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Novel Serine-Based Linker for the Solid-Phase Synthesis of Organic Compounds

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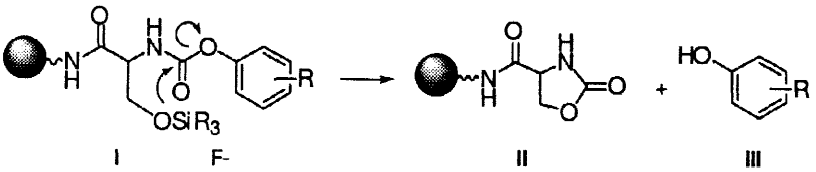
Abstract: A novel serine-derived linker has been developed that allows phenolic templates to be cleaved from the resin with fluoride ion. The linker is stable to acids such as TFA and bases such as pyrrolidine. The linker should provide utility in multi-step solid phase organic chemistry protocols where both acid and base chemistry is used. © 1998 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry of small molecules has generated a great deal of interest due to its impact on lead structure identification and optimization.[1] Rapid integration of solid-phase organic chemistry methods into traditional medicinal chemistry has been facilitated by the vast repertoire of linker methodologies available from the peptide chemistry literature.[2] One area of linkers that has not had much exposure in peptide literature, however, is the area of orthogonal linkers; those that are stable to nucleophiles and bases as well as to acidic exposure. Organic chemistry of small molecules on solid support, unlike peptide chemistry, often requires the use of both acids, bases and nucleophiles in a multi-step synthetic sequence and thus the development of orthogonal linkers has been the focus of much attention in the recent years.

In the course of our investigation into orthogonal linkers, we were intrigued by the prospect of utilizing a serine-based carbamate linker, wherein the intramolecular cyclization of protected serine hydroxyl group in polymer-linked template **I** with the carbamate carbonyl results in the formation of a polymer bound oxazolidinone **II** and concomitant release of the template **III** from the solid support. Intramolecular cyclizations on a polymer to initiate product release have been previously reported in an example where an azido group on a linker is utilized as a latent amino group that is involved in an intramolecular cyclization.[3] Reduction of the azide, however, is not a facile or efficient process on solid support, and as such this methodology requires extensive purification of the final products.



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Proof of concept of such a serine-based linker was initiated by constructing the appropriately protected carbamoyl derivative of serine as shown in Scheme 1[4]. L-Serine benzyl ester was reacted with triisopropylsilyl chloride (TIPSiCl)[5] in presence of triethyl amine and pyridine to provide the ether **2.** Reaction with phosgene in dichloromethane and triethylamine afforded the carbamoyl chloride **3.** Two representative phenols 5-hydroxy-Boc-L-tryptophan methyl ester **4a** and 5-hydroxyoxindole **4b** were then reacted with the carbamoyl chloride **3**, in presence of triethyl amine, to afford the serine-coupled tryptophan analog **5a** and the serine-coupled oxindole analog **5b** in quantitative yields.

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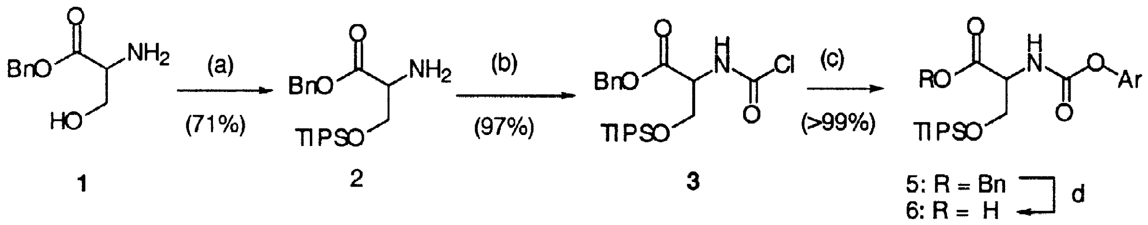
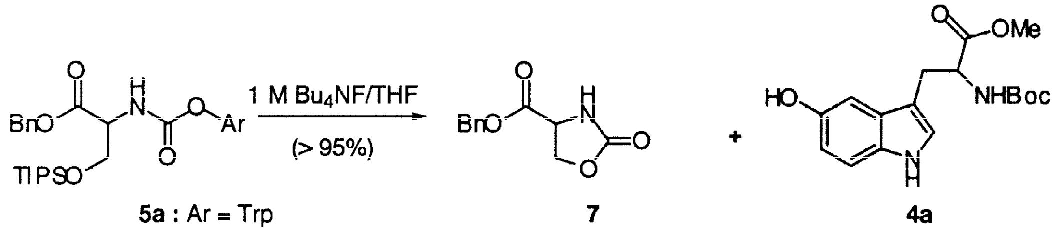


