

Microwave-Assisted Synthesis of Unsymmetrical Boc- Sulfamides and Boc- Cleavage by Silica-Phenyl Sulfonic Acid

Shahnaz Ghassemi, Kristin Fuchs
Biotage
Discovery Chemistry Group
1725 Discovery Drive
Charlottesville, VA 22911

Background

- **There is a constant need for new methodologies to produce focused libraries for unique compounds including protease inhibitors**
- **The sulfamide compounds are noted for their broad and potent antibacterial activity. The unsymmetrical sulfamides appear to be more potent as protease inhibitors than the symmetric analogues**
- **Unfortunately, most syntheses focus on symmetric sulfamides and the few methods available for non-symmetric compounds rely on low-yielding synthetic steps that are neither general nor selective**

Introduction

- **In an effort to find a fast and general synthetic method for unsymmetrical sulfamides, the scope and limitations of microwave heating were explored for the following reactions:**
 - **One-pot Boc-sulfamide synthesis**
 - **Alkylating Boc-sulfamide using Mitsunobu reaction to add more diversity**
 - **Removing Boc- group from sulfamide using silica-bonded phenylsulfonic acid**

Biotage Emrys™ Liberator Microwave System



- **Biotage Emrys™ Liberator microwave system was utilized for all the MAOS reactions**
- **Microwave system was equipped with:**
 - **Emrys™ Reaction Kits**
 - **Emrys™ PathFinder**
 - **Liquid handling for up to 60 samples**
 - **Built in user interface**
 - **Compatible with the 2-5 and 10-20 mL vessels**
- **All work reported in this poster was performed in the 2-5 mL round bottom reactor tube**



2-5 mL Round bottom reactor tube

Biotage SP4™ Automated Flash Purification System



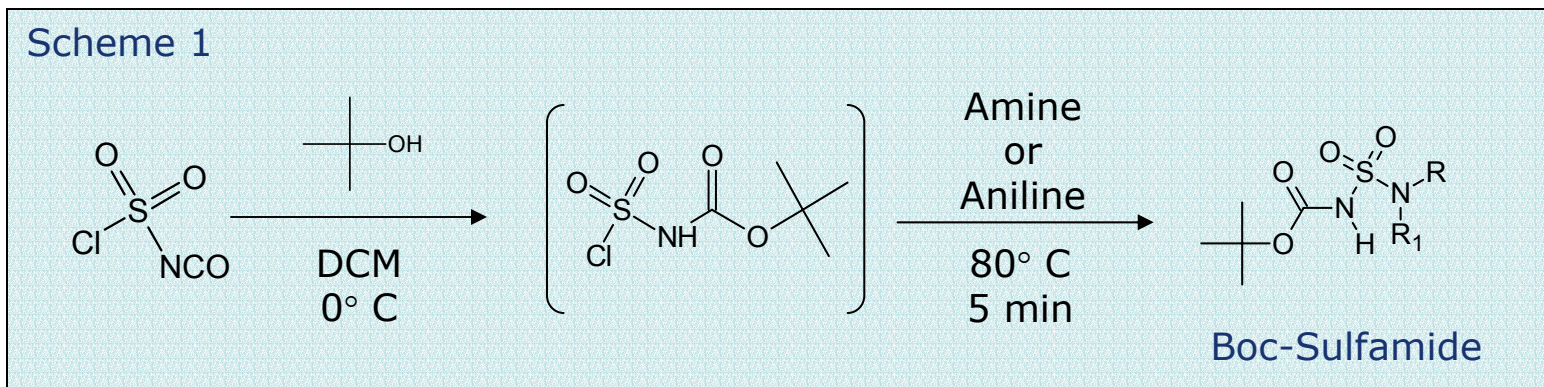
- **Biotage SP4™ automated FLASH™ chromatography purification system was used to purify all of the reaction mixtures, using gradient elution conditions**
 - **Tertiary gradient FLASH™ purification system with UV absorbance monitoring capable of performing four different unattended flash purifications**
- **Utilizes 12, 25, 40 and 65 mm diameter cartridge sizes with flow rate up to 100 mL/min**

