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A Highly Acid Labile Silicon Linker for Solid Phase Synthesis

Neal D. Hone,[a]* Stephen G. Davies,[b] Nicholas J. Devereux,[a] Sara L. Taylor[a] and Anthony D. Baxter[a]

[a] Oxford Diversity, A Division of Oxford Asymmetry Ltd, 57 Milton Park, Abingdon, Oxon, OX14 4RX, UK

[b] The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, UK

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Abstract: A novel arylsilane based linker has been prepared for the solid phase synthesis of small molecule combinatorial libraries. Efficient cleavage is achieved using TFA *via* anchimerically assisted protiodesilylation to yield aromatic products possessing no residual linker functionality.

The development of combinatorial synthetic techniques has been driven by the pharmaceutical industry's requirements for the rapid discovery and optimisation of active lead compounds. Of both solution and solid phase mediated syntheses, only the solid phase approach allows multistep synthesis, employing excess reagents to force reaction completion whilst avoiding purification and isolation of intermediates. The synthesis of numerous drug-like libraries on solid support have recently been disclosed.[1] In all cases, the final step requires cleavage of a covalent bond linking the product to resin, allowing its isolation, characterisation and biological evaluation. The most commonly used linkers are those originally developed for solid phase peptide synthesis which cleave to reveal polar functionality, such as carboxylic acids[2] and carboxamides.[3] More recent developments in linker technology have allowed cleavage to a wider range of functionality such as hydroxyl[4] and amino[5] groups, although the presence of such polar functionality may bestow undesirable physicochemical and pharmacokinetic properties. The development of linkers which release products with no polar 'trace' of their attachment point would represent a significant advance.

This approach has been demonstrated by the use of support bound arylsilane based linkers.[6] The release of functionalised aromatics from such linkers is typically achieved *via* protiodesilylation under acidic conditions. However, the poor efficiency of this process is demonstrated by their need for prolonged exposure to neat TFA or the use of liquid HF, a reagent which is incompatible with a variety of functionality and not amenable to automation.

We now report a novel arylsilicon linker exhibiting a considerably enhanced cleavage rate, *via* anchimerically assisted protiodesilylation. Using the carboxyalkyl arylsilane **1a**,[7,8] functionalisation of commercially available aminomethyl polystyrene was readily achieved under standard amide bond forming conditions (Scheme 1). Synthetic utility was demonstrated by the Suzuki coupling[9] of **2a** with naphthalene-1-boronic acid, yielding resin bound biaryl derivative **3**. Cleavage with 50% TFA in DCM at ambient temperature for 2 h gave **4** in quantitative yield based on original resin loading.

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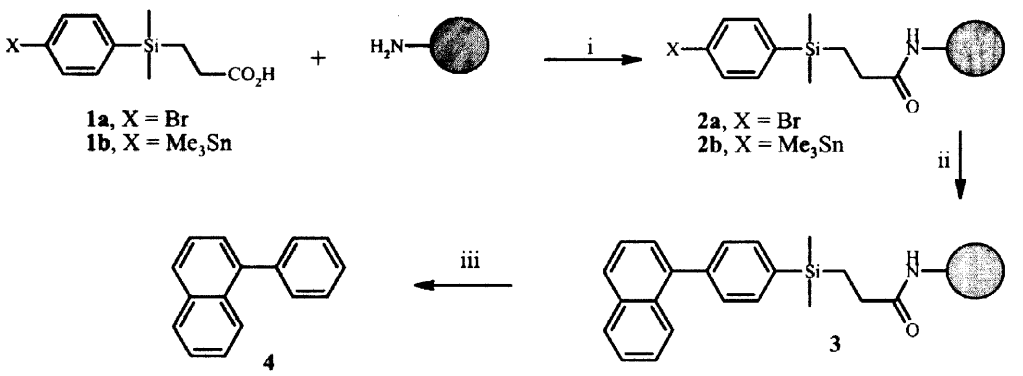


Scheme 1: (i) 4 Equivalents **1**, TBTU, HOBt, DIEA, DMF, rt, 1 h; (ii) 1-naphthaleneboronic acid, $Pd(PPh_3)_4$ (cat.), $Na_2CO_{3(aq)}$, 1,2-DME, Δ, 12 h; (iii) TFA-DCM (1:1), rt, 2 h.

A cleavage rate comparison of the amide based linker **5** and the ether based linker **6**[6a] was conducted by measuring the UV absorption (at 270 nm) of the Suzuki derived biaryl product **7** in the neat TFA cleavage solution (Fig. 1).[10] From linker **5**, complete cleavage was observed within 40 min, while cleavage from linker **6** was significantly slower.

