A Simple Large-Scale Synthesis of Cbz-Protected Taurylsulfonyl Azide

Arwin J. Brouwer, Rob M. J. Liskamp*

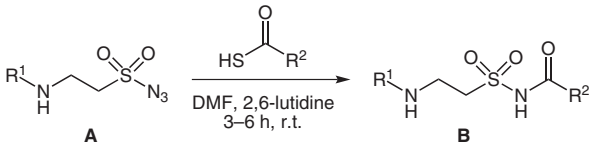
Department of Medicinal Chemistry and Chemical Biology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, PO Box 80082, 3508 TB Utrecht, The Netherlands
Fax +31(30)2536655; E-mail: R.M.J.Liskamp@uu.nl

Received 3 May 2011

Abstract: A simple and efficient method for the large-scale synthesis of Cbz-taurylsulfonyl azide is described. This sulfonyl azide is accessible from taurine using three or four synthetic steps.

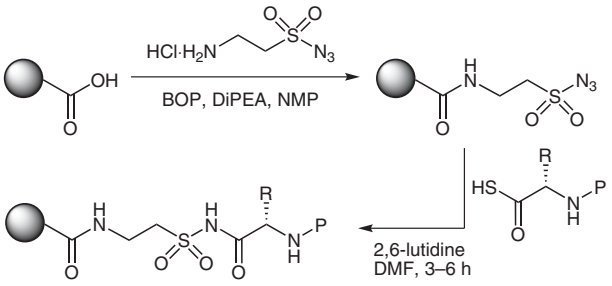
Key words: sulfonyl azide, sulfonyl chloride, large-scale synthesis, chemoselectivity, sulfo-click reaction

Sulfonyl azides have gained a lot of interest and importance in recent years, which is apparent from the large increase of scientific papers concerning sulfonyl azides.[1,2,4,5,7] Our contribution has been the development of the sulfo-click reaction, a new chemoselective reaction between a sulfonyl azide (**A**) and a thioacid (Scheme 1).[2]



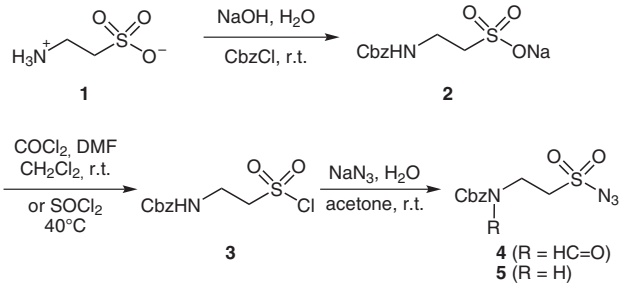
Scheme 1 Sulfo-click reaction of taurylsulfonyl azides with thioacids

Compared to the widely used azide-alkyne click reaction,[3] the sulfo-click reaction has the great advantage that it is a metal-free click reaction. The necessity of Cu catalysis was a major impetus to develop alternatives that do not include Cu catalysis. In general the synthesis of the required molecules is rather complicated. In contrast, synthesis of the components for the sulfo-click reaction is extremely simple and can be carried out conveniently on a large scale as will be described here. Recently, we described the synthesis and applications of aliphatic amino acid derived sulfonyl azides, β-aminoethanesulfonyl azides (**A**).[4] These were successfully applied in the sulfo-click reaction for peptide ligation and for bioconjugation.[2d,e] The Cbz-glycine derived sulfonyl azide, Cbz-protected taurylsulfonyl azide (**A**, R^1 = Cbz), was also used for surface immobilization of biomolecules[5] and for the preparation of the *N*-acyl sulfonamide linker for solid-phase synthesis (Kenner's safety catch linker).[6] An optimized protocol for the loading efficiency of the *N*-acyl sulfonamide linker using the sulfo-click reaction was recently described, in which taurylsulfonyl azide was first coupled to a carboxylic acid resin (Scheme 2).[7]



Scheme 2 Preparation of Kenner's *N*-acyl sulfonamide linker

Due to the recent increase of applications for sulfonyl azides, there is a growing need for large amounts of them. We herein describe a large-scale synthesis of Cbz-protected taurylsulfonyl azide, based on the previously reported small-scale synthesis.[4] The first step, Cbz-protection of taurine, was originally performed by reaction with Cbz-chloride and sodium hydroxide in a water–dioxane mixture. For the large-scale reaction it proved advantageous to discard the dioxane, decreasing the volume and simplifying the workup. To this end, taurine (**1**) was Cbz-protected under Schotten–Baumann conditions on a 500 mmol scale using neat Cbz-chloride and aqueous NaOH (Scheme 3).



