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Solid-phase synthesis of sulfamides

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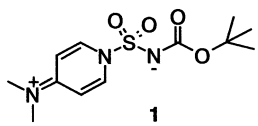
Abstract—A straightforward synthesis of diversely substituted sulfamides is described. The reaction of sulfamoylating agent **1** with solid-phase bound amines to give polymer bound BOC substituted sulfamides is described. Further *N*-alkylation is achieved under Mitsunobu conditions. Simultaneous deprotection and cleavage of the products leads to unsymmetrically substituted sulfamides.

In the area of combinatorial chemistry and solid-phase synthesis there is a constant need for new methodologies. As part of our effort to develop synthetic strategies for the preparation of diverse libraries for high throughput screening, we became interested in the synthesis of diversely substituted sulfamides.

Solution phase synthesis of unsymmetrically substituted sulfamides has been performed by reaction of sulfamoyl chlorides with amines,[1] by transamidation of monosubstituted sulfamides,[2] or by the stepwise addition of *tert*-butanol and a primary amine to chlorosulfonyl isocyanate (CSI), followed by Mitsunobu reaction and removal of the BOC group.[3]

Solid-phase synthesis of sulfahydantoins[4] and aminosulfonyl ureas[5] have been recently described. In the latter case, sulfamides were isolated as impurities. Recently, Winum and co-workers have described the preparation of a new stable and versatile sulfamoylating reagent **1** and described its reactivity in solution towards various amines.[6] We believed that a similar strategy on a solid-support would prove very useful because of the stability of reagent **1** with respect to CSI, resulting in an easier adaptation to automated library preparation.



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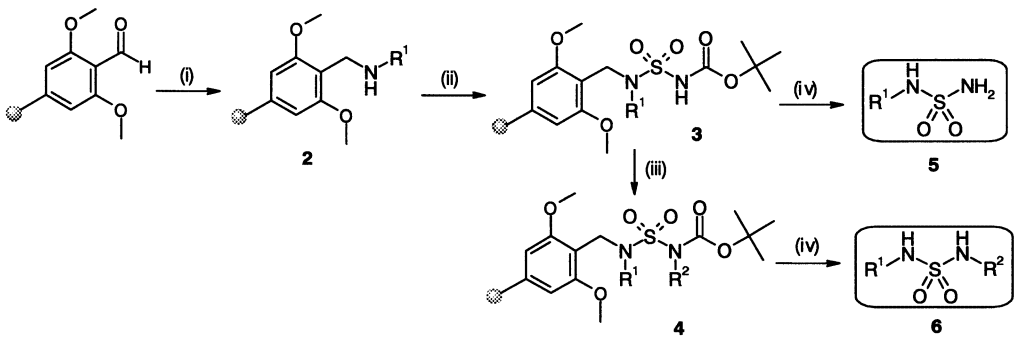
Our synthetic route, which is shown in Scheme 1, begins by attachment of a primary amine to a backbone amide linker (BAL) derivatised aminomethyl polystyrene resin (0.8–1.4 mmol/g, 1% crosslinked with



Scheme 1. *Reagents and conditions:* (i) R^1NH_2, $NaBH_3CN$, DMF–MeOH (8:2), 18 h, rt; (ii) **1**, DCM, 18 h, rt; (iii) 6 equiv. R^2OH–Bu_3P–ADDP, DMF, 18 h, rt; (iv) TFA–$CHCl_3$–H_2O (50:50:1).

Keywords: combinatorial chemistry; diversity; library; reductive amination; sulfamoylation; Mitsunobu reaction.
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Table 1. Yields and purities of sulfamides prepared according to Scheme 1

Entry	Amine R^1NH_2	Alcohol R^2OH	Purity[b]	Yield[c]
1[a]	2-(2-Chlorophenyl)ethylamine	–	80	45
2	2-(2-Chlorophenyl)ethylamine	Benzyl alcohol	88	61
3	2-(2-Chlorophenyl)ethylamine	4-Chlorobenzyl alcohol	92	42
4	2-(2-Chlorophenyl)ethylamine	3-Methoxybenzyl alcohol	95	45
5	2-(2-Chlorophenyl)ethylamine	2-Methoxybenzyl alcohol	75	51
6	2-(2-Chlorophenyl)ethylamine	3,4-Dimethoxybenzyl alcohol	80	40
7	2-(2-Chlorophenyl)ethylamine	2,6-Difluorobenzyl alcohol	88	50
8[d]	2-(2-Chlorophenyl)ethylamine	*sec*-Phenethyl alcohol	75	40
9	2-(2-Chlorophenyl)ethylamine	Propargyl alcohol	50	38
10[d]	2-(2-Chlorophenyl)ethylamine	3-Phenyl-2-propyn-1-ol	80	48
11[d]	2-(2-Chlorophenyl)ethylamine	3-(3,4-Dimethoxyphenyl)propan-1-ol	90	38
12[a]	4-Methoxyaniline	–	75	45
13	4-Methoxyaniline	Benzyl alcohol	93	55
14	4-Methoxyaniline	3-Methoxybenzyl alcohol	90	58
15	4-Methoxyaniline	4-Chlorobenzyl alcohol	95	55

[a] Obtained after cleavage of the product from resin **2**.
[b] Purity was determined by HPLC analysis of crude products at 210 nm. Products show satisfactory NMR and MS data, which are consistent with the proposed structure.
[c] The crude yields were based on weight of crude samples and were relative to the initial loading of the BAL linked resin.
[d] The Mitsunobu protocol was repeated twice.

