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Solid-Phase Polyamine Synthesis Using Piperazine and Piperidine Building Blocks

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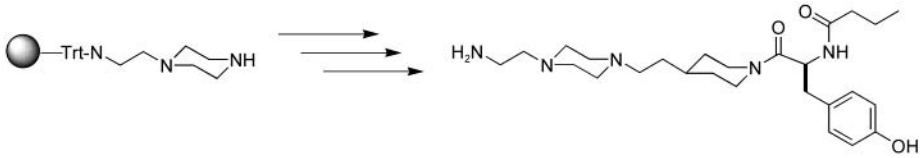
ABSTRACT



Polyamines containing piperidine and piperazine moieties have been synthesized on solid support using S_N2 alkylation of resin-bound secondary amines with 2-nitrobenzenesulfonates (nosylates). The effect of solvent on this alkylation was investigated. The methodology was employed for the total synthesis of novel analogues of wasp polyamine toxins (philanthotoxins).

Polyamines constitute an essential part of a large number of biologically active compounds, e.g., polyamine toxins such as philanthotoxin-433 [PhTX-433 (**1**)], an active constituent of the venom of the Egyptian digger wasp *Philanthus triangulum*.[1] PhTX-433 is a nonselective inhibitor of ionotropic glutamate receptors (iGluRs) and nicotinic acetylcholine receptors (nAChRs).[2] Because of their therapeutic potential,[3] methods for solid-phase synthesis of philanthotoxin analogues have attracted considerable interest. Wang et al. reported total syntheses of polyamine toxins using borane reduction of a polyamide as the key step.[4] A reductive amination strategy has been reported by Chhabra et al.[5] Also, alkylations under Fukuyama−Mitsunobu conditions[6] and alkylation of resin-bound sulfonamides with alkyl bromides[7] have been described. In the present work, simple S_N2 alkylation of resin-bound secondary amines with alkyl sulfonates has been investigated. Previously, N-alkylation of piperidine and piperazine derivatives with nitrobenzenesulfonates was demonstrated to be an efficient solution-phase method.[8] Furthermore, resin-bound sulfonates have been employed for the synthesis of secondary amines.[9]

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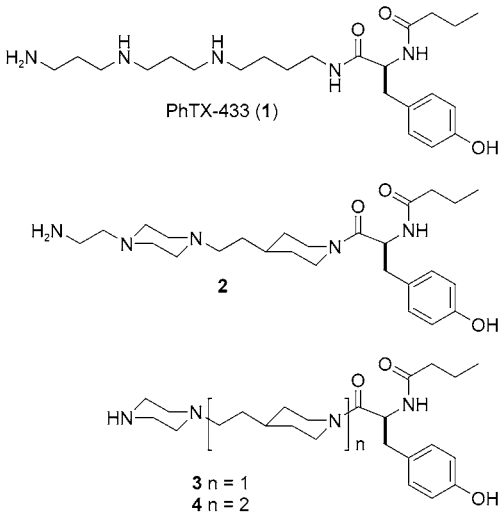
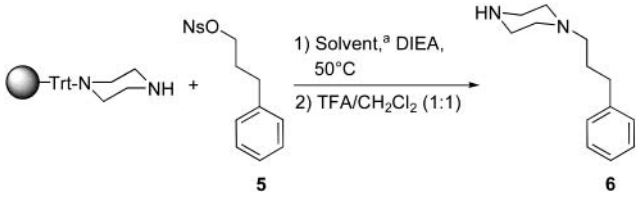
In previous SAR studies, enhanced biological activity of philanthotoxin analogues was observed for compounds having polyamine moieties with added alkyl branching[10] or lacking one of the inner basic sites.[11]

Bearing these results in mind, we envisaged that compounds **2** and **4** would represent a novel type of philanthotoxins with conformational rigidity, increased lipophilicity, and altered proteolytic properties.[11,12] Accordingly, we developed an elongation strategy using S_N2 alkylation of resin-bound secondary amines for the synthesis of **2** and **4**.