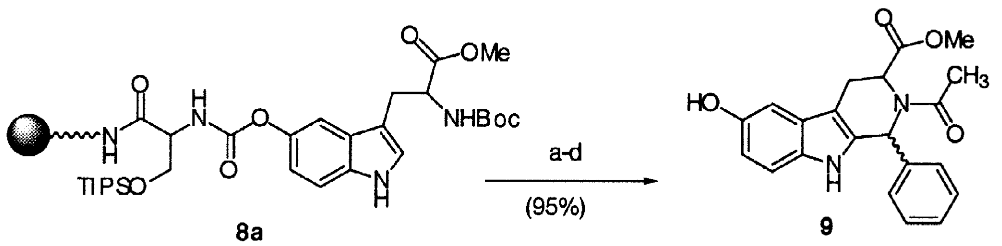
Scheme 1: (a) TIPSiCl, pyridine, Et_3N, CH_2Cl_2, reflux 24 h; (b) $COCl_2$, CH_2Cl_2, Et_3N; (c) 5-hydroxy-Boc-L-Tryptophan methylester (**4a**) or 6-hydroxy-1-methyl-oxindole (**4b**), Et_3N, CH_2Cl_2, 24 h; (d) 10% Pd/C, EtOH, 40 psi, 1.5 h.

Subjecting compound **5a** to tetrabutylammonium fluoride (TBAF) in THF resulted, as was predicted, in the quantitative release of the 5-hydroxy tryptophan analog **4a.** Compound **5b** similarly afforded 5-hydroxy oxindole **4b** as the cleavage product of TBAF treatment. The serine component of the cleavage process is transformed to the oxazolidinone derivative 7.[6]



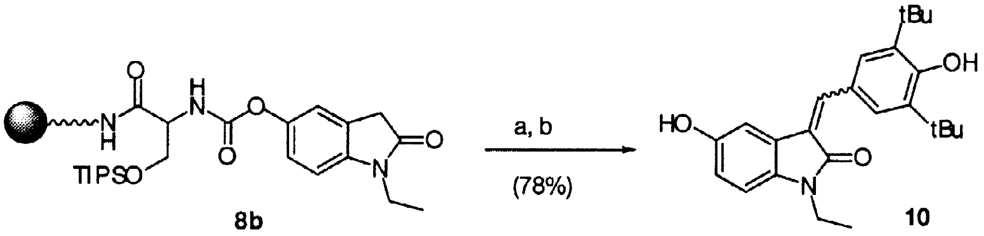
Having demonstrated that the intramolecular cyclization indeed occurs quantitatively, the next step was to demonstrate the orthogonal stability and utility of this linker. We chose as our experiments, the acid catalyzed Pictet-Spengler reaction and the base facilitated Knoevenagel condensation reaction. We have previously reported that tryptophan analogs such as **4a** undergo a Pictet-Spengler cyclization in presence of trifluoroacetic acid (TFA) to afford β-carbolines.[7] It is also known that oxindole analogs such as **4b**, in presence of pyrrolidine, undergo a facile Knoevenagel condensation with aldehydes.[8] Qualitative and quantitative analysis of the reaction products from the above sequences would validate our hypotheses. It is important to note that both sets of conditions would result in the cleavage of acid sensitive linkers (Shepherd, Wang, Rink) as well as base sensitive linkers (Fmoc, oxime).

Hydrogenolysis of the benzyl group of **5** to the acid **6**, followed by coupling with Tentagel-S-NH_2 resin (Rapp Polymere) provided the polymer bound precursors **8a** and **8b** (Scheme 1). The polymer bound tryptophan analog **8a** was subjected to the acid catalyzed Pictet-Spengler cyclization and acylation conditions as reported previously (Scheme 2).[9] Treatment of the functionalized polymer-bound β-carboline derivative with TBAF in THF afforded, after aqueous work-up, the β-carboline derivative **9** in 95% yield and 83% purity by HPLC.[10]



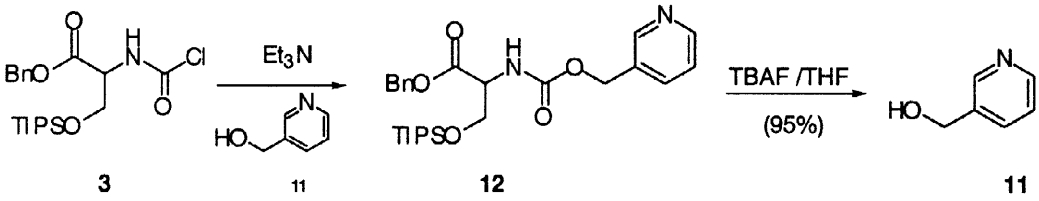
Scheme 2: (a) 25% TFA / CH_2Cl_2; (b) benzaldehyde; (c) Ac_2O, pyridine; (d) 1 M Bu_4NF / THF