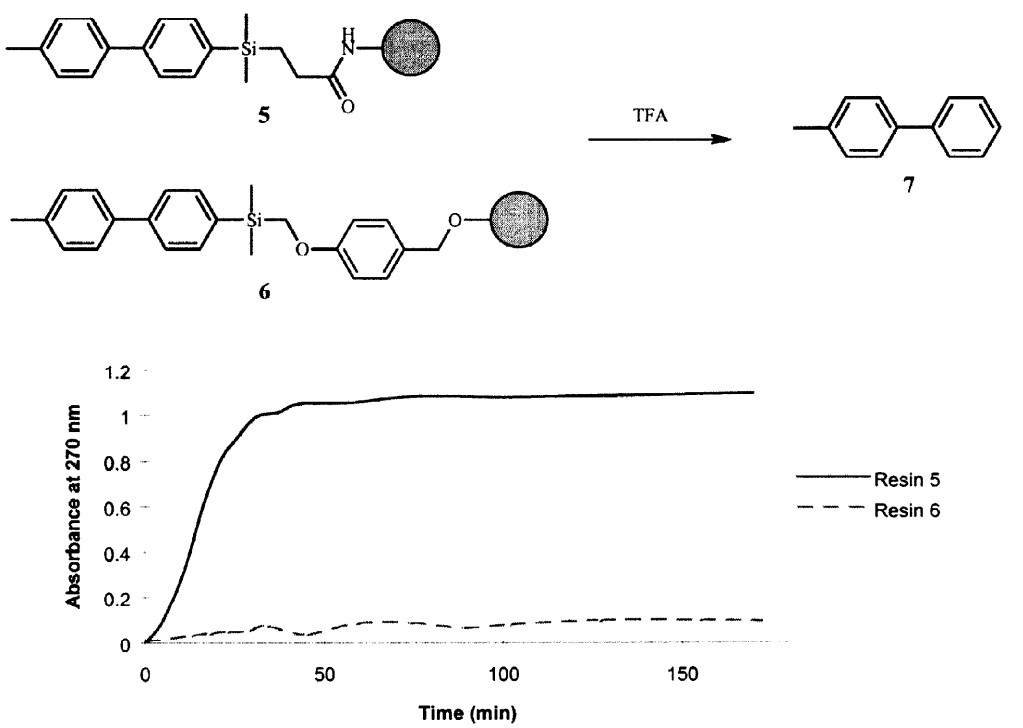
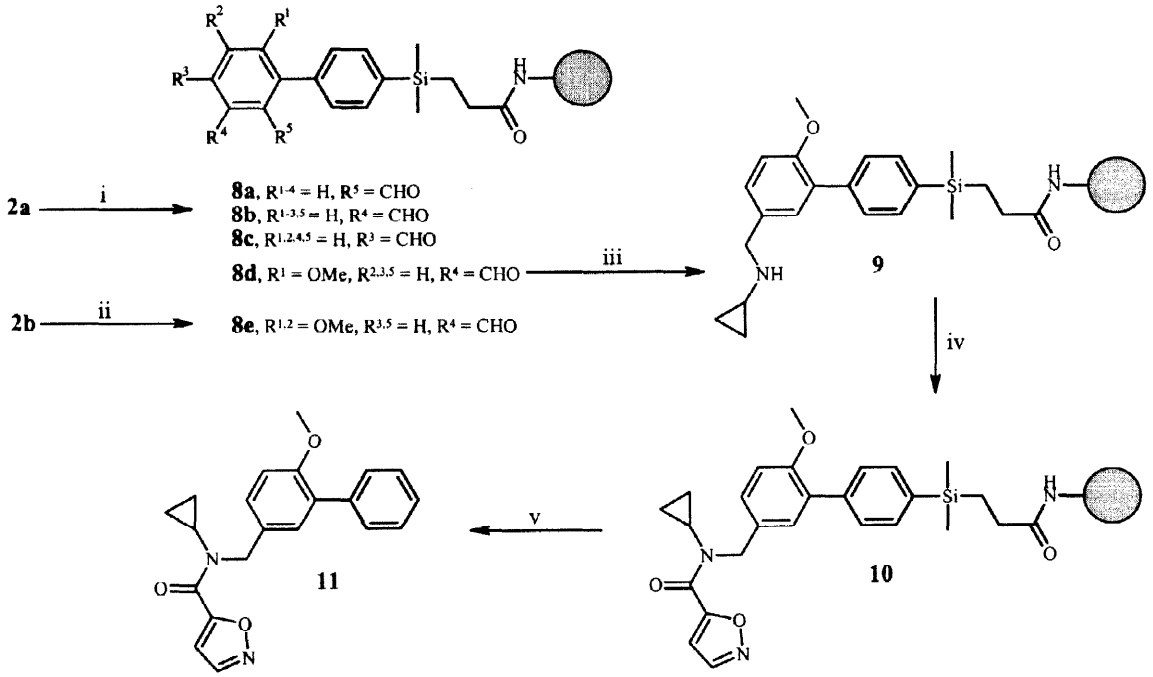


