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Total Synthesis of Polyamine Toxin HO-416b Utilizing the 2-Nitrobenzenesulfonamide Protecting Group

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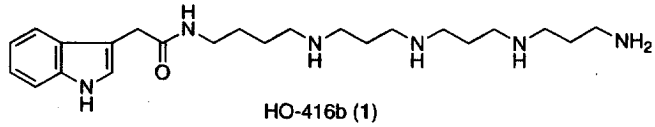
Abstract: The total synthesis of HO-416b (**1**) was accomplished using the 2-nitrobenzenesulfonamide (Ns) group as both a protecting and activating group. Starting with monosulfonylated diamines **2** and **3**, three C-N bonds were constructed *via* alkylation of sulfonamides with alkyl halides. Removal of the Ns groups while the substrate was attached to a novel solid support enabled the efficient isolation of pure **1**.

Keywords: HO-416b; polyamine toxin; 2-nitrobenzenesulfonamide (Ns); solid support

Polyamine toxins derived from spider venoms have been shown to be specific glutamate receptor blockers.[1] These compounds are expected to be useful tools for studying neurophysiology and as lead structures for pharmacological and agrochemical agents. Although extensive synthetic studies of these compounds have been reported to date,[2] there seem to be few versatile syntheses of the sequential secondary amines. Recently, we reported an efficient method for the construction of secondary amines utilizing the nitrobenzenesulfonamide (Ns) group as a protecting and activating group.[3] We envisioned that this protocol would provide an efficient synthetic route to polyamine toxins. Described herein is our practical total synthesis of the polyamine toxin HO-416b (**1**) isolated from venomous spider *Hololena curta*.[4]



HO-416b (1)

Mono-protected diamines seemed to be the ideal starting materials for incorporation into the polyamine chain. Although the selective protection of diamines has been found to be difficult,[5] use of the Ns group provided an efficient means for the preparation of the desired diamine derivatives (Scheme 1). Thus, treatment of 1,3-diaminopropane with 2-nitrobenzenesulfonyl chloride, followed by neutralization with

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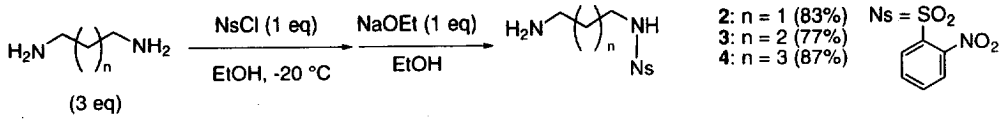
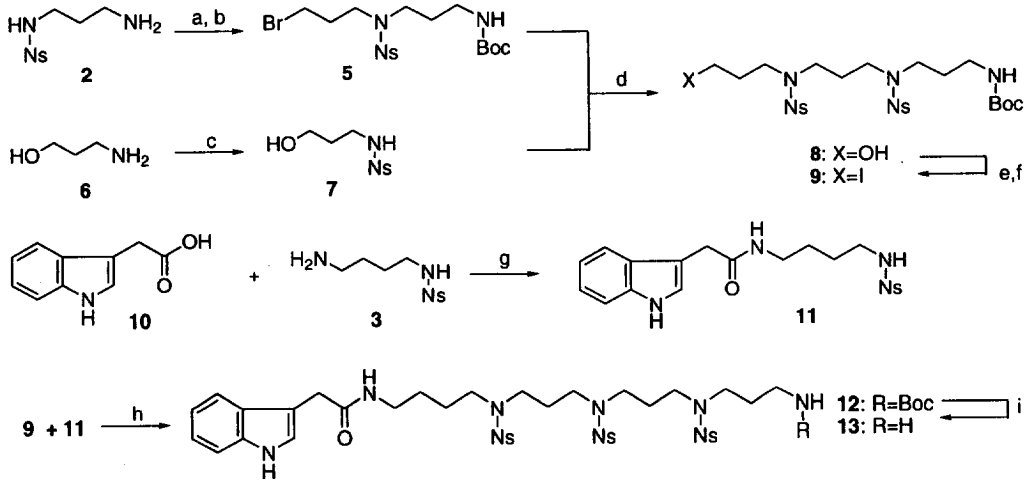
NaOEt, afforded the mono-nosylated product **2** in high yield. This procedure has been successfully applied to the preparation of several diamines on a multigram scale.[6] Using **2** and **3** as the key building blocks, the total synthesis of HO-416b (**1**) was accomplished in the following manner.



