

# The Sulfamate Functional Group as a New Anchor for Solid-Phase Organic Synthesis

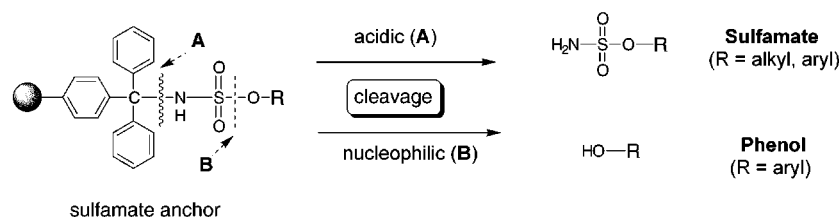
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## ABSTRACT



Sulfamate derivatives were loaded on trityl chloride resin, and two variants of cleavage were developed for this sulfamate anchor: an acid treatment to easily restore the free sulfamate and a nucleophilic treatment to generate the corresponding phenol. In addition to loading/cleavage assays and stability experiments, a model sequence of reactions was performed with the new sulfamate anchor to show its applicability in further combinatorial solid-phase synthesis of libraries of biologically relevant sulfamate derivatives.

Combinatorial chemistry has recently emerged as a powerful tool that can generate large and diversified molecular libraries.<sup>1</sup> Further development of solid-phase organic synthesis will certainly enhance the use of combinatorial chemistry. The discovery of new linkers and anchoring groups that accommodate various synthetic sequences of reactions will be instrumental to the preparation of new types

of libraries. Some of the currently available anchors that have been used to develop libraries of biologically active compounds include phosphonates,<sup>2</sup> carbamates,<sup>3</sup> and sulfonamides,<sup>4</sup> but to date the use of a sulfamate functional group as an anchor for solid-phase organic synthesis has not been implemented.

The sulfamate derivatives, which can be obtained from phenols or alcohols, possess numerous interesting biological properties, such as antibacterial,<sup>5</sup> antitumoral,<sup>6</sup> cytotoxic,<sup>7</sup> and anticonvulsive.<sup>8</sup> Moreover, steroidal and nonsteroidal sulfamates have been recently identified as potent inhibitors of steroid sulfatase.<sup>9</sup> The linkage of sulfamates to a solid

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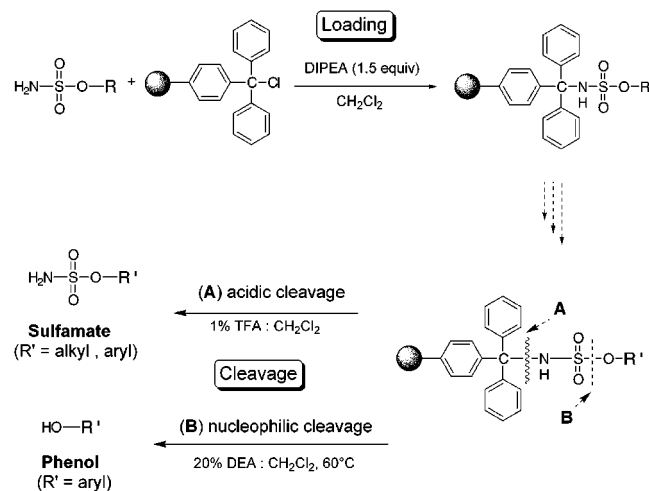
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polymer support and further introduction of molecular diversity will accelerate the discovery of new biologically active compounds through creation of sulfamate libraries. In this paper, we describe for the first time the loading of a sulfamate group to a trityl chloride polystyrene solid support and its use as an anchor or a linker for the solid-phase synthesis of sulfamates or phenols (Figure 1). The question



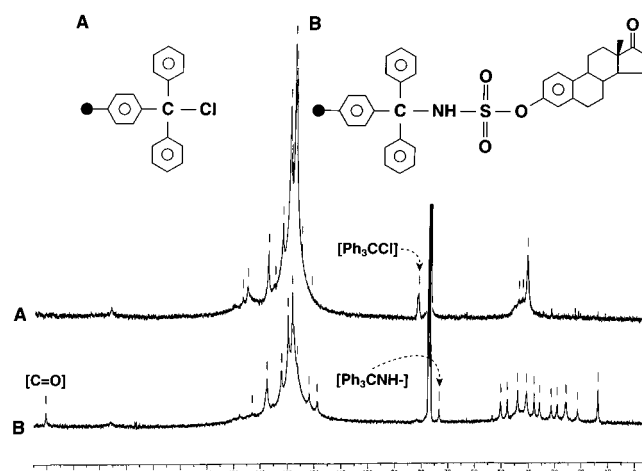
**Figure 1.** Loading of sulfamate on trityl chloride resin and both variants (A and B) for the cleavage of the new sulfamate anchor after introducing or not introducing molecular diversity ( $\text{R}'$ ).