Scheme 3 Synthesis of Cbz-taurylsulfonyl azide

The resulting crude Cbz-taurine (**2**) was used without purification in the next step; conversion into Cbz-taurylsulfonyl chloride (**3**) by reaction with phosgene and DMF in dichloromethane. This reaction could be easily scaled up to 500 mmol with only slight modifications in the workup. Originally, the reaction mixture was concentrated and directly purified using silica gel column chromatography. To avoid column chromatography, the concentrated mix-

SYNLETT 2011, No. 15, pp 2228–2230
Advanced online publication: 30.08.2011
DOI: 10.1055/s-0030-1261201; Art ID: D13811ST

ture was first extracted with ethyl acetate, to give, after filtration and concentration, the crude sulfonyl chloride **3**. Addition of a solution of crude **3** to an aqueous solution of sodium azide afforded Cbz-taurylsulfonyl azide (**5**). Unfortunately, it was found that varying amounts (0–10%) of N-formylated sulfonyl azide **4** were formed in a number of phosgene reactions, which had not been observed before in the small-scale reactions. The N-formylation is a side reaction which can occur by reaction of the Cbz-protected amine with the Vilsmeyer–Haack complex[8] generated from phosgene and DMF. Since the N-formylated sulfonyl azide could not be removed by crystallization, a deformylation reaction was performed by reaction of the crude sulfonyl azide (**5**) with $KHCO_3$, with water and acetone as solvents.[9] After 3 hours stirring at room temperature, Cbz-taurylsulfonyl azide (**5**) precipitated from the reaction mixture and was obtained in high purity after filtration in a very good overall yield of 71% (101 g) over four steps.

We envisaged that the use of thionyl chloride instead of phosgene could be a less toxic and cheaper alternative for the conversion of the sodium sulfonate **2** into sulfonyl chloride **3**. It was also expected that by using thionyl chloride we could prevent N-formylation, and thereby omit one reaction step. To this end, 500 mmol sodium sulfonate **2** was treated with thionyl chloride, as reagent and solvent. Due to the lower reactivity of thionyl chloride, compared to phosgene/DMF, the reaction was slower and an elevated temperature (40 °C) combined with a longer reaction time (20 h) was necessary. Reaction of the crude sulfonyl chloride with sodium azide afforded Cbz-taurylsulfonyl azide (**5**) in a reasonable yield of 50% (71.5 g). Although this yield was clearly lower than the yield from the phosgene route, it is an attractive alternative. The synthesis contains one reaction step less, and thionyl chloride is less toxic and much cheaper than phosgene. Characterization data of both Cbz-taurylsulfonyl azides (**5**) from both large-scale synthetic routes were found to be identical to previous data obtained after small-scale synthesis.

In conclusion, we have developed two efficient synthesis routes for the large-scale synthesis of Cbz-taurylsulfonyl azide (**5**). The key step in both routes, conversion of the sodium sulfonate to the sulfonyl chloride was achieved using either thionyl chloride or phosgene. The phosgene route gave the highest overall yield (71%), but contains one synthetic step more. The thionyl chloride route gave a lower yield (50%), but has the advantage that thionyl chloride is less toxic and is much cheaper. We expect that the convenient access of large amounts of Cbz-taurylsulfonyl azide (**5**) will stimulate the use of the sulfo-click reaction and its application in the use of the safety-catch linker strategy.

Cbz-Tau-N_3 (5) (Phosgene Route)

Taurine (62.6 g, 500 mmol) was dissolved in aq NaOH (250 mL, 2.0 M) using a large magnetic oval stirring bar. To this solution were simultaneously added CbzCl (78.5 mL, 550 mmol) and aq NaOH (250 mL, 2.0 M), using two dropping funnels. After stirring vigorously for 1 h at r.t., the mixture was washed with EtOAc (3 × 200 mL). The H_2O layer was concentrated in vacuo, and the residue was dried over P_4O_{10} in a vacuum desiccator under reduced pressure, yielding the crude sodium sulfonate **2** as a white solid (165 g). To a cooled (ice/water bath) suspension of **2** in dry CH_2Cl_2 (650 mL) was added a phosgene solution in toluene (470 mL, 20%, w/w) and dry DMF (43 mL). After stirring for 1 h the cooling bath was removed, and stirring was continued for 1 h. The solvents were evaporated, and the residue was suspended in EtOAc (800 mL). Filtration over Hyflo® followed by concentration in vacuo afforded the crude sulfonyl chloride **3** as a yellowish oil, which was directly dissolved in acetone (1.0 L). This sulfonyl chloride solution was added dropwise to a vigorously stirred solution of NaN_3 (32.5 g, 500 mmol) in H_2O (1.0 L) in approximately 30 min, during which the color of the reaction mixture changed from yellowish to pink/orange. After stirring overnight the acetone was evaporated in vacuo, and EtOAc (1.0 L) was added. After separation, the organic layer was washed with a $NaHCO_3$ solution (5%, w/w) and brine. Drying (Na_2SO_4) followed by concentration in vacuo afforded the crude sulfonyl azide (mixture of **4** and **5**) which was directly dissolved in MeOH (2.0 L). A solution of $KHCO_3$ (12.6 g, 125 mmol) in H_2O (1.5 L) was added, and the mixture was stirred at r.t. During the reaction, the sulfonyl azide **5** precipitated from the reaction mixture. After 3 h stirring, additional H_2O (1.5 L) was added, and the mixture was filtered. The solid residue was dried over phosphorus pentoxide under reduced pressure to yield Cbz-taurylsulfonyl azide (**5**) as a colorless crystalline solid (101 g, 71% overall yield from taurine); mp 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.51 (m, 2 H, CH_2SO_2), 3.66 (m, 2 H, NCH_2), 5.10 (s, 2 H, CH_2Ph), 5.56 (br s, 1 H, NH), 7.33 (s, 5 H, ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.6 (NCH_2), 55.0 (CH_2SO_2), 67.0 (OCH_2Ph), 128.0, 128.2, 128.5, 135.9 (ArC), 156.1 [C=O (Cbz)]. IR (KBr): 2151 (s) cm^{-1}.

