Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2403–2404
Tetrahedron Letters

Synthesis of a novel silicon bearing linker for solid phase synthesis

Robert Ramage,[a,*] Martin J. I. Andrews,[a] Jenny Raphy[b] and Pu Wang[a]

[a]*Department of Chemistry, University of Edinburgh, Joseph Black Building, West Mains Road, Edinburgh EH8 3JJ, UK*
[b]*Parke-Davis Pharmaceuticals, Forvie Site, Robinson Way, Cambridge, UK*

Received 4 December 2003; revised 7 January 2004; accepted 16 January 2004

Abstract—A novel linker for solid phase synthesis is described, which exhibits rapid cleavage under selective, orthogonal conditions, including stability under acidic conditions. The linker incorporates a pyridyl propionate system, with a pendant β-silyl group. Rapid cleavage of the product is effected by elimination of the silyl group on treatment with fluoride. Two systems of this type have been synthesised, and the stability of the linkers has been tested under acidic and basic conditions in solution.

The continued development of solid phase peptide synthesis depends on the development of improved methodology, thus allowing the synthesis of more complex structures. Previously a linker system **1** was designed that would allow cleavage of a tethered ester using fluoride ions, thus ensuring retention of ancillary protecting groups.[1] This system was found to undergo rapid cleavage using TBAF in DMF. However, it was also found to be labile under acidic conditions, and attempts to improve acid stability by aryl substitution with electron withdrawing groups were unsuccessful (Fig. 1).

The pyridine analogue **2** of this linker should avoid this unwanted instability, due to pyridine protonation and destabilisation of the cationic intermediate invoked in the proposed alkyl-oxygen mechanism of acidolytic cleavage, without affecting the fluoride ion cleavage process. In other respects the linker design was based on the systems previously examined. The established route used for the synthesis of this type of molecule was found to be troublesome when applied to the pyridine analogues. In particular, the route shown (Scheme 1), although effective, was found to be lengthy and conjugate silyl addition was found to be low yielding.[2,3] It is possible that the cyanocuprate salts used were chelated strongly by the pyridine ring, thus hindering the desired reaction. However, in each case the major product was the required linker **3**.

An alternative strategy (Scheme 2) has now been devised, based upon the nucleophilic free radical substitution of pyridines.[4] This process uses the susceptibility of protonated pyridine rings to free radical

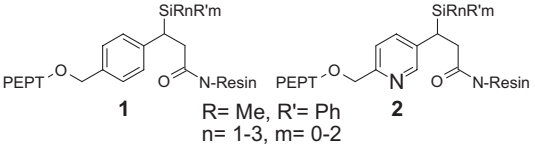
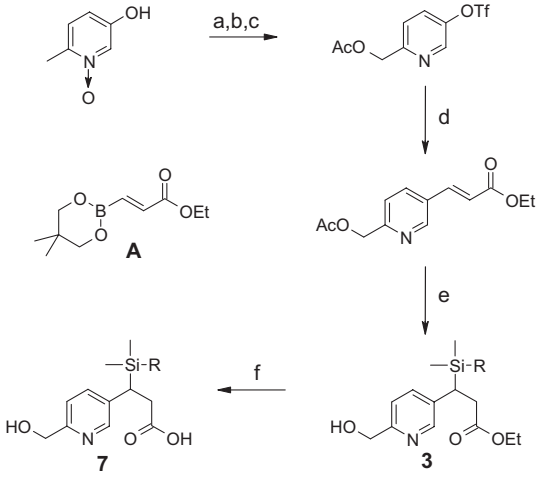


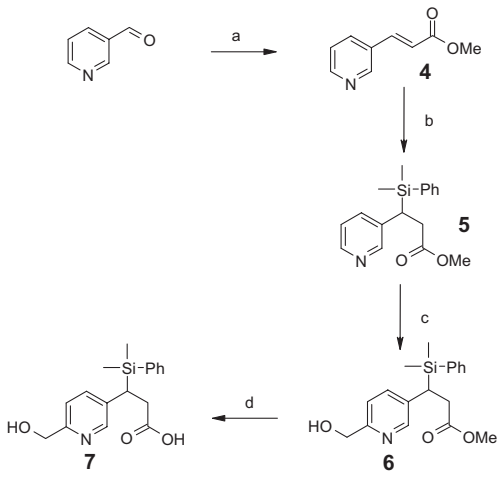
Figure 1. Structure of linkers.



Scheme 1. Reagents and conditions: (a) Ac_2O, (b) H_2O_2, pH 9.5, (c) Tf_2O, (d) **A**, $Pd(PPh_3)_4$, TEA, (e) $Li(SiMe_nPh_m)$, CuCN, −78 °C and (f) 0.5 M HCl.