One-Pot Microwave-Assisted Boc-Sulfamides Synthesis



Figure 1

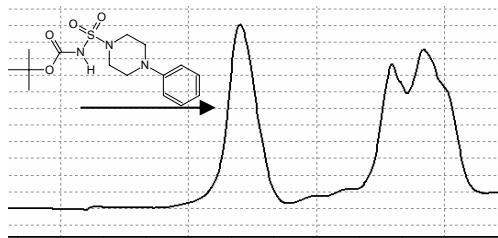
- **Boc-sulfamides were prepared following the reaction scheme 1**
 - The step-wise addition of chlorosulfonyl isocyanate (CSI) to tert-butanol at 0 °C under helium in a capped vial (Figure 1) was followed by the addition of anilines or amines
 - Reaction mixture was heated in the Emrys™ Liberator microwave system for 5 minutes at 80 °C



General Flash Purification of Boc-Sulfamides



Figure 2: Samplet containing product is inserted onto Flash 25+™M cartridge



Chromatogram 1: Compound 7 separation from reaction mixture on Flash 25+™M cartridge

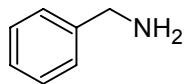
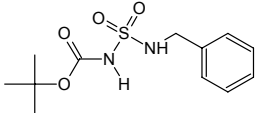
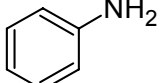
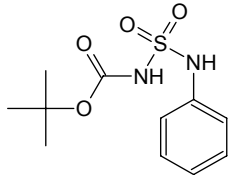
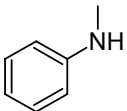
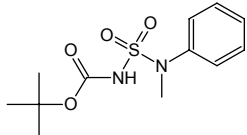
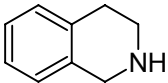
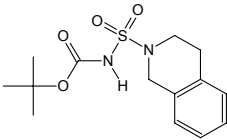
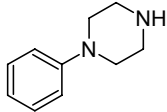
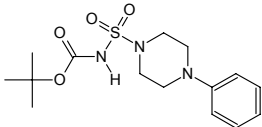
- Reaction mixture directly transferred onto a Samplet™ and inserted on top of a Flash 25+™ M cartridge (Figure 2)
- Gradient condition used to isolate pure products at 55-86% isolated yield

Cartridge	FLASH 25+™M KP-Sil
Solvent	A: Hexane, B: EtOAc
Gradient Program	Equilibrated: 20% B in 140 mL Step 1: 20-45% in 750 mL Step 2: 45-100% B in 400 mL
Flow rate	51 mL/min
UV detection	254 nm

- Chromatogram 1 shows a typical purification, using Flash 25+™M cartridge with SP4™ automated FLASH™ chromatography system