Cbz-Tau-N_3 (5) (Thionyl Chloride Route)

The synthesis route using $SOCl_2$ differs from the phosgene route as follows: After drying the crude sulfonate **2** over P_4O_{10}, it was added portionwise to $SOCl_2$ (500 mL). The mixture was stirred for 20 h at 40 °C, after which it was concentrated in vacuo. After co-evaporation with $CHCl_3$ (3 × 200 mL), the residue was suspended in EtOAc (800 mL), and workup was carried out similarly to the workup of the phosgene reaction. After the reaction with NaN_3, the crude sulfonyl azide **5** was purified by re-crystallization from EtOH–H_2O. Cbz-taurylsulfonyl azide (**5**) was obtained as a colorless crystalline solid (71.5 g, 50% overall yield from taurine); mp 81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (m, 2 H, CH_2SO_2), 3.69 (m, 2 H, NCH_2), 5.11 (s, 2 H, CH_2Ph), 5.46 (br s, 1 H, NH), 7.34 (s, 5 H, ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.7 (NCH_2), 55.1 (CH_2SO_2), 67.2 (OCH_2Ph), 128.1, 128.3, 128.5, 135.9 (ArC), 156.2 [C=O (Cbz)]. IR (KBr): 2151 (s) cm^{-1}.

Acknowledgment

We thank Steffen van der Wal for helpful discussions.

References

(1) (a) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (b) Song, W.; Lei, M.; Shen, Y.; Cai, S.; Lu, W.; Lu, P.; Wang, Y. *Adv. Org. Synth. Catal.* **2010**, *352*, 2432. (c) Krisnamoorthy, K.; Begley, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 11608. (d) Xu, X.; Ge, Z.; Cheng, D.; Ma, L.; Lu, C.; Zhang, Q.; Yao, N.; Li, X. *Org. Lett.* **2010**, *12*, 897. (e) Raghuraman, G. K.; Schuh, K.; Prucker, O.; Ruhe, J. *Langmuir* **2010**, *26*, 796. (f) Cho, S. H.; Hwang, S. J.; Chang, S. *Org. Synth.* **2008**, *85*, 131. (g) Kim, J.-G.; Jang,

D. O. *Synlett* **2008**, 2885. (h) Hu, X.; Sun, J.; Wang, H.-G.; Manetsch, R. *J. Am. Chem. Soc.* **2008**, *130*, 13820. (i) Wang, F.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2008**, *350*, 1830. (j) Raushel, J.; Pitram, S. M.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3385. (k) Mandal, S.; Gauniyal, H. M.; Pramanik, K.; Mukhopadhyay, B. *J. Org. Chem.* **2007**, *72*, 9753.

(2) (a) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754. (b) Barlett, K. N.; Kolakowski, R. V.; Katukojvala, S.; Williams, L. J. *Org. Lett.* **2006**, *8*, 823. (c) Kolakowski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 5695. (d) Merkx, R.; Brouwer, A. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125. (e) Yim, C.-B.; Dijkgraaf, I.; Merkx, R.; Versluis, C.; Eek, A.; Mulder, G. E.; Rijkers, D. T. S.; Boerman, O. C.; Liskamp, R. M. J. *J. Med. Chem.* **2010**, *53*, 3944. (f) Rijkers, D. T. S.; Merkx, R.; Yim, C.-B.; Brouwer, A. J.; Liskamp, R. M. J. *J. Pept. Sci.* **2010**, *16*, 1.

(3) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

(4) Brouwer, A. J.; Merkx, R.; Dabrowska, K.; Rijkers, D. T. S.; Liskamp, R. M. J. *Synthesis* **2006**, 455.

(5) Govindaraju, T.; Jonkheijm, P.; Gogolin, L.; Becker, C. F. W.; Niemeyer, C. M.; Waldmann, H. *Chem. Commun.* **2008**, *32*, 3723.

(6) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *Chem. Commun.* **1971**, 636.

(7) Merkx, R.; van Haren, M. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2007**, *72*, 4574.

(8) (a) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119. (b) Maheas, M.-R. *Bull. Soc. Chim. Fr.* **1962**, 1989.

(9) Beumer, R.; Bubert, C.; Cabrele, C.; Vielhauer, O.; Pietzsch, M.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 8960.