Pergamon

Tetrahedron Letters, Vol. 37, No. 8, pp. 1145-1148, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02418-X

Application of the Sulfonamide Functional Group as an Anchor for Solid Phase Organic Synthesis (SPOS)

Krista A. Beaver, Aaron C. Siegmund and Kerry L. Spear*

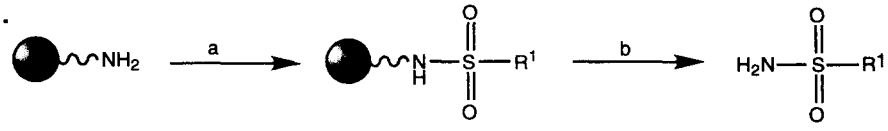
Chiron Corporation
4560 Horton St., Emeryville, CA 94608 USA

Abstract: Sulfonyl chlorides have been found to readily couple to an amino functionalized resin. The resulting sulfonamide anchoring group is stable to a variety of reactions commonly used in SPOS. Acid induced cleavage is facile, affording functionalized sulfonamides in high yields.

Chemical synthesis on a solid support has been used for several decades to prepare biopolymers such as peptides[1] or oligonucleotides.[2] More recently, this tool has been increasingly applied to the synthesis of small organic molecules[3] as individual compounds or libraries. In each of these cases, one of the reactants must be attached to the solid support prior to initiation of the synthesis. Commonly, this anchoring group is also the point of detachment after completion of the synthesis, thereby becoming a functional group of the cleaved product(s). Solid phase peptide synthesis has provided a number of ways of attaching carboxylic acids to a resin[4] as the ester or amide and synthesis of oligosaccharides on solid supports have afforded methodologies for anchoring alcohols via an ether linkage.[5] However, the rapid development of solid phase organic synthesis (SPOS) brings with it the need for expanding the variety of anchors in order to accommodate new synthetic methods and, especially in the case of combinatorial chemistry, to allow for inclusion of additional diversity elements. One such anchoring group is the sulfonamide. Attachment of a sulfonamide to resin via the sulfur to afford a polymer-SO_2NH_2 "safety-catch" linker is known,[6] although cleavage leaves a carboxylic acid or amide attached to the target molecule. Surprisingly few reactions of a sulfonyl chloride with the N-terminus of a resin-bound peptide have been reported.[7] Moreover, cleavage of the resulting sulfonyl peptide will also afford a C-terminus acid or amide functionality. Recently, Dankwardt and co-workers[8] anchored two sulfonamides directly to a solid support via the nitrogen, but both failed to react as expected in the subsequent step. We wish to report that a variety of sulfonyl chlorides will react readily with an amino functionalized solid support. Furthermore, the polymer-$NHSO_2R$ linkage appears to be stable to a variety of reaction conditions and can be readily cleaved in very good to excellent yields leaving a sulfonamide functional group attached to the target molecule(s).

Sulfonyl chlorides are known to react with amines in solution under quite mild conditions to afford sulfonamides and extension of this reaction to a solid support proved to be straightforward. While a number of amino functionalized solid supports are readily available, we limited our initial

Scheme 1.



1 2 3

(a) R^1SO_2Cl, pyridine/CH_2Cl_2; (b) trifluoroacetic acid, CH_2Cl_2

studies to the corresponding reaction of a sulfonyl chloride with Rink amide resin (see Scheme 1). Treatment of the resin with a sulfonyl chloride in the presence of pyridine at room temperature readily afforded the corresponding resin-bound sulfonamide **2**.[9] The extent of coupling was monitored by cleaving the product from resin using trifluoroacetic acid (TFA) and characterizing the recovered sulfonamide **3**. As shown in Table 1 (entries A-D), sulfonamidation of **1** is facile with aryl or alkyl sulfonyl chlorides to afford resin-bound sulfonamides of the type **2A-D**. Moreover, while cleavage from the resin (to give **3A-D**) is facile using conditions which are known to release the more typically encountered carboxamide-Rink resin linkage, the sulfonamide anchoring group appears to be stable to milder acids. No cleavage was found after treatment of **2A** with 50% acetic acid in methylene chloride at room temperature for 24h.

Table 1.

