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Acetophenone-based Linker for Solid Phase Synthesis of Secondary Amides and Sulfonamides on the Multipin™ Support.

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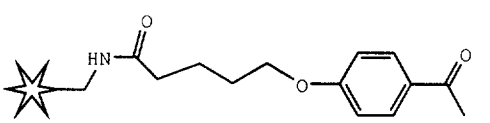
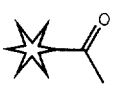
Abstract: A new and simple linker has been developed for synthesis of secondary amides and sulfonamides. This application is based on the reductive amination reaction between the acetophenone subunit of the linker and a wide range of primary amines including aliphatic and aromatic amines. Cleavage is effected under mild acidic conditions (20% TFA/DCM) to release the products in good yield and purity.

With the rapid increase in the numbers of nonpeptidic small molecule compounds being prepared by solid phase synthesis,[1,2] there is a growing need for linkers that cleave to give some important structural elements like secondary amides, sulfonamides, and ureas which are embedded in many druglike molecules. Such linker systems include reductive alkylation of the acid labile Seiber[3] and Rink[4] linkers with ketones and aldehydes, and reductive amination of support-bound 4-formyl-3,5-dimethoxyphenoxyvaleric acid linker (Barany),[5] its monomethoxy analog (Acid Sensitive Methoxy Benzaldehyde, AMEBA),[6] and more recently an indole-3-carboxaldehyde based linker.[7] Each application has its merits although some appear to have significant limitations such as complicated synthetic pathways, expensive starting materials, high % TFA required for cleavage (>90%), steric hindrance within the structure, etc.[8] Here, we report a new, cost effective linker for the synthesis of secondary amides and sulfonamides that addresses some of these limitations. This linker is based on reductive amination after reaction of primary amines with a ketone functional group of the acetophenone subunit of **1**. A comparative study of this linker was carried out with two commercially available linkers, 4-formyl-3,5-dimethoxyphenoxy valeric acid **3** (Barany linker), and its monomethoxy analog **4** (AMEBA), using the Multipin™ system.[9]



1



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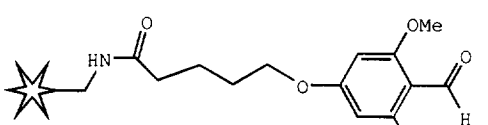
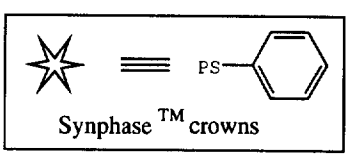


3 R = OMe
4 R = H



In principle, polystyrene resins or SynPhase™ crowns can be functionalised by Friedel Craft's acylation (CH_3COCl/ $AlCl_3$/ CH_2Cl_2) to give directly the acetophenone subunit **2** which is functionally identical to **1**.[10] However, our initial efforts were focussed on the preformed linker **1** for two main reasons, (i) flexibility to allow attachment of the acetophenone moiety via an amide linkage to a range of different aminomethylated solid supports and (ii), addition of the spacer component that is known to improve accessibility and hence