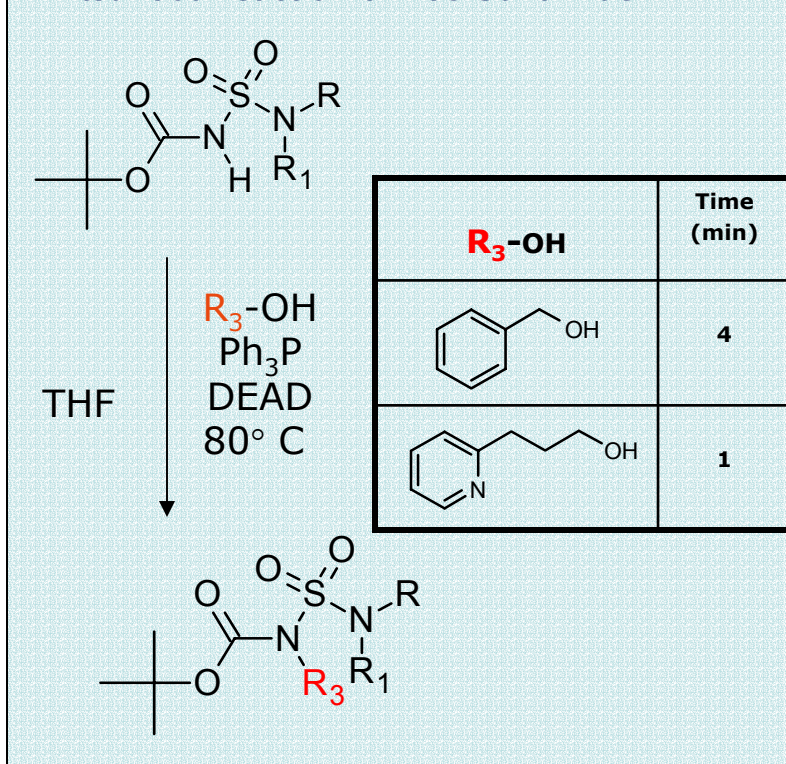
Boc-Sulfamides Synthesized

One-pot microwave-assisted Boc-sulfamides synthesized followed by FLASH Chromatography purification. All products were verified by MS and H-NMR

	Amines	Products	% Isolated Yield	% Purity	<i>m/z</i> (M ⁺ + Na)	¹ H NMR
3			80	96	309.93	1.462 (s, 9H), 4.24 (d, 2H), 7.34 (m, 5H)
4			55	97	295.94	1.39 (s, 9H), 6.85 (s, 1H), 6.95 (s, 1H), 7.15-7.3 (m, 5H)
5			62	93	308.93	1.410 (s, 9H), 3.433 (s, 3H), 6.812 (s, 1H), 7.333 (m, 5H)
6			67	96	334.97	1.388 (s, 9H), 2.88 (t, 2H), 3.62 (t, 2H), 4.54 (s, 2H), 6.93 (s, 1H), 7.15 (m, 4H)
7			86	97	363.93	1.425 (s, 9H), 3.187 (t, 4H), 3.486 (t, 4H), 6.867 (m, 3H), 7.03 (s, 1H), 7.189 (m, 2H)

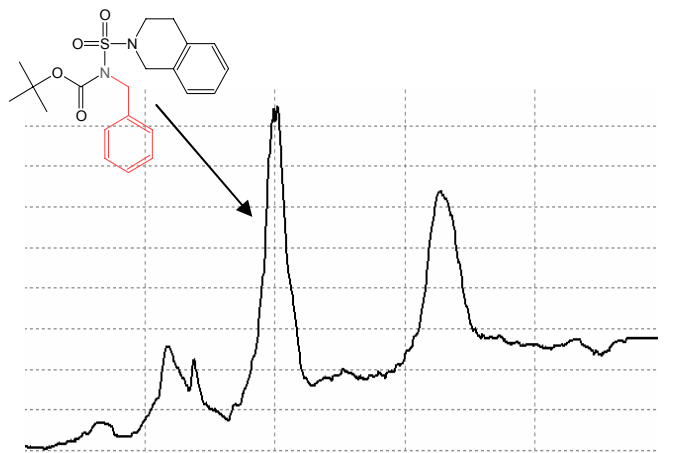
N-Alkylation of Boc-Sulfamides Using Microwave-Assisted Mitsunobu Reaction

Reaction Scheme 2: Microwave-assisted Mitsunobu reaction of Boc-Sulfamide



- **Boc-sulfamide's nitrogen were alkylated using the Mitsunobu reaction**
 - Diethyl diazenedicarboxylate (DEAD) was added to a solution containing triphenyl phosphine, alcohol ($R_3\text{-OH}$) and the Boc-sulfamide in anhydrous THF
 - Microwave reaction required 1-4 minutes at 80°C depending on the specific R_3 group (reaction scheme 2)
- **Scheme provides unsymmetrical diversity to the sulfamides**

General Flash Purification of *N*-Alkylated Boc-Sulfamides



Chromatogram 2: Compound 11 separation from reaction mixture on Flash 12+™M cartridge