of the sulfamate anchor stability under conditions commonly used in solid-phase organic reactions is also addressed. Finally, a sequence of reactions is reported that illustrates the viability of sulfamate anchoring.

The triphenylmethyl (trityl) group was previously used to protect sulfamates of primary alcohols in the synthesis of nucleocidin.<sup>10</sup> Acidic deprotection recovers the initial sulfamates without producing side products. Because these protection–deprotection reactions were almost quantitative in solution, it prompted the investigation of the efficiency of coupling–decoupling sulfamate molecules with commercially available trityl chloride polystyrene resin. Before attempting the solid-phase experiments (Table 1), preliminary liquid-phase tests were first performed with sulfamates **1–4**, which were derived from corresponding phenols or alcohols by known methodology.<sup>11</sup> These sulfamates were treated with trityl chloride (1.2 equiv) in the presence of diisopropylethylamine (DIPEA) (1.5 mL/mmol) and dichloromethane to yield the *N*-trityl sulfamate derivatives. These yields varied between 75% and 96% for the trityl sulfamate model compounds and were found to be particularly high for phenolic sulfamates **1** and **4**. The free sulfamate compounds **1–4** were then regenerated by reacting the corresponding trityl sulfamates with a solution of 1% trifluoroacetic acid

(TFA) in dichloromethane. Under these conditions, the relative chemical stability of the recovered sulfamates was found to be phenolic > primary alcohol > secondary alcohol (phenolic and primary alcohol sulfamates being stable for several hours). As expected, the sulfamates **1**, **2**, and **4** were completely recovered within 1 h after acidic cleavage, while the sulfamate **3** was isolated in the form of a trifluoroacetate derivative **3A** of the corresponding primary alcohol **3B**.

Sulfamate derivatives **1–4** were then loaded onto trityl chloride resin (Novabiochem, 0.95 mmol/g) before being cleaved from the solid support by procedures similar to those used for the model reaction assays in solution described above.<sup>12,13</sup> The  $^{13}\text{C}$  NMR spectra of the resin that reacted with estrone-3-*O*-sulfamate (**1**) clearly revealed the presence of the C-17 carbonyl group of the estrone derivative along with additional evidence of the steroid backbone (Figure 2).



**Figure 2.**  $^{13}\text{C}$  NMR spectra of trityl chloride resin (A) and estrone-3-*O*-sulfamate (**1**) loaded to trityl resin (B). The spectra were recorded at 75.5 MHz using 100 mg of resin swelled in 0.6 mL of  $\text{CDCl}_3$ , within a total experiment time of 12 h with the following conditions:  $d_1 = 1.0$  s,  $p_1 = 30^\circ$  (3.0  $\mu\text{s}$ ),  $aq = 430$  ms, RG 800, SI = 32 K.

Furthermore, a characteristic shift of the tertiary carbon signal of the triphenylmethyl group signaled the formation of a C–N covalent bond and, correspondingly, the loading of the compound **1** on the resin. The results summarized in Table 1 (part A) show high overall yields (80–96%) for coupling and cleavage of both alkyl and aryl sulfamates. The lower yield of compound **3B** (64%) could be explained by the additional reaction step (1.2 equiv of NaOH from a 4 N

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(12) **General Procedure for Loading Sulfamate Derivatives on Trityl Chloride Resin.** A solution of sulfamate derivative (3 equiv) and diisopropylethylamine (1.5 mL/mmol) were added successively to the trityl chloride resin (Novabiochem, 0.95 mmol/g) previously swelled in the corresponding volume of  $\text{CH}_2\text{Cl}_2$ , and the mixture was agitated for 3–12 h. The resin was filtered and washed with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ ) and methanol (3 $\times$ ).