In the second example, polymer bound oxindole analog **8b** was reacted with 3,5-di-t-butyl-4-hydroxybenzaldehyde in presence of pyrrolidine as shown in Scheme 3.[11] Treatment of the polymer bound oxindole derivative with TBAF in THF afforded the functionalized oxindole analog **10** in 78% isolated yield and 92% purity by HPLC.[10]



Scheme 3: (a) 4-hydroxy-3,5-di-t-butylbenzaldehyde /pyrrolidine/CH_2Cl_2-MeOH (b)1 M Bu_4NF/THF

In preliminary work, we have also demonstrated that primary alcohols, attached via the carbamate to the serine linker, are also quantitatively released by fluoride treatment. As an example, 3-pyridyl methanol **11** was coupled to the carbamoyl chloride **3** to form the alkyl carbamate **12**. Treatment of this carbamate with TBAF resulted in the formation of the parent alcohol in 95% yield and >90% purity by NMR.



In summary, we have developed a novel linker mechanism that is compatible with both acid as well as base chemistry in a multi-step solid-phase synthetic sequence. Efforts to expand the scope of this cyclization to include other favorable cyclizations, such as lactone formation, are currently underway.

REFERENCES AND NOTES

1. For recent reviews see (a) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288-2237. (b) Bristol, James A. *Tetrahedron*, **1997**,*53*, 6573-6706
2. Stewart, J. M. and Young, J. D. *Solid Phase Peptide Synthesis*, Pierce Chemical Co., Rockford, IL **1984**, pp. 9-14.
3. Osborn, N. J. and Robinson, J. A. *Tetrahedron*, **1993**, *49*, 2873-2884.
4. Preparation of Intermediate **6**: To a solution of L-serine benzyl ester hydrochloride in CH_2Cl_2 was added pyridine and triethylamine the reaction was stirred for 3 min followed by the addition of triisopropylsilyl chloride. The reaction was refluxed for 24 h then filtered to remove the triethylamine salt. The filtrate was concentrated and chromatographed on silica gel (5% EtOAc in CH_2Cl_2) to afford 30.5 g (71%) of the silylether **2.** To the silylether **2** in 100 mL CH_2Cl_2 and 13.5 mL of triethylamine was added phosgene (90 mL, 1.93 M in toluene) followed by 500 mL of CH_2Cl_2. The reaction was stirred for 0.5 h then purged with N_2 for 1 h to remove excess phosgene. The solution was concentrated and 300 mL ether was added. The mixture was filtered and the filtrate evaporated at 30 °C, in vacuo, to afford 34.5 g of the carbamoyl chloride **3** as an oil. ^1H NMR ($CDCl_3$) 1.00 (m, 21), 3.90 (m, 2), 4.05 (m, 2), 5.10 (dd, 2), 7.05-7.40 (m, 6).
5. The triisopropyl silyl group was chosen as the silyl group because of its relative stability to TFA as well as the fact that triisopropyl fluoride, the byproduct of the cleavage process, is a volatile compound and can be easily removed in vacuo.
6. All intermediates **2, 3, 5** and **6** and cleavage products **7, 4a** and **4b** were isolated by flash chromatography on silica gel and fully characterized by ^1H NMR and mass spectroscopy.
7. Mohan, R; Chou, Y-L; Morrissey, M. M. *Tetrahedron Lett.* **1996**, *23*, 3963-3966.
8. Valentine, J. J.; Nakanishi, S.; Hageman, D. L.; Snider, R. M.; Spencer, R. W. and Vinick, F. W. *Biorganic and Med. Chem. Lett.* **1992**, *2*, 333-338.
9. The deprotection of the Boc group and the Pictet-Spengler cyclization-acylation sequence was carried out as described earlier.[7] The resin was washed with MeOH and CH_2Cl_2 to remove excess reagents. The resin was then treated with 1 M tetrabutyl ammonium fluoride in THF for 1 h, filtered and the filtrate extracted with CH_2Cl_2 (3 X 2 mL). The combined CH_2Cl_2 layers were washed with 10% $NaHCO_3$, dried and evaporated to afford the β-carboline compound **9** in 95% yield. NMR and mass spectral data are consistent with the product and with published data.[7]
10. HPLC purity determined from area of peak corresponding to correct molecular weight by LC ES/MS.
11. In a typical procedure, 1 g of the resin (0.32 mmole) was mixed with 4-hydroxy-di-t-butylbenzaldehyde (243 mg, 1 mmole) and 83 uL pyrrolidine in 10 mL of 4:1 CH_2Cl_2/MeOH and agitated for 24 h. The resin was washed and treated with tetrabutyl ammonium fluoride in THF for 1 h. Work-up, as in the previous example, afforded 102 mg (78%) of the oxindole analog **10**, identical by TLC and NMR with the literature compound synthesized via an independent synthesis.[8]