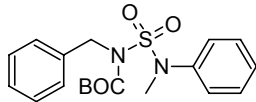
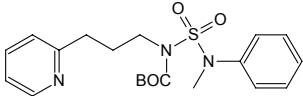
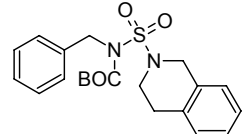
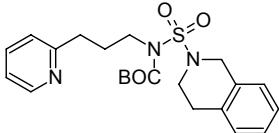
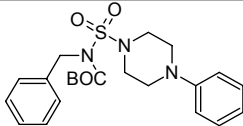
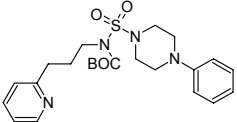
- The reaction mixture directly transferred onto a Samplet™ cartridges
 - Solvent was evaporated by heating in an oven for 10 minutes at 60 °C
- Samplet was inserted on top of Flash 12+™M cartridge
- Gradient condition used to isolate pure products at 44-75% isolated yield

Cartridge	FLASH 12+™M KP-Sil
Solvent	A: Hexane, B: EtOAc
Gradient Program	Equilibrated: 0% B in 24 mL Step 1: 40% B in 120 mL Step3: 100% B in 60 mL
UV detection	254 nm
Flow rate	13 mL/min

- Chromatogram 2 shows a typical purification, using Flash 12+™M cartridge on SP4™ automated FLASH™ chromatography system

N-Alkylated Boc-Sulfamide Synthesized

N-alkylated Boc-sulfamides synthesized by microwave-assisted Mitsunobu reaction, followed by Flash chromatography purification

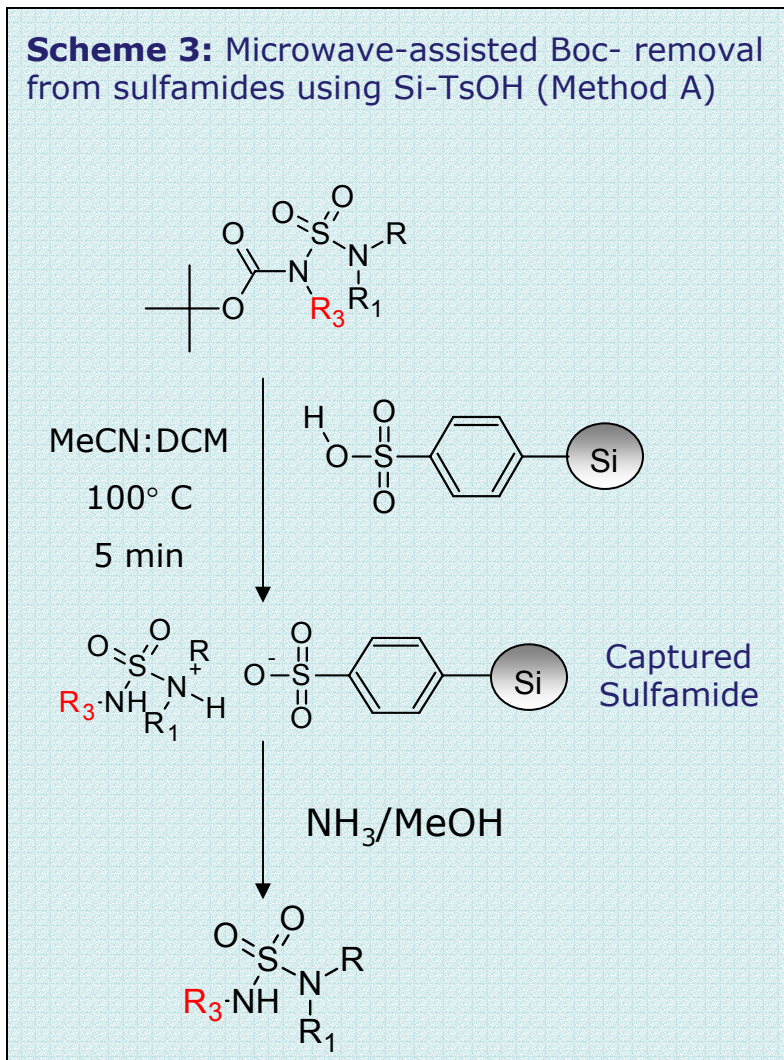
	Products	% Isolated Yield	<i>m/z</i>	¹ H NMR
9		62	(M ⁺ + Na) 399.01	1.45 (s, 9H), 3.50 (s, 3H), 4.58 (s, 2H), 7.35 (m, 9H), 7.10 (m, 2H), 7.24 (m, 3H), 7.3 (m, 2H)
10		44	(M ⁺ + 1) 406.03	1.41 (s, 9H), 2.01 (m, 2H), 2.60 (t, 2H), 3.44 (t, 2H), 3.52 (s, 3H), 7.5 (m, 9H), 8.45 (d, 2H)
11		60	(M ⁺ + Na) 424.92	1.39 (s, 9H), 2.78 (t, 2H), 3.46 (t, 2H), 4.26 (s, 2H), 4.88 (s, 2H), 6.89 (m, 1H), 7.01 (m, 1H), 7.10 (m, 2H), 7.24 (m, 3H), 7.3 (m, 2H)
12		75	(M ⁺ + 1) 432.07	1.35 (s, 9H), 1.78 (m, 2H), 2.68 (m, 4H), 3.23 (m, 2H), 3.49 (m, 2H), 4.41 (s, 2H), 5.68 (bs, 1H), 6.5-7.5 (m, 10H)
13		66	(M ⁺ + 1) 432.7	1.40 (s, 9H), 3.13 (t, 4H), 3.42 (t, 4H), 4.58 (s, 2H), 7.21 (m, 10H)
14		56	(M ⁺ + 1) 461.04	1.40 (s, 9H), 1.86 (m, 2H), 2.54 (s, 3), 3.127 (t, 4H), 3.423 (t, 4H), 4.578 (s, 5H), 6.56 (m, 3H), 7.28 (m, 9H)