(13) **General Procedure for the Acidic Cleavage of Sulfamate Derivatives from Trityl Resin.** To the loaded resin (Table 1) swelled in  $\text{CH}_2\text{Cl}_2$  was added sufficient trifluoroacetic acid (TFA) to obtain a 1% solution of TFA in  $\text{CH}_2\text{Cl}_2$ . After 1 h, the resin was filtered and washed with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ ). The solution containing the recovered sulfamate derivative was washed with water (2 $\times$ ) and evaporated to dryness.

**Table 1.** Cleavage Studies of Sulfamate Anchor to Generate Sulfamates **1–4** (A) or Phenols **5** and **7** (B)

Compound linked on trityl resin <sup>12</sup>	A Acidic cleavage (1% TFA in CH <sub>2</sub> Cl <sub>2</sub> ) <sup>13</sup>	Reaction time (h)	Yield <sup>a</sup> (%)	HPLC Purity <sup>b</sup> (%)	B Nucleophilic cleavage (20% DEA in CH <sub>2</sub> Cl <sub>2</sub> , 60°C) <sup>14</sup>	Reaction time (h)	Yield <sup>a</sup> (%)	HPLC Purity <sup>b</sup> (%)
		12	96	95		8	90	99
		1	86	95 <sup>c</sup>		24	0	-
		12	64 ( <b>3B</b> )	98 ( <b>3B</b> )		12	80	99
		3	80	98		24	0	-

(a) For a coupling – cleavage sequence; (b) C18-NovaPak column using a mixture of CH<sub>3</sub>CN-H<sub>2</sub>O-CH<sub>3</sub>OH as eluent; (c) Purity estimated by TLC and <sup>1</sup>H NMR (compound does not absorb in UV).

aqueous solution, THF) needed to hydrolyze the trifluoroacetate intermediate **3A**.

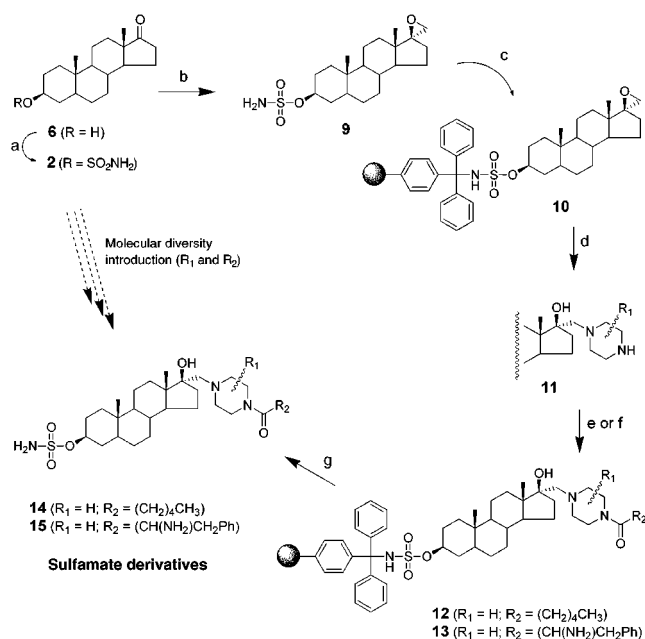
An interesting feature of the sulfamate anchor is its stability with regard to nucleophiles. In a liquid-phase model study, the *N*-trityl derivative of sulfamate **1** was found to be resistant to nucleophilic cleavage for 3–5 h when treated with 20% piperidine in dichloromethane at room temperature. This proves that the sulfamate anchor can withstand conditions that are currently used in peptide synthesis when removing Fmoc amine protecting groups. Alkyl sulfamates are even more resistant to nucleophilic attack than aryl sulfamates. After several days of heating with 20% diethylamine in dichloromethane, the *N*-trityl derivatives of alkyl sulfamates **2** and **4** were practically unchanged. In contrast, the *N*-trityl derivatives of aryl sulfamates **1** and **3** liberated the corresponding phenols in high yields when heated with either 20% piperidine in dichloromethane or with 20% diethylamine (DEA) in ethanol at 50–60 °C for 1 day. Compounds **1** and **3** were then loaded onto trityl chloride resin, and the sulfamate anchor was cleaved by 20% DEA in ethanol.<sup>14</sup> The coupling-cleavage yields and the purity of the resulting phenols **5** and **7** are presented in Table 1 (part B). Thus, two variants may be used for the cleavage of phenolic trityl sulfamates from solid support (Figure 1).

