmol, 1M in THF) was added and the reaction was allowed to stand at ambient temperature for 1h. The resin was filtered, washed with DMF (3x1 ml) and the filtrate concentrated under reduced pressure. The residue was dissolved in methanol (spectroscopic grade, 5 ml), 1 µl of acetic acid was added then 200 µl of the acidified methanolic solution were removed and further diluted with methanol (spectroscopic grade, 5 ml). The absorbance at 240 nm was measured on either an ATI UNICAM UV/VIS spectrometer or a CECIL CE 1020S scanning UV spectrometer.
15. ***Procedure for the release of 4-bromobenzoic acid by CsF and determination of yield by UV spectroscopy.***
Resin **4** (19.2 mg, 0.009 mmol of resin-bound 4-bromobenzoic acid) was swollen in anhydrous DMF (0.1 ml), CsF (11.9 mg, 0.078 mmol.) was added and the reaction was allowed to stand at ambient temperature for 24h. Work up as for ref. 14.
16. ***Procedure for the release of 4-bromobenzoic acid by TFA and determination of yield by UV spectroscopy.***
Resin **4** (29.7 mg, 0.013 mmol of resin-bound 4-bromobenzoic acid) was swollen in CH_2Cl_2 with 1% TFA (1 ml), the reaction was allowed to stand at ambient temperature for 0.5h. The resin was filtered, washed with CH_2Cl_2 (3x1 ml), further work up as for ref. 14, except addition of acetic acid was omitted.
17. For both linkers the yield of released 4-bromobenzoic acid appeared to reach a maximum value, but inspection of the FTIR spectra of the resin after cleavage showed no discernible ester carbonyl and acidolysis with 50% TFA gave almost quantitative release. This suggests the apparent plateau in cleavage yield is not due to 4-bromobenzoic acid being irreversibly bound to the resin *via* ester formation directly onto hydroxymethyl polystyrene (present as a by-product on the commercial formyl polystyrene or from hydrolysis of Merrifield resin.).
18. Gel-phase FTIR for **6** (ν cm^{-1}) 1761 (C=O).
19. Determined by elemental analysis for nitrogen.
20. The addition of molecular sieves had be shown to be beneficial for the cleavage of SEM ethers.
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