Scheme 1

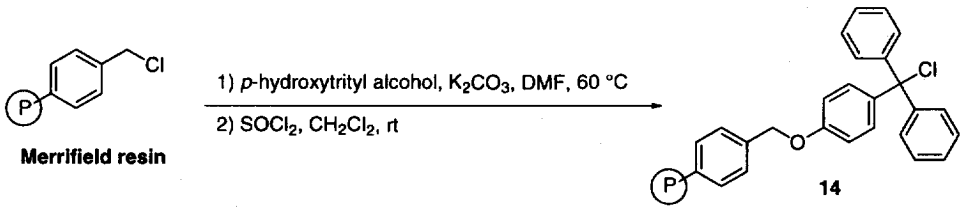
Protection of the amine **2** as its *t*-butyl carbamate (*t*-Boc) and the selective alkylation of the nosylamide with excess 1,3-dibromopropane and K_2CO_3 in DMF furnished bromide **5** (Scheme 2). Coupling of **5** with sulfonamide **7**, readily obtained from 3-aminopropanol **6**, was effected by treatment with **5** and Cs_2CO_3 and n-Bu_4NI in CH_3CN, giving the triamine derivative **8** in high yield. The left-hand fragment **11** was obtained by condensation of 3-indoleacetic acid **10** and **3** via a mixed anhydride. While the sulfonamide **11** can be *N*-alkylated with the primary alcohol **8** under Mitsunobu conditions, purification of the product **12** from the byproducts derived from the reagents was somewhat troublesome. We thus opted to employ the more conventional alkylation method. Conversion of alcohol **8** to iodide **9** was performed in a two-step procedure. Upon heating the mixture of iodide **9**, the sulfonamide **11**, and Cs_2CO_3 in CH_3CN at 60 °C, smooth alkylation occurred to give **12** in 94% yield. Subsequent removal of the Boc group with methanolic HCl furnished the desired primary amine **13**.



(a) Boc_2O, Et_3N, CH_2Cl_2, rt (99%) (b) dibromopropane, K_2CO_3, DMF, 60 °C (97%) (c) NsCl, Py, CH_2Cl_2, 0 °C (98%)
(d) Cs_2CO_3, *n*-Bu_4NI, CH_3CN, 60 °C (86%) (e) MsCl, Et_3N, CH_2Cl_2, rt (99%) (f) NaI, 2-butanone, 60 °C (99%)
(g) PivCl, Et_3N, CH_2Cl_2, rt; **3**, Et_3N, DMAP (97%) (h) Cs_2CO_3, CH_3CN, 60 °C (94%) (i) $SOCl_2$, MeOH, rt (96%)

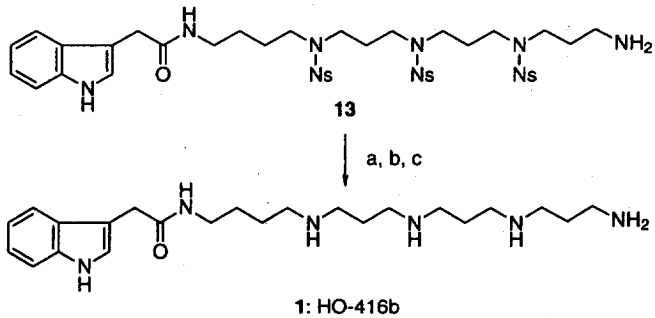
Scheme 2

Solid supports have proved effective as tools for the isolation of highly polar compounds, making their use an attractive method for our final deprotection. However, initial attempts to load **13** onto an expensive 2-chlorotrityl chloride resin were less than satisfactory in terms of the loading efficiency. We thus investigated the preparation of a new resin, **14**. This resin, we felt, would be more reactive since a phenol unit separates the polystyrene support from the reactive site and at the same time the *p*-alkoxy group would stabilized the trityl cation. Treatment of inexpensive Merrifield resin[7] with *p*-hydroxytrityl[8] alcohol and K_2CO_3 followed by reaction with $SOCl_2$ afforded the desired resin **14** (Scheme 3).[9]



Scheme 3

The Ns-protected HO-416b **13** was loaded onto the resin **14** in the presence of $i\text{Pr}_2\text{NEt}$ (Scheme 4). The nosyl groups were then deprotected by treatment of the loaded resin with a large excess of mercaptoethanol and DBU at room temperature.[10] Cleavage of the product from the resin was effected under acidic conditions (1% TFA/CH_2Cl_2) to give, after evaporation, the trifluoroacetic acid salt of **1**.[11] ^1H and ^{13}C NMR spectral data of the crude product indicated that the material was practically pure **1**. The identity of the synthetic HO-416b was further verified by tandem FAB MS-MS spectroscopy.



