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A Novel, Chemically Robust, Amine Releasing Linker

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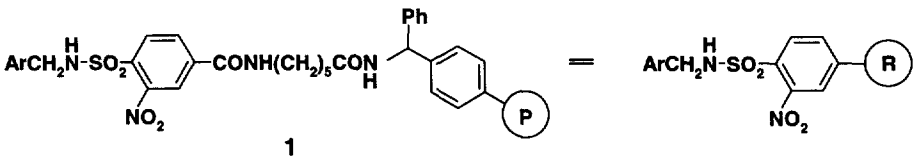
Abstract: A polymer supported sulfonamide **1**, based on an amine protective group, has been developed as a novel linker for solid phase organic synthesis. The linker permits the immobilisation of alcohol substrates, and releases *N*-protected amines under mild nucleophilic cleavage conditions.

The rapidly developing technologies of compound library generation and high throughput screening are revolutionising the drug discovery process in the pharmaceutical industry. The creation of large collections of structurally diverse, non-oligomeric molecules is now routinely undertaken using solid phase combinatorial chemistry[1], a process which is increasingly the target of automation. Central to the effective application of solid phase organic synthesis[2] is the availability of a tool box of suitable linkers. These permit substrates to be bound reversibly to a polymeric support, are inert to the synthetic sequence and subsequently allow the chemoselective release of the final products from the resin.

As part of a medicinal chemistry programme we required a chemically robust linker which would reveal an amino group on cleavage, but tolerate exposure to acidic, basic and oxidative reaction conditions. Herein we report the preparation and use of a polymer bound sulfonamide **1** which releases amines on nucleophilic cleavage.



1

The strategy of immobilising a suitable amine blocking group to provide a linker for solid phase synthesis has long been recognised by others[3]. The application of this principle has already delivered resin supported versions of commonly encountered nitrogen protective groups, such as the Cbz[3,4], Fmoc[5], Alloc[6], *p*-alkoxybenzyl carbamate[5,7], and alkyl carbamate[7b] functions.

A novel linker[8] for primary amines based on the acetyldimedone-derived, Dde[9] protective group has also been described. Rees *et al.* have recently reported[10] a particularly versatile protocol for ligating both

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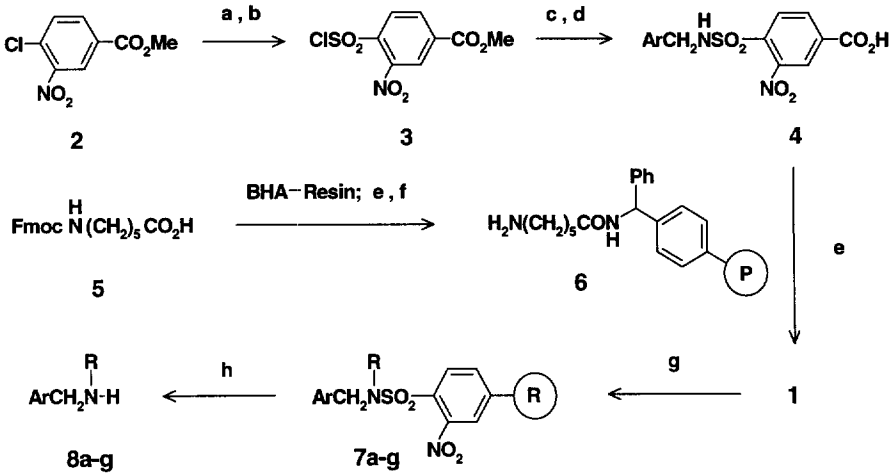
primary and secondary amines to resin by Michael addition to a polymer bound acrylate. This approach permits the solid phase functionalisation of secondary β-amino esters[11] by reductive *N*-alkylation. A method of encoding resin bound, combinatorial libraries has been developed[12] utilising chemically robust, *N*, *N*-disubstituted sulfonamides, which allows the chemoselective release of the secondary amines 'tags' on photolysis. In the course of the present study, workers at Parke-Davis have added a Boc-like linker[13] to the growing repertoire of amine anchoring strategies.

Despite these more recent developments there remains a paucity of linkers available for the amino group, which allow the immobilisation and chemoselective manipulation of compounds containing multiple basic centres. For this reason, the disclosure by Fukuyama[14] of the use of 2- and 4-nitrobenzenesulfonamides for the preparation and protection of secondary amines has prompted us to examine the utility of this type of functionality on a solid support. Attractive features of these amine derivatives are their stability to a wide range of reaction conditions, the efficiency with which they can be alkylated under Mitsunobu and conventional procedures, and their facile cleavage with thiolate anion.

Scheme



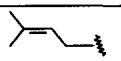
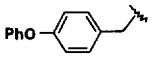
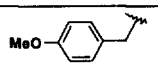
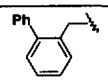
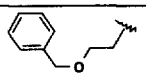
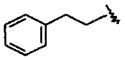
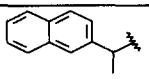
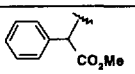
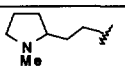
Reagents: **a)** Na_2S_2, DMSO, EtOH, RT, 92%; **b)** Cl_2, AcOH, H_2O, RT, 92%; **c)** *p*-(Me)$C_6H_5CH_2NH_2$ CH_2Cl_2, 86%; **d)** NaOH, MeOH, CH_2Cl_2, RT, 90%; **e)** PyBOP, HOBT, DIPEA, DMF, CH_2Cl_2, >95%; **f)** 20% Piperidine, DMF >95%; **g)** ROH, Ph_3P, DEAD, THF; **h)** PhSH, K_2CO_3, MeCN.