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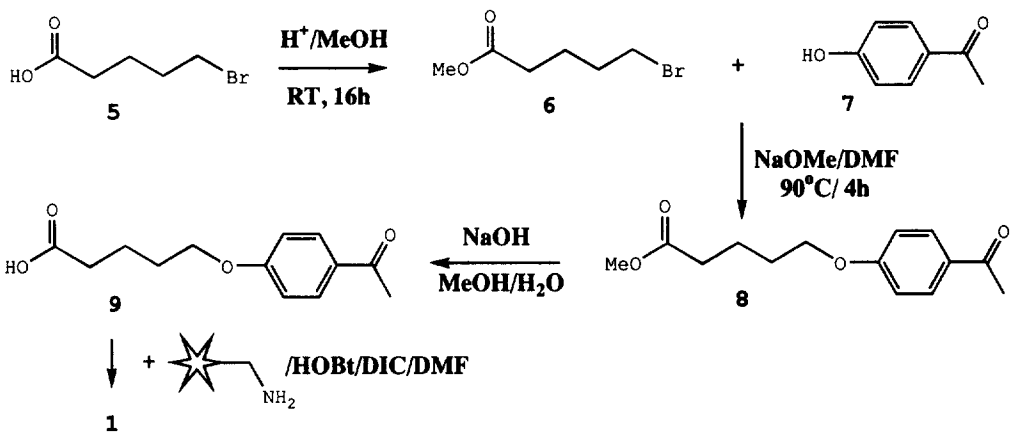
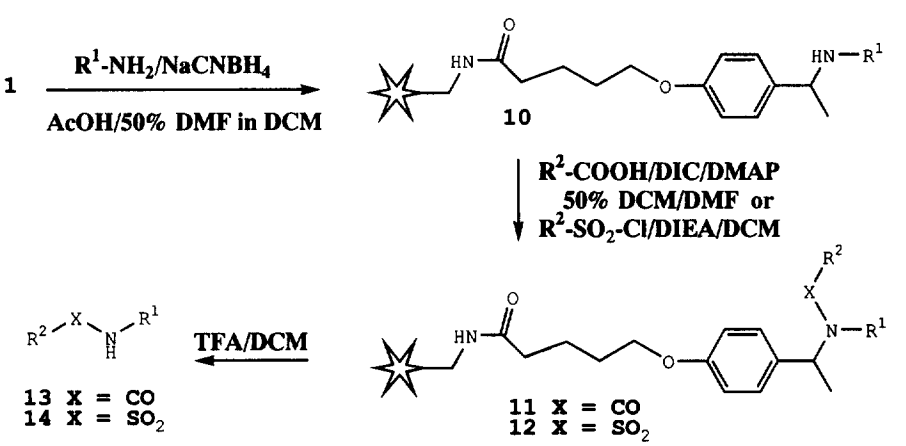
yield.[11] Synthesis of linker **1** (Scheme 1) was readily achieved using cheap and commercially available 5-bromovaleric acid and 4-hydroxyacetophenone as starting materials. On esterification of the 5-bromovaleric acid with methanol, the ester **6** was treated with 4-hydroxyacetophenone **7** in the presence of NaOMe to afford the product **8**. Saponification of **8** with a 40% aqueous solution of 4M NaOH in methanol afforded the linker **9** in 76% overall yield (3 steps, from **5**).[12] Derivatization of the commercially available aminomethyl-PS crowns with linker **9** using standard coupling conditions (HOBt/DIC) gave the linker-bound solid support **1**.[13]



Scheme 1: Synthesis of linker **1**

To assess its performance, **1** was subjected to reductive amination with a broad range of primary amines using a one step process (Scheme 2).[13] The resulting product **10** was then acylated with carboxylic acids (Fmoc protected amino acids) using DIC and DMAP in DMF/DCM (1:1) or sulfonyl chlorides / DIEA in DCM to afford captive amide **11** and sulfonamide **12** respectively.[6] Finally, **11** and **12** were cleaved in > 20% TFA in DCM without using any scavenger to give the targets **13** and **14** respectively.



Scheme 2: Synthesis of **13** & **14** on linker **1**

This reaction path was applied to a broad range of primary amines using linker **1**. In all cases, the reactions gave the expected products in excellent purity. This was confirmed by independent solution phase synthesis of the products and comparative analyses of the products by HPLC and Electrospray MS (Table 1). A comparative study of this new linker with the two commercially available ones, 4-formyl-3,5-dimethoxyphenoxyvaleric acid (Barany) linker and its monomethoxy analog (AMEBA) is presented in Table 2. Both products **13** and **14** derived from the 3 linkers were assessed on the basis of purity at 214 nm by HPLC and overall yield (4 steps from aminomethyl-PS crown, loading value of 20 μmol/ I-series crown) by HPLC peak area based on a standard curve established from a range of concentrations of the authentic compounds run under standardized conditions. Preliminary results obtained from three linkers are similar although % yield does vary for the same product from different linkers. The synthesis of sulfonamides was reported to be unsuccessful on linker **3** bound resin[7] but it was not the case here, as shown with successful examples, **14a** to **14c**. Although there were some variations in yield between the linkers in this example further comparative studies with other reaction schemes need to be performed if trends are to be identified.

Table 1. Characterisation Data for Compounds **13** and **14** .