(a) resin **14**, *i*-Pr_2NEt, CH_2Cl_2, rt; (b) mercaptoethanol, DBU, DMF, rt; (c) TFA, CH_2Cl_2 (68% from **13**).

Scheme 4

In summary, the total synthesis of HO-416 (**1**) has been completed in 12 steps from 1,3-diaminopropane in 41% overall yield. This approach should be applicable to the synthesis of a wide range of polyamine toxins, which will be the subject of our future investigation.

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References and Notes

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4. Quistad, G. B.; Reuter, C. C.; Skinner, W. S.; Dennis, P. A.; Suwanrumpha, S.; Fu, E. W. *Toxicon.* **1991**, *29*, 329.
5. Fiedler, W. J.; Hesse, M. *Helv. Chim. Acta* **1993**, *76*, 1511.
6. Purification of monosulfonylated diamines was performed by silica gel column chromatography (elution first with 2% MeOH in CH_2Cl_2 and then with *i*-$PrNH_2$: MeOH : CH_2Cl_2 (2.5 : 2.5 : 95)). Large-scale preparation was accomplished by the following procedure. To a stirred solution of 55.6 g (0.750 mol) of 1,3-diaminopropane in 1 l of EtOH cooled to –20 °C under an argon atmosphere was slowly added 55.4 g (0.250 mol) of 2-nitrobenzenesulfonyl chloride. After 30 min, the reaction mixture was neutralized with 1N EtONa, filtered through a Celite pad, and concentrated *in vacuo*. Excess diamine was removed by heating under reduced pressure (40-50 °C/0.02 mmHg). Purification of the residue by recrystallization (AcOEt-Et_2O) gave **2** (38.0 g, 58.8 %) as a yellow powder.
7. Burton, H.; Cheeseman, G. W. H. *J. Chem. Soc.* **1955**, *887*, 3089.
8. The Merrifield resins (2 % DVB, 100-200 mesh) were purchased from Novabiocheme.
9. Preparation of the resin **14** was carried out according to the following procedure. To a suspension of 1.40 g (1.68 mmol) of Merrifield resin and 4.64 g (16.8 mmol) of *p*-hydroxytrityl alcohol in 30 ml of DMF was added 11.6 g (84.0 mmol) of potassium carbonate at room temperature under an argon atmosphere. The reaction mixture was heated at 60 °C for 20 hr, and then cooled to room temperature. The resin was filtered, washed with H_2O : THF (1 : 9), THF, and Et_2O, and then dried *in vacuo* to afford 1.54 g of the alcohol-functionalized resin. To a suspension of this resin in CH_2Cl_2 was added $SOCl_2$ at room temperature under an argon atmosphere. After stirring for 30min, the solvent was evaporated and the residue dried *in vacuo* to provide 1.54 g of the resin **14**.
10. Although Ns group can be deprotected by treatment with a variety of thiolates, we used the conditions already tested for a solid-state synthesis. Miller, S. C.; Scanlan, T. S. *J, Am. Chem. Soc.* **1997**, *119*, 2301
11. Removal of the Ns groups and isolation of **1** was accomplished by the following procedure. To a suspension of the freshly prepared resin **14** and 65 mg (0.068 mmol) of amine **13** in 2.5 ml of CH_2Cl_2 was added 0.141 ml (0.828 mmol) of *i*-Pr_2NEt at room temperature. After shaking for 48 hr, 0.1 ml of MeOH was added to the reaction mixture. The resin was filtered, washed with MeOH : CH_2Cl_2 (1 : 9), H_2O : MeOH : CH_2Cl_2 (1 : 1 : 8), and CH_2Cl_2, and then dried *in vacuo*. To a suspension of the dry resin in 1.5 ml of DMF was added 0.140 ml (2.00 mmol) of mercaptoethanol and 0.30 ml (2.00 mmol) of DBU at room temperature under an argon atmosphere. After shaking for 26 h, the resin was filtered, washed with H_2O : THF (1 : 9), MeOH : CH_2Cl_2 (1 : 9), and CH_2Cl_2 and dried *in vacuo*. To a mixture of the resulting resin in 2.5 ml of CH_2Cl_2 was added 25 µl (0.324 mmol) of TFA at room temperature. After shaking for 5 min, the resin was filtered and washed with MeOH : CH_2Cl_2 (1 : 9). These acidic cleavage and rinsing processes were repeated three more times. The combined washings were evaporated and dried *in vacuo* to provide HO-416 (**1**) (25.5 mg, 68 %) as the TFA salt. The used resin could be repeatedly used by mere treatment with $SOCl_2$: CH_2Cl_2 (1 : 9).