The system was assembled on BHA resin[15] and incorporates an aminocaproic acid spacer **5** (Scheme). Sulfenylation[16] of methyl-4-chloro-3-nitrobenzoate **2** and oxidative chlorination of the resulting disulfide gave the sulfonyl chloride **3**. Reaction with 4-methylbenzyl amine, followed by saponification of the ester provided the benzoic acid **4** (m.p. 184-187°). This was coupled to the modified BHA resin **6** to give the polymer supported sulfonamide **1**.

Allylic, benzylic and primary alcohols reacted efficiently with the linker **1,** under standard Mitsunobu conditions[12,17], to provide resin bound, tertiary sulfonamides **7** (Table, Entries b-g). For these classes of substrate the conversion to *N*-disubstituted products was essentially quantitative[18] when conducted under a double coupling protocol. However, secondary alcohols, including the activated substrate, methyl mandelate,

failed to alkylate the sulfonamide linker under these conditions (Entries h, j). Our limited experience suggests that tertiary amines are incompatible with the Mitsunobu reaction (cf. Entry k) and that substrates containing this functional group would need to be coupled using conventional procedures.

Table: Mitsunobu Coupling of **1** and Reductive Cleavage of Sulfonamides **7**.

Entry	R	Mitsunobu Coupling % Yield **7** [a,c]	Amine Cleavage % Yield **8** [b,c]
a	H	--	100
b		78 (98)	89 (100)
c		95	48 (67)
d		90 (100)	64 (100)
e		78 (100)	65 (88)
f		90	62 (88)
g		86 (100)	65 (100)
h		0	0[d]
j		0	0[d]
k		0	0[d]

a) Yields were determined by HPLC, post cleavage, using evaporative light scattering detection and are based on resin. b) Yields are for isolated amine products. c) Values in parentheses represent yields obtained for double coupling or double cleavage reactions. d) Primary amine **8a** recovered

Treatment of the resin bound sulfonamides **7** with a preformed solution of potassium thiophenoxide cleaved[19] secondary amines **8** from the polymeric support. Since the reductive cleavage results in the sulfur nucleophile becoming covalently bound to the linker, products of high purity are generated directly in this process, provided less than a stoichiometric amount of thiophenol is used. In general however, it was found that the modest yield of amine obtained with this protocol was significantly increased by using two equivalents of thiophenol (eg. Entries d,e) In this case the excess reagent was readily removed with a basic extraction during work-up.

In summary we have developed a novel linker which permits the solid phase immobilisation of alcohols as tertiary sulfonamides *via* the Mitsunobu reaction. These substrates, which should be stable towards a wide range of synthetic transformations, are cleaved under exceptionally mild conditions to provide the corresponding secondary amines in high yield.

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15. NovaSyn BHA resin, *ex* NovaBiochem, loading: 0.78 mmol/g. The aminocaproic acid spacer was incorporated to improve the efficiency of coupling the sulfonamide linker to the polymeric support; both amide couplings gave a negative Kaiser test.
16. See; Bogert, M.T.; Stull, A. *Org. Synth.* **Coll. Vol. I**, 220.
17. *Typical Experimental Procedure for Mitsunobu Couplings* [Preparation of **7f**]:
To the sulfonamide resin **1** (260 mg, 0.156 mmol equiv.) was added a solution of triphenylphosphine (3.9 ml, 0.80M in THF, 3.12 mmol), followed by a solution of 2-benzyloxyethanol (7.8 ml, 0.40M in THF, 3.12 mmol) and the mixture agitated (slow stream of nitrogen or gentle stirring) for 2 min. A solution of diethyl azodicarboxylate (7.8 ml, 0.40M in THF, 3.12 mmol) was added in four portions over 30 min and the mixture was agitated intermittently for 2 h and then allowed to stand for 18 h. The supernatant was removed by suction and the resin was washed sequentially with THF (3 x 2 ml), CH_2Cl_2 (4 x 2 ml), and ether (2 x 2 ml) and then dried *in vacuo* to give the **resin bound sulfonamide 7f.**
18. Yields for the Mitsunobu couplings were determined by HPLC, using evaporative light scattering detection, following cleavage of the amines from the resin. Products were characterised by HRMS and (in some cases) independant synthesis. HPLC was performed on a Hewlett Packard 1050 instrument using a C_{18} reverse phase column (Dynamax 60A, 250 mm, 4.6 mm ϕ) with 10 to 95 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 1% TFA in water; Solvent B; 0.5% TFA in MeCN:water (10 : 1), 15 min gradient time].
19. *Typical Experimental Procedure for the Reductive Cleavage of Amines* [Preparation of **8f**]:
The polymer supported sulfonamide **7f** (130 mg, 78 μmol equiv.) was treated with a preformed solution of potassium phenylthiolate (0.50 ml, 78 mM in CH_3CN, 39 μmol) and the mixture agitated gently for 30 min. A second portion of phenyl thiolate solution (0.50 ml, 78 μmol in total) was added and the reaction mixture agitated for 1 h and then allowed to stand for 18 h. The solution was collected by suction and the resin was washed sequentially with CH_3CN (5 x 1 ml) and CH_2Cl_2 (5 x 1 ml). The combined filtrands were evaporated under reduced pressure to give the **amine 8f** as a colourless oil (11.6 mg; 62%). HRMS calcd. for $[M+H]^+$ $C_{17}H_{22}NO$: 256.1701; found: 256.1705.

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