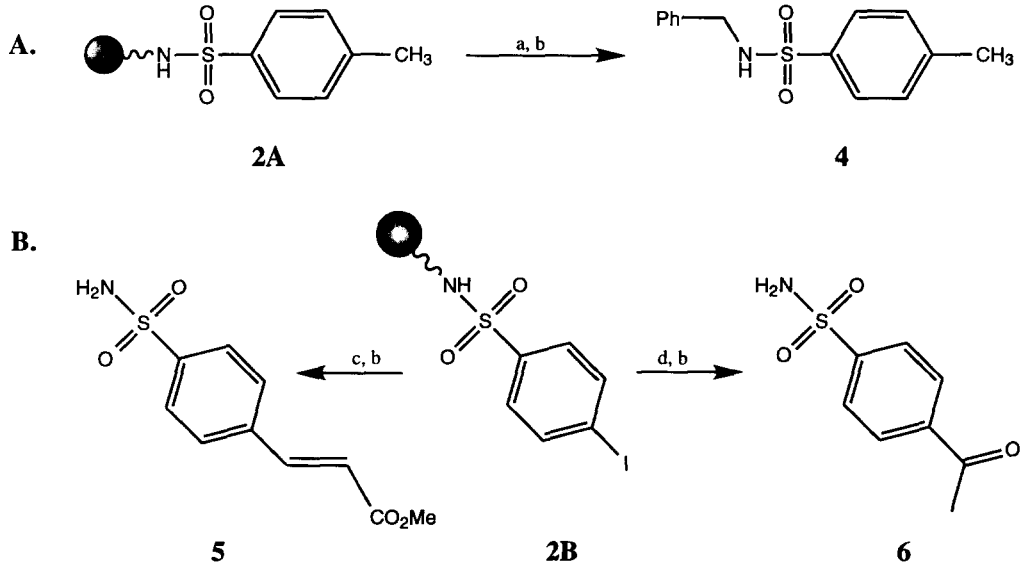
			Purity[a]		Mass	
Entry	Reactant	Product	GC/MS	HPLC	Calcd.	Observed
A	p-toluenesulfonyl chloride	**3A**	100%	78%	171	171
B	pipsyl chloride	**3B**	100%	100%	283	283
C	2-carbomethoxysulfonyl chloride	**3C**	100%	80%	215	215
D	10-camphorsulfonyl chloride	**3D**	78%	95%	231	231
E	2A	**4**	100%[b]	73%[b]	260	260
F	2B	**5**	100%[b]	95%[b]	241	241
G	2B	**6**	100%[b]	79%[b]	199	199

a. Yield of crude product after cleavage. b. Overall yield including attachment to resin and cleavage.

The anchoring group of **2** is sufficiently stable to permit further elaboration of either the sulfonamide NH or other functional groups present in the attached molecule. For example, treatment of **2A** with base followed by the addition of benzyl bromide and warming readily afforded the N-benzylated sulfonamide **4** (see Scheme 2A and Table 1, entry E) in very high purity by GC.[9] Additionally, the stability of the sulfonamide anchor to other reaction types was explored. Since it was reported[10] that the resin-bound ester of 4-iodobenzoic acid will readily undergo a Heck reaction, we decided examine this reaction using a sulfonamide anchored aryl iodide

derived from pipsyl chloride (4-iodophenylsulfonyl chloride). In an analogous reaction, **2B** was coupled with methyl acrylate in the presence of palladium(II) acetate to give **5**[9] (see Scheme 2B and Table 1, entry F). The purity, as determined by NMR, was nearly quantitative. The Stille coupling was also recently shown[11] to be compatible with SPOS and, in a final example, the sulfonamide anchor was also found to be stable to conditions required for this reaction. Sulfonamide **2B** was treated with 1-(ethoxyvinyl)tributyltin in the presence of Pd(0) and triphenylarsine to afford, after cleavage, the 4-acetyl sulfonamide **6**[9] (see Scheme 2B and Table 1, entry G). Hydrolysis of the initially formed enol ether presumably occurred during the cleavage.

Scheme 2. Examples of Reactions with Resin-Bound Sulfonamides



(a) KOtBu, THF,BnBr; (b) trifluoroacetic acid, CH_2Cl_2; (c) $Pd(OAc)_2$, Et_3N, $(nBu)_4NCl$, methyl acrylate, DMF; (d) Pd_2dba_3, triphenylarsine, 1-(ethoxyvinyl)tributyltin, NMP

We have shown here that sulfonamides can serve as anchoring groups for SPOS. Initial attachment of sulfonyl chlorides to resin is readily achieved in excellent yields under mild conditions. Moreover, the anchor is stable to a variety of reaction conditions, permitting the ready alkylation of the sulfonamide nitrogen as well as further elaboration of other attached functionalities. Finally, cleavage from the resin is facile under conditions which are commonly used in SPOS. The ready availability of a wide variety of sulfonyl chlorides will facilitate using the sulfonamide anchoring group in SPOS and molecular diversity. We are currently exploring several additional applications.