Figure 1: Time course of biaryl **7** release from resins **5** and **6**

We postulate that the rapid cleavage from **5** is achieved through enhancement of the rate determining ipso-protonation step[11]. This may be facilitated by intramolecular delivery from the protonated amide carbonyl, or through carbonyl co-ordination to the mildly Lewis acidic silane, enhancing both nucleophilicity of the ipso site and β-stabilisation of the resultant Wheland intermediate. Opportunity for such interaction is not present within the ether tethered linker **6**.

The utility of linker **2** was demonstrated by the synthesis of a 100 member library based on the privileged biaryl nucleus. Four resin bound biaryl aldehydes (**8a-d**) were prepared by Suzuki coupling of the 4-bromophenylsilane **2a** with four formylboronic acids. A fifth aldehyde was prepared by a Stille coupling[12] of the arylstannane **2b**[13] and *O*-methyl-5-iodovanillin as outlined in sheme 2.



Scheme 2: (i) Arylboronic acid, $Pd(PPh_3)_4$ (cat.), $Na_2CO_{3(aq)}$, 1,2-DME, Δ, 12 h; (ii) *O*-methyl-5-iodovanillin, Pd_2dba_3 (cat.), $AsPh_3$, DMA, 45 °C, 12 h; (iii) cyclopropylamine, AcOH, Na_2SO_4 anh., THF, Δ, 12 h; then $Na(OAc)_3BH$, THF, Δ, 3 h; (iv) isoxazole-5-carbonyl chloride, DIEA, THF 50 °C, 12 h; (v) TFA-DCM (1:1), rt, 2 h.

Reductive amination of each aldehyde with four primary amines[14] was performed using a one pot procedure, followed by capping of the resultant secondary amines with five electrophiles.[15] Product cleavage was effected using 50% TFA in DCM at room temperature for 2 h. The transformation **8d** to **11**[16] (Scheme 2) exemplifies the route. All products were characterised by ^1H NMR and +ve ES-MS and were generally isolated in excellent yield and purity. Benzylic cleavage was observed in some cases from the 3,4-dimethoxy derivatives of **8e** by a 'Rink' type mechanism.[3]

In conclusion, we have demonstrated the synthesis and application of a novel silicon linker offering highly efficient cleavage to small molecule libraries bearing no 'memory' of resin attachment. The linker also provides the opportunity for direct cleavage to deuterium and tritium labelled products. Arylsilane cleavage in the presence of electrophilic halogen and acyl sources has also been achieved and may offer a further dimension in product diversity.

Acknowledgements

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7. Monolithiation of 1,4-dibromobenzene using one equivalent of *n*-BuLi in THF at -78 °C for 1 h, followed by treatment with one equivalent of chloromethyldimethylchlorosilane provided chloromethydimethyl-4-bromophenylsilane. This reagent was converted to **1a** following ref. 8.
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13. Prepared from **1a** by methyl ester formation (MeI, TEA, EtOAc, Δ), stannylation ($(Me_3Sn)_2$, $Pd(PPh_3)_4$, toluene, Δ), saponification and TBTU mediated coupling to aminomethyl polystyrene.
14. Cyclopropylamine, 2,2,2-trifluoroethylamine, 1-(3-aminopropyl)-2-pipecoline and 4-methylbenzylamine.
15. Morpholine-4-carbonyl chloride, thiophene-2-carbonyl chloride, isoxazole-5-carbonyl chloride, 4-bromophenyl isocyanate and 1-methylimidazole-4-sulphonyl chloride.
16. **11** Was isolated in 64% crude yield, ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.64 (2H, m), 0.82 (2H, m), 2.96 (1H, m), 3.83 (3H, s), 4.76 (2H, s), 6.80 (1H, s), 6.95-7.60 (8H, m), 8.34 (1H, s); m/z (ES^+) 394 $(MH)^+$.