Microwave-Assisted Sulfamide Synthesis

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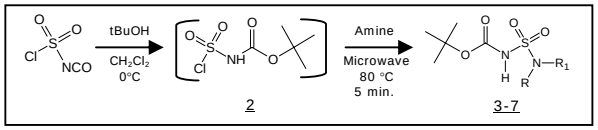
Introduction

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].



The microwave assisted Mitsunobu reaction was used for alkylation of Bocsulfamides 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.

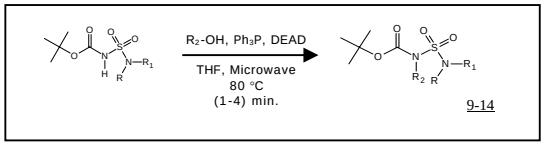
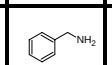
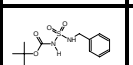
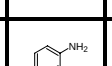
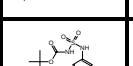
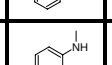
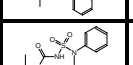
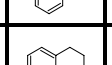
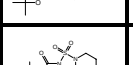
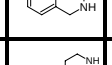
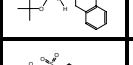
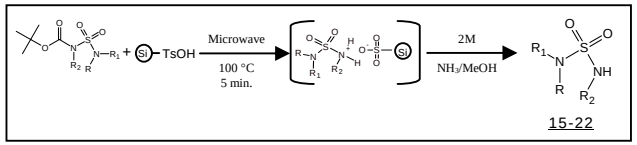


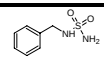
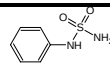
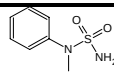
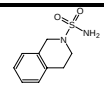
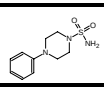
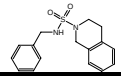
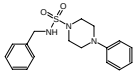
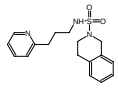
Table 1: One-pot microwave-assisted sulfamides synthesis

#	Amines	Products [a]	% Yield [b]	% Purity [c]	(M+ + Na)
3			80	96	309.93
4			55	97	295.94
5			62	93	308.93
6			67	96	334.97
7			86	97	363.93

[a] Reactions were performed in the Biotage EMRYS™ Liberator microwave system in 2-5 mL reaction vials at 80 °C. [b] Yield of isolated product: All products were isolated on the Biotage Sp automated flash chromatography system (Flash 25+ M, 25 x 150, 40-63 µm, 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] ^{1}H NMR data in $CDCl_3$ 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 CH_2Cl_2 [14]. Since CF_3COOH 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). Boc-sulfamides 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 NH_3/MeOH (scheme 3).



#	Products [a]	% Yield [b]	M+ + Na [c]
15		90	209.11
16		75	195.03
17		75	209.05
18		61	235.63
19		91	264.02
20		71	325.38
21		92	353.99
22		89	354.42

[a] Reactions were performed in the Biotage EMRYS™ Liberator microwave system in 2-5 mL reaction vials. [b] Yield of isolated product. [c] Mass spectroscopy was carried out on a Micromass® ZQ (Waters). [e] ^{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-deblocked sulfamides were captured by Si-TsOH, depending on their pKa,. The captured sulfamides were released from surface of Si-TsOH by using NH_3 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.

Table 3: Microwave-assisted BOC- deblocking using Si-TsOH

References:

1. Alcaraz, L; Bennion, C; Morris, J; Meghani, P; Thom, S. Org. lett. (2004). 0, A-D
2. Nishino, Y, Komurasaki, T; Yuasa, T; Kakinuma M; Izumo, K; Kobayshi, T; Masui, Y, Fujie, S; Gotoh, T; Hajima, M; Takahira, M; Kataoka, T; Okuyama, A. Organic Process Research and Development. (2003) 7, 846-850.
3. Markgren, P; Schaal, W; Hamalainen, M; Karlen, A; Hallberg, A; Samuelsson, B; Danielson, H. J. Med. Chem. (2002). 45, 5430-5439.
4. Schaal, W; Karlsson, A; Ahlsen, G; Lindberg, J; Andersson, H; Danielson, H; Classon, B; Unge, T; Samuelsson, B; Hulten, J; Hallberg, A; Karlen, A. J. Med. Chem. (2001) 44, 155-169
5. Hof, F; Iovine, P; Johnson, D; Rebek, J. Org Lett. (2001) 3, 4247-4249
6. Masui, T; Kabaki, M; Watanabe, H; Kobayshi, T; Masui, Y. Organic Process Research and Development. (2004) 8, 408-410.
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 isocynate (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™ cartridgeand purified by flash chromatography
8. *General procedure for microwave assisted Boc-sulfamides cleavage with Si-TsOH:* **Method A**: Silica-bound *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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