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9. *Typical Experimental Conditions*:

   4-Iodobenzenesulfonamide (3B) Fmoc protected Rink amide resin (Novabiochem; 0.5 g having a loading of 0.5 mmol/g, 0.25 mmol) was treated with a solution of 1:1:1/piperidine: toluene: DMF. After 30 min the resin was washed with DMF (4X) and CH_2Cl_2 (4X). To a slurry of deprotected resin in 50% pyridine: CH_2Cl_2 was added pipsyl chloride (378 mg, 1.25 mmol). The reaction was agitated at room temperature for 15 h. The resin (**2B**) was then filtered and washed with DMF (4X) and CH_2Cl_2 (4X). The resin was treated with 20% TFA: CH_2Cl_2 for 15 min. It was then filtered and the eluant evaporated to dryness to afford a white solid. HPLC: 18.68 min, 100%; GC-MS (M) for $C_6H_6NO_2SI$: calc. 283, found (M) 283 (100%).

   N-Benzyl-4-toluenesulfonamide (4) To a slurry of resin bound sulfonamide **3A** (50 mg, 0.025 mmol) in THF was added potassium tert. butoxide (1M in THF, 250 µl, 125 mmol) followed by benzyl bromide (30 µl, .250 mmol). The reaction was heated to 50° C for 2 h, at which point the resin was filtered and washed with DMF (4X) and CH_2Cl_2 (4X). Cleavage from resin as described above and evaporation to dryness afforded the product as a white solid. HPLC: 22.3 min, 73%; GC-MS (M) for $C_{14}H_{15}NSO_2$: calc. 260, found (M) 260 (100%).

   Methyl 4-aminosulfonylcinnamate (5) To a slurry of resin bound sulfonamide **3B** from above (100 mg, 0.05 mmol) in DMF was added palladium(II) acetate (10 mg, .045 mmol) and tetra n-butyl ammonium chloride (10 mg, 0.035 mmol), followed by triethylamine (25 µl, .18 mmol) and methyl acrylate (90 µl, 1 mmol). The reaction was rocked at 90° C for 18 h. The resin was filtered and washed with DMF (4X) and CH_2Cl_2 (4X). Cleavage from resin as described above and evaporation to dryness afforded the product as a clear oil. HPLC: 16.83 min, 95%; GC-MS (M) for $C_{10}H_{11}NSO_4$: calc. 241, found (M) 241 (100%); ^{1}H NMR (d_6-DMSO, 300 MHz): δ 3.8 (s, 3H, OCH_3), 3.9 (s, 2H, NH_2), 6.8 (d, J = 17 Hz, 1 H, =CH), 7.7 (d, J = 17 Hz, 1H, =CH), 7.9 (dd, J=32, 9 HZ, 2H, Ar).

   4-Acetylbenzenesulfonamide (6) To a slurry of resin bound sulfonamide **3B** from above (100 mg, 0.05 mmol) in NMP was added Pd_2dba_3•$CHCl_3$ (5 mg, .0025 mmol) followed by triphenylarsine (6 mg, 0.01 mmol). The slurry was sparged with argon and allowed to stand at room temperature for 5 min. 1-(Ethoxyvinyl)tributyl tin (336 µl, .25 mmol) was added and the reaction shaken for 15 h at 70° C. The resin was filtered and washed with DMF (4X), CH_2Cl_2 (4X), pentane (1X) and dilute KCN in DMSO (1X). Cleavage from resin as described above afforded a white solid. HPLC: 17.78 min, 78% GC-MS (M) for $C_8H_9NSO_3$: calc. 199, found (M) 199 (100%). ^{1}H NMR (CD_3OD, 300 MHz) δ 2.8 (s, 3H, CH_3), 8.1 (dd, J=36, 9 Hz, 4H, Ar)
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(*Received in USA* 22 *November* 1995; *revised* 8 *December* 1995; *accepted* 11 *December* 1995)