* Corresponding author. Tel.: +44-(0)-1875-408150; fax: +44-(0)-1875-408151; e-mail: r.ramage@albachem.co.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.01.093

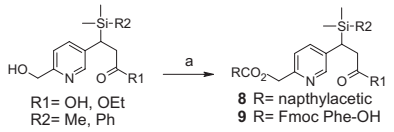


Scheme 2. Reagents and conditions: (a) NaH, $(EtO)_2P(O)CH_2CO_2Me$, (b) $Li(SiMe_2Ph)$, $ZnMe_2$, (c) $(PhCO_2)_2$, MeOH, TFA and (d) 0.5 M HCl.

substitution, most usually by radicals generated from alcohols or aldehydes. The route requires the synthesis of a simpler pyridyl propionate system prior to incorporation of the desired silyl side chains. The initial step in this synthesis was condensation of 3-formylpyridine under Horner–Wadsworth–Emmons conditions to give the pyridyl cinnamate system **4**.[5] The silyl groups were now introduced to afford **5** by use of either higher order cyanocuprates, or the silyl alkyl zinc reagents.[3,6] The trimethyl- and phenyldimethyl silyllithium species used in the study were generated by literature procedures.[7] The latter method using dimethylzinc has been found to be superior, requiring only 1 equiv of the silyllithium species. Higher yields were obtained in shorter reaction times, and with a simplified workup.

Hydroxymethylation was now performed using the Minisci reaction. Heating **5** at reflux in methanol/TFA in the presence of a stoichiometric quantity of benzoyl peroxide gave the desired product **6** in acceptable yield.[4,8] Only the desired 6-substituted product was obtained, presumably due to steric hindrance preventing reaction at the 2- and 4-positions. No cleavage of the silyl group was observed over the reaction times used. The linker **7** was obtained by cleavage of the ester group of **6** using either sodium hydroxide in aqueous THF or, preferably, 0.5 M aqueous HCl/THF mixture.[1]

The stability of the linker design has been exemplified under normal peptide synthetic conditions in solution, allowing monitoring by HPLC. 2-Naphthylacetic acid and Fmoc-phenylalanine were coupled by standard methods to the free alcohol **3**, and the stability of the products **8** and **9** on exposure to 20% piperidine in DMF was followed over 1 h. Only cleavage of the Fmoc group was observed. A series of cleavage conditions were then tested employing **9**, using both TFA and TBAF,[1] which showed that the linker system exhibits stability under acidic conditions, whilst showing very rapid cleavage on treatment with fluoride ions. Previous results[1] with the more hindered phenyldimethylsilyl group in **1** had suggested that TBAF cleavage would be more difficult (Scheme 3).



Scheme 3. Reagents and conditions: (a) RCO_2H, DIC, DMAP.

In conclusion, a fluoride ion-cleavable linker has been designed and synthesised, which has orthogonality with respect to the conditions required for the removal of acid and base labile protecting groups. The potential exists for use of this linker in the synthesis of full side chain protected peptide fragments by solid phase synthesis after specific fluoride cleavage from resin. This linker could now be applied to peptide and small molecule synthesis.

Acknowledgements

The authors would like to thank Brian Whigham and Kevin Shaw for technical assistance, and Parke-Davis Pharmaceuticals for funding.

References and notes

1. Ramage, R.; Barron, C. A.; Bielecki, S.; Holden, R.; Thomas, D. W. *Tetrahedron* **1992**, *48*, 499–514.
2. Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208; Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A. *Synth. Commun.* **1993**, *23*, 2851–2859.
3. Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805–1808.
4. Citterio, A.; Gentile, A.; Minisci, F.; Serraavalle, M.; Ventura, S. *Tetrahedron* **1985**, *41*, 617–620.
5. Agarwal, K. C.; Knaus, E. E. *J. Heterocycl. Chem.* **1985**, *22*, 65–69.
6. Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701–706.
7. Schlosser, M. Organometallics in Synthesis, 2nd ed.; Wiley: NY, pp 726–727.
8. A solution of **5** (2.40 g, 8.03 mmol), trifluoroacetic acid (0.67 mL, 8.80 mmol) and benzoyl peroxide (5.83 g, 24.1 mmol) in methanol (100 mL) was degassed thoroughly (Ar stream, 15 min), and then heated to reflux for 4 h. After this time, the solvents were removed in vacuo, and the residue was taken up in EtOAc (60 mL). The organic solution was then washed with satd $NaHCO_3$ solution, and then brine. After drying (Na_2SO_4), the residue on evaporation was purified by silica chromatography (70% EtOAc/hexane), to give **6** yield 0.811 g, 2.46 mmol, 31%. (250 MHz, $CDCl_3$) $\delta_H = 8.20$ (1H, d, J 1.99), 7.35 (5H, s), 7.16 (2H, m), 5.14 (1H, s), 3.21 (3H, s), 2.69 (3H, complex m), 2.13 (2H, s), 0.25 (6H, s); (67.8 MHz, $CDCl_3$) $\delta_C = 172.3$, 170.6, 151.9, 148.5, 136.9, 135.2, 129.6, 127.8, 121.3, 66.5, 60.4, 34.3, 29.5, 20.8, 13.8, −4.5, −5.6; m/z (FAB) 331 (M+1, 82%), 300 (29), 135 (100).