(14) **General Procedure for Nucleophilic Cleavage of Phenolic Sulfamates from Trityl Resin.** The loaded resin (Table 1) was swelled in CH<sub>2</sub>-Cl<sub>2</sub>, and a corresponding amount of diethylamine (DEA) was added to obtain a 20% v/v solution of DEA in CH<sub>2</sub>Cl<sub>2</sub>. The mixture was heated overnight at 55–60 °C, filtered, and washed with CH<sub>2</sub>Cl<sub>2</sub> (2×). The resulted solution was washed with water (2×) and evaporated to dryness.

Treatment with 1% TFA in dichloromethane easily recovers the free sulfamates, while a convenient treatment with nucleophiles (DEA or piperidine) can be used to obtain the corresponding phenols.

The *N*-trityl derivatives of sulfamates **1–4** were tested in liquid phase for their stability under basic, oxidative, and reductive reaction conditions. The *N*-trityl derivative of estrone-3-*O*-sulfamate (**1**) was reacted with tetrabutylammonium fluoride (3–9 equiv) in THF and with 4 N sodium hydroxide (20 equiv) in water–dioxane (1:1). In both assays, after 1 day at room temperature, followed by another day in refluxing solvents, no reaction occurred. *N*-Trityl derivatives of sulfamates **2–4** were also tested in these conditions, and the anchoring group remained stable. Reduction of the C17-ketone of the *N*-trityl derivative of estrone (or epiandrosterone)-3-*O*-sulfamates **1** (or **2**) with LiAlH<sub>4</sub> in THF and oxidation (TPAP, 4-Me-NMO, CH<sub>2</sub>Cl<sub>2</sub>) of their corresponding 17β-OH derivatives were completed without affecting the sulfamate anchor.

To show the viability of the sulfamate anchor for solid-phase organic synthesis, a sequence of reactions was performed (Figure 3). The oxirane **9** was synthesized from epiandrosterone-3-*O*-sulfamate (**2**) and linked to a trityl chloride resin following standard procedure. The opening of the oxirane **10** with an excess of piperazine in ethanol at 55–60 °C was completed in 2 days to yield the secondary amine **11**. This later was then converted to amides **12** or **13** by reacting with hexanoyl chloride or *N*-Fmoc phenylalanine. Finally, the treatment of resins **12** or **13** with 1% TFA in



**Figure 3.** Solid-phase synthesis of sulfamate derivatives **14** and **15**. (a) H<sub>2</sub>NSO<sub>2</sub>Cl, 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; (b) (CH<sub>3</sub>)<sub>3</sub>S<sup>+</sup>I<sup>-</sup>, NaH (12 equiv), DMSO, rt, 12 h; (c) trityl chloride resin, DIPEA (6 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h; (d) piperazine (R = H) (200 equiv), EtOH, 55–60 °C, 48 h; (e) CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>COCl, pyridine (6 equiv), rt, 2 h; (f) (1) *N*-α-Fmoc-L-phenylalanine, PyBrOP, HOBT, DIPEA, DMF, rt, 2 h; (2) piperidine (20%), CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; (g) 1% TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h.

dichloromethane yielded the sulfamate derivatives **14** or **15** after washing with K<sub>2</sub>CO<sub>3</sub>/MeOH (HPLC purities of 93%

and 97%, respectively). Compounds **14** and **15** were characterized by IR, MS, and <sup>1</sup>H and <sup>13</sup>C NMR analysis.

In summary, we have shown that sulfamates of phenols and alcohols can be easily loaded onto and cleaved from a trityl resin solid support. The sensitivity of the anchor to nucleophiles limits the use of phenolic sulfamates in solid-phase organic synthesis, but careful planning of the synthetic strategies may overcome this problem. In fact, this sensitivity provides the means to produce biologically active sulfamates and phenols through either acidic or nucleophilic cleavage, respectively. The newly developed sulfamate anchor is also resistant to basic, oxidative, and reductive conditions. Following the successful solid-phase synthesis of model compounds **14** and **15**, work is in progress to extend the use of the sulfamate anchor to the preparation of combinatorial libraries of steroid sulfatase inhibitors.<sup>15,16</sup>

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**Supporting Information Available:** HPLC chromatograms of compounds **1**, **3–5**, **7**, **14**, and **15** and spectroscopic data of compounds **14** and **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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