Alternative Boc- Removal Method from Boc-Sulfamides

- **Tert-butoxycarbonyl (Boc-) group removal is generally carried out with trifluoroacetic acid (CF_3COOH) either neat or in combination with DCM. Since CF_3COOH is volatile, harsh and corrosive a search for an alternative deblocking method has been ongoing**
- **Recently it has been reported that strong acidic resin can remove the Boc- protecting group. This technique, however, requires long reaction times (12-24 hours) at room temperature and results in incomplete removal of the Boc group**
- **The next section of this poster explores the scope and limitations of de-blocking the BOC-group from sulfamides using silica-bonded phenylsulfonic acid (Si-TsOH), and the effects of microwave heating in reducing the reaction time**

Microwave-Assisted Boc- Removal from Sulfamides Using Si-TsOH

Scheme 3: Microwave-assisted Boc- removal from sulfamides using Si-TsOH (Method A)

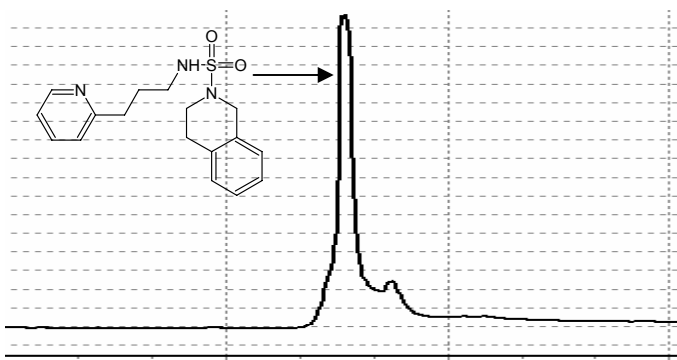


- **Method A**
 - In a 1:1 MeCN:DCM solution, Boc-sulfamides were treated with 3 equivalents of Si-TsOH in a 2-5 mL round bottom reaction tubes and heated by *microwaves* at 100 °C for 5 minutes (scheme 3)
- **Method B**
 - To suppress t-butyl cation attack on product (Compounds 16,17) a cocktail containing of MeCN (97.5), Phenol (1.0), H₂O (1.0), Trisisopropylsilane (0.5) is used instead of 1:1 solution of MeCN:DCM
- Boc- removed sulfamides were captured on the surface of Si-TsOH depending on their pKa (7-11)
- The captured sulfonamides were released from Si-TsOH surface using NH₃ in MeOH followed by flash chromatography purification