DVB) through a reductive amination to give **2**.[7] Conversion to the BOC substituted sulfamide is accomplished by reaction with excess (5 equivalents) sulfamoylating reagent **1** in DMF–DCM at room temperature overnight.[8] After a washing regimen, the products (**5**) were efficiently and simultaneously deprotected and cleaved from the resin with TFA–$CHCl_3$–H_2O (50:50:1). We found that either anilines or aliphatic primary amines attached to the BAL linker were efficiently sulfamoylated (entries 1 and 12).

Furthermore, we decided to explore the scope and limitations of the Mitsunobu reaction on the resin bound intermediate **3**. The reaction of different polymer supported BOC sulfamides with 6 equivalents of the alcohol, tributylphosphine and 1,1′-(azodicarbonyl)dipiperidine (ADDP) in DCM provided cleanly *N*-alkylated products (Scheme 1).[9] Again, after a washing regimen and treatment with TFA–$CHCl_3$–H_2O (50:50:1), unsymmetrically substituted sulfamides (**6**) were obtained.

Further results, which illustrate the scope of this synthesis, are listed in Table 1. As shown in Table 1, benzylic alcohols substituted by either electron donating or electron withdrawing groups work well even in hindered benzylic alcohols (entries 2–7). Analogously, sulfamoylated anilines are also cleanly alkylated (entries 13–15).

Secondary benzylic alcohols (entry 8), propargylic alcohols (entries 9–10) as well as aliphatic alcohols (entry 11) work equally well although a double Mitsunobu treatment was required. This result provides a clear advantage of the solid-phase approach with respect to what we observed when we performed the same experiment in solution phase where the final compound was contaminated with a large excess of phosphine and ADDP related impurities. ^1H NMR, HPLC and MS were performed on all sulfamides to determine the purity and confirm the structure.

N-Alkylation could not be achieved or gave products with very low HPLC purity with heteroarylmethyl alcohols (2-thiophenemethanol, 3-pyridylcarbinol), or other aliphatic alcohols such as 2-(*N*,*N*-dimethylamino)-ethanol.

In summary, we describe an efficient and convenient method for the solid-phase preparation of unsymmetrically substituted sulfamides. Reaction of solid-phase bound amines with the sulfamoylating reagent **1**, followed by *N*-alkylation under Mitsunobu conditions, and deprotection and cleavage from the resin leads to the target compounds with acceptable yields and good purities. This method is presently being automatised for the production of libraries of compounds.

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References

1. (a) Spillane, W. J.; McHugh, F. A.; Burke, P. O. *J. Chem. Soc., Perkin Trans. 2* **1998**, *1*, 13–18; (b) Kloek, J. A.; Leschinsky, K. L. *J. Org. Chem.* **1976**, *41*, 4028–4029.
2. McDermott, S. D.; Spillane, W. J. *Synthesis* **1983**, 192–195.

3. (a) Dewynter, G.; Aouf, N.; Criton, M.; Montero, J.-L. *Tetrahedron* **1993**, *49*, 65–76; (b) Regaïnia, Z.; Abdaoui, M.; Aouf, N.; Dewynter, G.; Montero, J.-L. *Tetrahedron* **2000**, *56*, 381–387.
4. Albericio, F.; Bryman, L. M.; Garcia, J.; Michelotti, E. L.; Nicolás, E.; Tice, C. M. *J. Comb. Chem.* **2001**, *3*, 290–300.
5. Fitzpatrick, L. J.; Rivero, R. A. *Tetrahedron Lett.* **1997**, *38*, 7479–7482.
6. Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241–2243.
7. (a) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vágner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441–5452; (b) Alsina, J.; Jensen, K. J.; Albericio, F.; Barany, G. *Chem. Eur. J.* **1999**, *5*, 2787–2795.
8. *General procedure for sulfamoylation of resin bound amines*: In a typical experiment, resin **2** (100 mg, approx. 0.1 mmol) was preswollen in CH_2Cl_2 (1.5 mL). A solution of **1** (0.15 g, 0.5 mmol, 5 equiv.) in DMF (1.5 mL) was added, and the mixture was stirred at room temperature for 20 h. The resin was filtered, washed sequentially with DMF, MeOH, CH_2Cl_2 and THF, and dried.
9. *General procedure for Mitsunobu reactions*: PBu_3 (148 μL, 0.6 mmol, 6 equiv.) followed by the corresponding alcohol (0.6 mmol, 6 equiv.) were added to resin **3** (0.1 g, approx. 0.1 mmol) preswollen in CH_2Cl_2 (1 mL). The reaction was cooled to 0°C and a solution of ADDP (0.15 g, 0.6 mmol, 6 equiv.) in CH_2Cl_2 (1 mL) was added. The reaction was warmed to room temperature and stirred for 20 h. The resin was filtered, washed sequentially with DMF, MeOH, CH_2Cl_2 and THF, and dried.
The product was cleaved from the resin with TFA–$CHCl_3$–H_2O (50:50:1).