Com-pound	R^1-NH_2	R^2-COOH or R^2-SO_2Cl	HPLC[a] (min)	ES-MS[b] $[M+H]^+$ Observed	ES-MS $[M+H]^+$ Calculated
13a	Ethylamine	Fmoc-β-Ala-OH	6.58	339.0	339.3
13b	Cyclopropylamine	Fmoc-Phe-OH	7.69	427.2	427.2
13c	Butylamine	Fmoc-β-Ala-OH	7.25	367.0	367.2
13d	Benzylamine	Fmoc-β-Ala-OH	7.23	401.3	401.2
13e	4-Methoxybenzylamine	Fmoc-β-Ala-OH	7.20	431.2	431.2
13f	2,2-Diphenylethylamine	Fmoc-β-Ala-OH	8.20	491.2	491.2
13g	2-Methoxyphenethylamine	Fmoc-β-Ala-OH	7.62	445.1	445.2
13h	Benzylamine	Dnp-β-Ala-OH	6.59	345.1	345.2
14a	Butylamine	C_6H_5-SO_2Cl	7.40	214.3	214.2
14b	Cyclopropylamine	C_6H_5-SO_2Cl	6.12	198.2	198.2
14c	2-Methoxyphenethylamine	C_6H_5-SO_2Cl	8.27	292.1	292.2

[a] HPLC retention times were identical with the authentic compounds obtained from solution phase syntheses. Analytical HPLC was conducted with a Rainin, Microsorb-MV Cat.# 86-200-F3, 50x4.6 mm column using mobile-phase gradient 0-100% B over 11.5 mins. Flow rate: 1.5 ml/min.(Solvent A: 0.1% ortho-phosphoric acid in water; Solvent B: 0.1% ortho-phosphoric acid in 90% acetonitrile).
[b] ES-MS data were identical to the authentic compounds obtained from solution phase syntheses. Mass spectrometer analysis was conducted with a Perkin-Elmer Sciex API III using 0.1% acetic acid in 60% acetonitrile as carrier solvent.

In conclusion, a new, simple and cheap method to generate the secondary amide forming linker has been described. Like **3** and **4**, linker **1** seems to be a very versatile and valuable tool for the preparation of a wide range of secondary amides. Attachment of this handle to solid supports is easily achieved and the anchor remains intact through synthesis. The mild acidic cleavage step from the handle provides the target products in high yield and purity.

Table 2. Comparative Study between Three Linkers **1**, **3** and **4**:

Compound	Linker 1	Linker 3	Linker 4
	% Purity[a] / % Yield[b]	% Purity[a] / %Yield[b]	%Purity[a] /%Yield[b]
13a	99 / 33	78 / 29	98 / 33
13b	90 / 43	84 / 45	95 / 36
13c	98 / 44	86 / 42	77 / 46
13d	95 / 50	99 / 70	98 / 75
13e	97 / 56	91 / 34	95 / 35
13f	97 / 37	80 / 57	80 / 40
13g	90 / 41	91 / 64	90 / 67
13h	94 / 79	94 / 63	72 / 38
14a	97 / 38	99 / 42	98 / 60
14b	88 / 25	97 / 28	89 / 64
14c	86 / 55	94 / 40	94 / 47

[a] % purity was based on HPLC peak area at 214 nm.

[b] Overall yield (4 steps, based on the initial loading of aminomethyl-PS crown) was calculated from the standard curve of the authentic compounds obtained from solution phase syntheses. Identical reaction conditions were applied to three linkers and the experiments were not individually optimized.

References and notes:

Abbreviations: DCM: dichloromethane, DIC: diisopropylcarbodiimide, DIEA: diisopropylethylamine, DMAP: dimethylaminopyridine, DMF: dimethylformamide, Dnp: 2,4-dinitrophenyl, ES-MS: electrospray mass spectrometry, Fmoc: 9-fluorenyl-methoxycarbonyl, HOBt: 1-hydroxybenzotriazole, PIP: piperidine, PS: polystyrene, TFA: trifluoroacetic acid, TNBSA: 2,4,6-trinitrobenzene sulfonic acid.

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12. HPLC, ES-MS and spectroscopic data for compound **9**: R_f = 0.39 (40% EtOAc in petroleum spirit 40-60), Rt = 6.2 mins. ES-MS m/z 237.0 $[M+H]^+$, 254.1 $[M+NH_4]^+$, 472.8 $[2M+H]^+$, 490.2 $[2M+NH_4]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.93 (d, J = 9 Hz, 2H), 6.91 (d, J = 9 Hz, 2H), 4.05 (t, J = 6 Hz, 2H), 2.56 (s, 3H), 2.46 (t, J = 7 Hz., 2H), 1.83-1.89 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 197.0, 179.3, 162.8, 130.6, 130.2, 114.1, 67.5, 33.5, 28.5, 26.3, 21.3.
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