General Flash Purification of Sulfamide



Figure 3: After evaporating solvent, reaction mixture is transferred onto the top of the Biotage Flash 25+™S for use with the Biotage Dry-loading compression module



Chromatogram 3: Compound 22 isolation on Flash 25+S cartridge

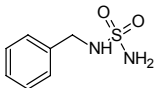
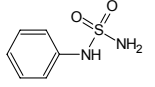
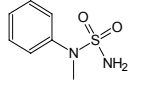
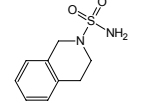
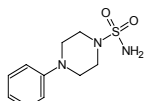
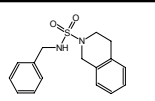
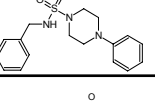
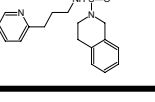
- Solvent was evaporated from reaction tubes using a flow of helium gas
- Resultant solid, containing capture product was transferred to the top of the Flash 25+™S cartridge that was subsequently placed into the new Biotage dry loading compression module (Figure 3)
- Gradient condition was used to collect pure product at 75-91% isolated yield

Solvent	A: Hexane, B: EtOAc
Gradient Program	0% B in 48 mL Step 2: Inject 1 mL, 2M NH₃/MeOH Step 3: 0-50% B in 120mL Step 4: 50-100% in for 100 mL Step 5: 100% B for 100 mL
UV detection	254 nm
Flow rate	25 mL/min

- **Chromatogram 3 shows a typical flash purification on a Flash 25+™S KP-Sil cartridge using the Biotage SP4™ automated FLASH™ chromatography system**

Unsymmetrical Sulfamides Synthesized Combining Microwave and New Si-TsOH De-blocking Technique

Products formed by microwave-assisted BOC- removal using Si-TsOH, followed by quick Flash chromatography purification

	Products	% Isolated Yield	Method	M ⁺ + Na	¹ H NMR
15		90	A	209.11	4.198 (s, 2H), 4.2 (br s, 2H), 7.257 (m, 4H)
16		75	B	195.03	2.48 (s, 1H), 6.93(t, 1H), 7.053 (m, 2H), 7.168 (m, 2H), 9.22 (s, 1H)
17		61	B	209.05	3.172 (s, 3H), 5.02 (s, 2H), 7.306 (m, 5H)
18		91	A	235.63	0.92 (t, 2H), 3.327(t, 2H), 4.193 (s, 2H), 6.891 (s, 2H), 7.163 (m, 4H)
19		71	A	264.02	3.11 (t, 4H), 3.21 (t, 4H), 6.837 (m, 1H), 6.98 (d, 2H), 7.389 (t, 2H)
20		72	A	325.38	2.50 (m, 1H), 2.79 (t, 2H), 3.44 (t, 2H), 4.20 (d, 2H), 4.29 (s, 2H), 7.33 (m, 9H)
21		92	A	353.99	3.127 (t, 4H), 3.086 (t, 4H), 4.169 (s, 2H), 4.608 (s, 1H), 6.832 (m, 3H), 7.2222 (m, 7H)
22		89	A	354.42	1.92 (m, 2H), 2.68 (m, 4H), 3.23 (m, 2H), 3.49 (m, 2H), 4.54 (s, 2H), 5.68(bs, 1H), 7.1-7.5 (m, 10H)

Summary of Results

- **A general one-pot microwave-assisted synthesis of unsymmetrical Boc-sulfamides is demonstrated**
- **Additional diversity was easily and rapidly introduced on the Boc-sulfamides *via* microwave assisted Mitsunobu reaction**
- **An alternate method for Boc- removal from sulfamide requiring only 5 minutes was established using Si-TsOH in conjunction with the Biotage Emrys™ Liberator microwave system compared to the previously reported 12-24 hours at room temperature**
 - **Boc- removed sulfamides were captured on surface of Si-TsOH depending on their pKa**
 - **The captured sulfamides were released from surface of Si-TsOH using NH₃ in MeOH and quickly isolated using FLASH™ chromatography**
 - **This new technique eliminates need to use TFA as the de-blocking agent**