**Introduction**

In the area of combinatorial library synthesis for medicinal agents there is a constant need for new methodologies [1]. The sulfamide compounds are noted for their broad and potent antibacterial activity [2-3]. The unsymmetric sulfamides appear to be more potent as protease inhibitors than the symmetric analogues due to the flipped conformation that occurs during binding [4]. Unfortunately, most syntheses focus on symmetric sulfamides. The few methods available for unsymmetrical compounds rely on low-yielding synthetic steps that are neither general nor selective [1,5]. A novel transition-metal-catalyzed process for making unsymmetric sulfamides that was recently reported has several limitations, especially with ortho-isomers [1]. Even though other available methods report high yields, they either require reagents that are not readily accessible or they focus on specific structures rather than a general procedure [6]. Winum and co-workers reported a novel sulfamoylating reagent used in the synthesis of sulfamides [8]. However, our study showed that using the sulfamoylating reagent added additional steps and resulted in slow, low-yielding reactions. In an effort to find a fast and general method for sulfamide synthesis we found that microwave heating facilitates the synthesis of sulfamides. This was accomplished in one-pot reaction by a stepwise addition of CSI to tertbutanol at 0 °C to form the N-(tert butoxycarbonyl) sulfamoyl chloride intermediate 2 (scheme 1). Anilines or amines were added the reaction mixture was heated using microwave heating at 80 °C for five minutes. The resulting products were isolated using normal-phase flash chromatography with a good yield (table 1). Microwave synthesis provided great improvements in increasing product yield and decreasing reaction time [7].

![Scheme 1](image)

The microwave assisted Mitsunobu reaction was used for alkylation of Boc-sulfamides with different alcohols (Scheme 2) [9]. The reaction time depended on the structure of alcohols. For example, microwave irradiation of benzyl alcohol mixture with Boc - sulfamides, triphenyl -phosphine and diethyl azodicarboxylate (DEAD) in THF provided N-alkylated products in four minutes at 80 °C. In the case of 2- pyridinepropanol (compounds 10,12,14), one minute of microwave heating was enough to complete reaction.
Table 1: One-pot microwave-assisted sulfamides synthesis

<table>
<thead>
<tr>
<th>#</th>
<th>Amines</th>
<th>Products*</th>
<th>% Yield</th>
<th>% Purity</th>
<th>(M⁺ Na⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>80</td>
<td>96</td>
<td>309.93</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>55</td>
<td>97</td>
<td>295.94</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>62</td>
<td>93</td>
<td>308.93</td>
</tr>
<tr>
<td>6</td>
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<td>67</td>
<td>96</td>
<td>334.97</td>
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<td>7</td>
<td></td>
<td></td>
<td>86</td>
<td>97</td>
<td>363.93</td>
</tr>
</tbody>
</table>

* Reactions were performed in the Biotage EMRYS™ Liberator microwave system in 2-5 mL reaction vials at 80 °C. 

Yield of isolated product: All products were isolated on the Biotage Sp automated flash chromatography system (Flash 25+ M, 25 x 150, 40-63 mm, 60 Å), using ethyl acetate and hexane gradient. 

C Purity is calculated by HPLC (Waters, C8 4.6 x 50 mm, S-3 120 Å). 

D Mass spectroscopy was carried out on a Micromass® ZQ (Waters). 

E 1H NMR data in CDCl₃ was collected on a 500 MHz Bruker spectrometer.

The tert-butoxycarbonyl group removal is generally carried out with trifluoroacetic acid either neat or in combination with CH₂Cl₂ [14]. Since CF₃COOH is volatile, harsh and corrosive, a search for an alternative method of deblocking is ongoing.

Recently was reported that Amberlyst 15, a strong acidic resin, can remove the Boc protecting group and form salts with the deprotected amines [15]. This method has been used to facilitate the generation and purification of amines. However, this technique requires a long reaction time (12-24 hours). We decided to explore the scope and limitations of deblocking the BOC-group from sulfamides using silica-bonded phenylsulfonic acid, and the effects of microwave heating in altering the reaction time (scheme 3). Bocsulfamides were treated with Si-TsOH and heated by microwaves at 100 °C. In all the examples, the Boc-protecting group was completely removed within five minutes [16]. Here we report that microwave heating with Si-TsOH significantly shortens the Boc-removal time.

The formation of salts between the sulfamide and silica bonded acid depends on subsituents on the sulfamide nitrogen (pKa of sulfamides 7-11). The desired products were released from Si-TsOH surface using NH₃/MeOH (scheme 3).
Table 3: Microwave-assisted BOC- deblocking using Si-TsOH

<table>
<thead>
<tr>
<th>#</th>
<th>Products(^a)</th>
<th>% Yield(^b)</th>
<th>M+ + Na(^c)</th>
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<tbody>
<tr>
<td>15</td>
<td></td>
<td>90</td>
<td>209.11</td>
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<tr>
<td>16</td>
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<td>75</td>
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<td>22</td>
<td></td>
<td>89</td>
<td>354.42</td>
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</table>

\(^a\) Reactions were performed in the Biotage EMRYSTM Liberator microwave system in 2-5 mL reaction vials. \(^b\) Yield of isolated product. \(^c\) Mass spectroscopy was carried out on a Micromass \(^\circledR\) ZQ (Waters). \(^\circledR\) \(^1\)H NMR data was collected on a 500 MHz Bruker spectrometer.
Conclusion
A general microwave assisted reaction in preparation of unsymmetric Boc-sulfamides is demonstrated. Also, an alternative method of Boc-removal from sulfamide was introduced using Si-TsOH in conjunction with microwave heating. Boc-de-blocked sulfamides were captured by Si-TsOH, depending on their pKa. The captured sulfamides were released from surface of Si-TsOH by using NH3 in MeOH, followed by quick flash purification. This new method of microwave-assisted, Boc-cleavage group from sulfamides facilitates the preparation and purification of unsymmetric sulfamides.

References:
1. Alcaraz, L; Bennion, C; Morris, J; Meghani, P; Thom, S. Org. lett. (2004). 0, A-D
7. Alcaraz, L; Bennion, C; Morris, J; Meghani, P; Thom, S. Org. lett. (2004). 0, A-D
8. General procedure for Boc-sulfamides using microwave heating: In a typical experiment, chlorosulfonyl isocyanate (0.24 ml, 2.7 mmol) was added dropwise to a solution of tert-butyl alcohol (0.26 ml, 2.7 mmol) in anhydrous dichloromethane (3 ml) in a sealed Pyrex tube under inert gas at 0°C. Amine (5.5 mmol) was then added and the reaction was heated in a microwave cavity for 5 minutes at 80°C. The reaction mixture was added to a Samplet™ cartridge and purified by flash chromatography.
8. General procedure for microwave assisted Boc-sulfamides cleavage with Si-TsOH: Method A: Silicabound p-toluenesulfonic acid (1.26g, 0.96 mmol) was added to the Boc-protected sulfamide (0.32 mmol) in 1:1 acetonitrile:DCM (4ml). The reaction was heated to 100°C in a microwave cavity for 5 minutes. The reaction mixture was then loaded onto a silica column. Using the following conditions on flash chromatography yielded the desired compound.
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