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A base labile handle for solid phase organic chemistry

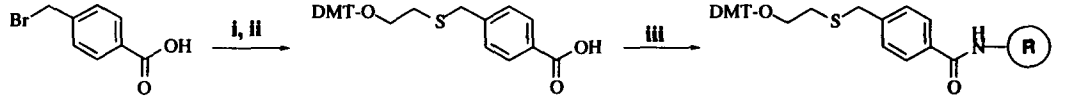
Carlos García-Echeverría

Oncology Research, Novartis Pharma Inc., CH-4002 Basel, Switzerland

Abstract: *Several arylsulfonamides have been synthesised on solid phase using a new base labile handle. Cleavage from the solid support is accomplished by oxidation of the sulfide to the sulfone, followed by β-elimination in base media.* © 1997 Elsevier Science Ltd.

Recently, polymer-supported organic synthesis has received an increase attention mainly in the field of combinatorial chemistry.[1] Although a series of reactions have been applied and optimized on solid supports,[2] the number of ways the building blocks or scaffolds are attached to the resin is still quite limited and rely mainly on the used of handles originally designed for the synthesis of biopolymers. In this letter, we report the synthesis and initial studies of a base labile linker — 4-{2-[4,4'-dimethoxytriphenyl-methoxy]-ethylsulfanylmethyl}-benzoic acid, **1** — for solid phase organic synthesis. The attached molecule is cleaved from the solid support by oxidation of the sulfide to the sulfone, followed by β-elimination in base media.[3] The application of the handle is illustrated with the synthesis on solid phase of several arylsulfonamides.

The handle **1** was prepared in two steps by alkylation of 2-mercaptoethanol to the commercially available α-bromo-*p*-toluic acid, followed by protection of the alcohol function with 4,4'-dimethoxytriphenylmethyl chloride (Scheme 1). The incorporation of **1** to the 4-methyl-benzhydrylamine [copolystyrene-1% DVB] resin (MBHA-R) was mediated with 2-(2-oxo-1(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluorofluoroborate (TPTU) or N-[(dimethylamino)1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethan-aminium hexafluorophosphate *N*-oxide (HATU) in the presence of diisopropylethylamine. The coupling efficiency and the loading of the newly functionalized support were determined by recording the UV-visible absorption of the 4,4'-dimethoxytriphenyl carbocation obtained upon treatment of an aliquot of the solid support with 3% dichloroacetic acid in dichloromethane and dilution of the effluent with a 0.1 M solution of *p*-toluenesulfonic acid.[4]

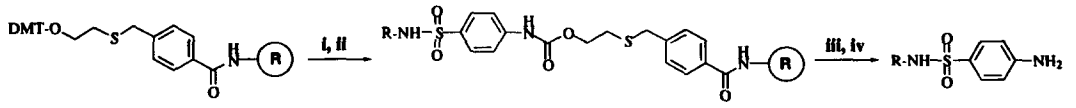


1

Scheme 1. i) 2-mercaptoethanol (1.1 equiv.), triethylamine (2.1 equiv.) in MeOH, 2 h at r.t., 88%; ii) 4,4'-dimethoxytriphenylmethyl chloride (1.7 equiv.) in anhydrous pyridine, 16 h at r.t. under argon, 78%; iii) MBHA-R (1 equiv.), **1** (3 equiv.), TPTU or HATU (3 equiv.), and diisopropylethylamine (6 equiv.) in *N*-methylpyrrolidin-2-one, 2 h at r.t., quant.

The synthesis of the arylsulfonamides **2-4** (Figure 1) was carried out following the protocol reported by Han *et al.*[5] (Scheme 2). After completion of the syntheses, **2-4** were removed from the solid support by oxidation of

the thioether to the sulfone with *m*-chloroperbenzoic acid, followed by β-elimination with a 10% solution of NH_4OH in 2,2,2-trifluoroethanol. The basic solution was neutralized with acetic acid and lyophilized several times to remove the solvent and the ammonium acetate salts. The crude compounds were characterized by ^1H NMR and mass analyses,[6] and the purity was assessed by analytical HPLC (Figure 1).[7]



Scheme 2. i) 3% dichloroacetic acid in DCM, 10 x 2'; ii) 4-(chlorosulfonyl)-phenyl-isocyanate (3.0 equiv.) and dibutyltinlaurate (0.4 equiv.) in *N*-methylpyrrolidin-2-one, 20 h at r.t.; isobutylamine, benzylamine or 3-amino-5-methyl-isoxazole (10 equiv.) in pyridine, 5 h at 40 °C; iii) *m*-chloroperbenzoic acid (5.0 equiv.) in DCM, 4 h at r.t.; iv) 10% solution of NH_4OH in TFE, 4 h at 40 °C.

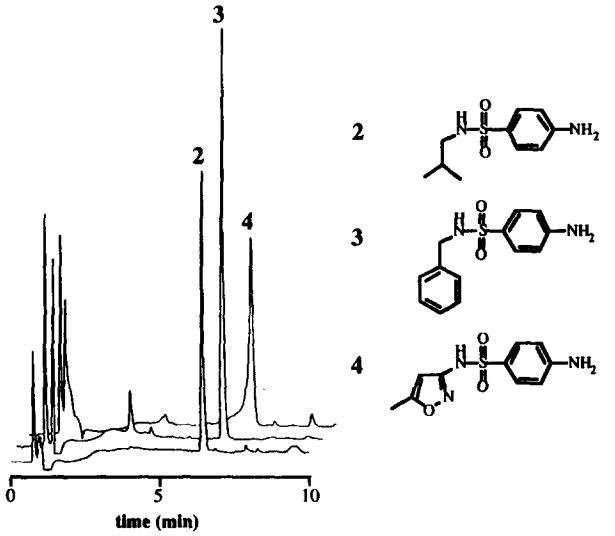


Figure 1. Analytical reversed-phase HPLC chromatograms on a C_{18} Nucleosil column (250 x 4 mm; 5 μm; 300 Å): linear gradient over 10 min of MeCN-0.09% TFA and H_2O-0.1% TFA from 1:49 to 1:0 (**2**,**3**) or 1:49 to 3:2 (**4**), flow rate 2.0 ml/min, detection at 215 nm.

References and Notes

1. a) Gordon, E.M.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gallop, M.A. *J. Med. Chem.* **1994**, 37, 1233-1251; b) *ibid*, 1385-1401.
2. Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron* **1997**, 16, 5643-5678.
3. This work rests on the ground of previously reported base labile linkers: a) Schwyzer, R.; Felder, E.; Failli, P. *Helv. Chim. Acta* **1984**, 67, 1316-1327; b) Buis, J.T.; Tesser, G.I.; Nivard, R.J. *Tetrahedron* **1976**, 32, 2321-2325.
4. $\varepsilon = 75\,310\ M^{-1}\ cm^{-1}$ ($\lambda = 497$ nm) and $\varepsilon = 30\,356\ M^{-1}\ cm^{-1}$ ($\lambda = 410$ nm) in 0.1 M *p*-toluenesulfonic acid.
5. Han, H.; Wolfe, M.M.; Brenner, S.; Janda, K.D. *Proc. Natl. Acad. Sci. USA* **1995**, 92, 6419-6423.
6. All the compounds exhibited satisfactory spectral and mass data.
7. Taking into account the loading of the initial resin (MBHA-R), the amount of crude compound obtained after cleavage from the solid support and the HPLC traces, we can estimate the following overall yields: 74% (**2**); 65% (**3**); and 43% (**4**).

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