Initially, a commercially available trityl resin preloaded with piperazine was monoalkylated with the *O*-(2-nitrobenzenesulfonyl) derivative of 3-phenylpropanol, **5**, in selected solvent mixtures (Scheme 1). The product was cleaved from

Scheme 1. Test Reaction for Assessment of Solvent Effect on Single Alkylation of Resin-Bound Piperazine

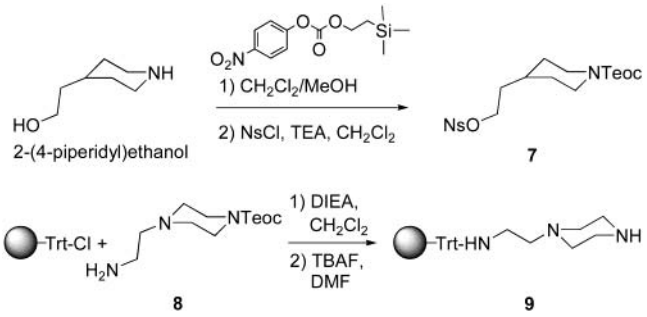


[a] THF/DMF, THF/CH_2Cl_2, or THF/PhMe (1:1).

the resin with TFA/CH_2Cl_2 (1:1) and quantitatively analyzed by ^{1}H NMR (CD_3OD) using toluene as an internal standard. Surprisingly, use of THF/DMF as a solvent gave the lowest yield and also the highest degree of transsulfonation of the secondary amine (giving sulfonamides as products). The solvent mixtures THF/CH_2Cl_2 and THF/toluene gave comparable results, the first affording a slightly higher yield and the latter less transsulfonation.[13] On the basis of these results, the THF/CH_2Cl_2 mixture was chosen for the synthesis of **2**. Contrary to model experiments in solution, transsulfonation appeared to be a much more pronounced side-reaction on solid phase.[14]

For the synthesis of the polyamine moiety of **2**, building block **7** and resin **9** were prepared (Scheme 2). The

Scheme 2. Preparation of Building Block **7** and Resin **9**



2-(trimethylsilyl)ethoxycarbonyl (Teoc) group was chosen for N-protection of 2-(4-piperidyl)ethanol due to its convenient deprotection with tetrabutylammonium fluoride (TBAF).[15]

Treatment of the N-protected amino alcohol with 2-nitrobenzenesulfonyl chloride (NsCl) and triethylamine (TEA) afforded **7** in 74% overall yield. Loading of *N*-aminoethyl-*N*′-Teoc-protected piperazine (**8**) onto a polystyrene trityl chloride resin followed by treatment with TBAF afforded resin **9**. Direct loading of an unprotected triamine gave only 75% selectivity in favor of the primary amino group, which necessitated introduction of the Teoc group prior to resin derivatization.

Compound **2** was synthesized by the sequence shown in Scheme 3. Resin **9** was shaken with **7** (3 equiv) in the presence of diisopropylethylamine (DIEA) for 16 h at 50 °C, and the Teoc group was removed to afford resin **10**. The amino acid residue (Tyr) was introduced by acylation of **10** with an active pentafluorophenyl (Pfp) ester, Fmoc-Tyr(Bu^t)-OPfp.[16] Removal of the Fmoc group with piperidine was

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(13) From ^{1}H NMR, the yields of coupling product (**6**) were estimated to be: 30% (THF/DMF), 82% (THF/CH_2Cl_2), and 73% (THF/PhMe).

(14) In a larger scale solid-phase experiment, the preloaded piperazine resin (300 mg) was alkylated with **5** in THF/CH_2Cl_2 resulting in isolation of N^1-mononosylpiperazine (18%), while no sulfonamide formation was observed in solution-phase reactions.

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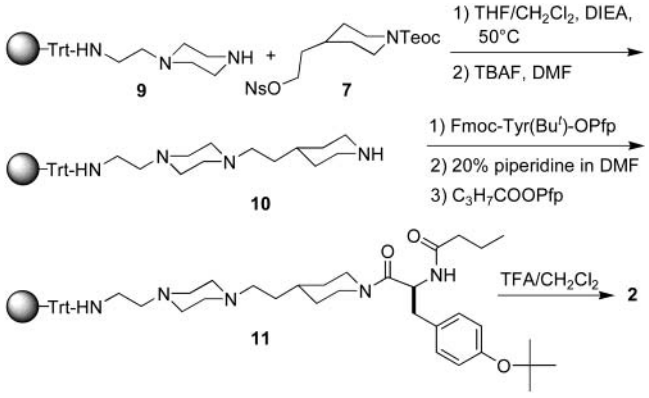
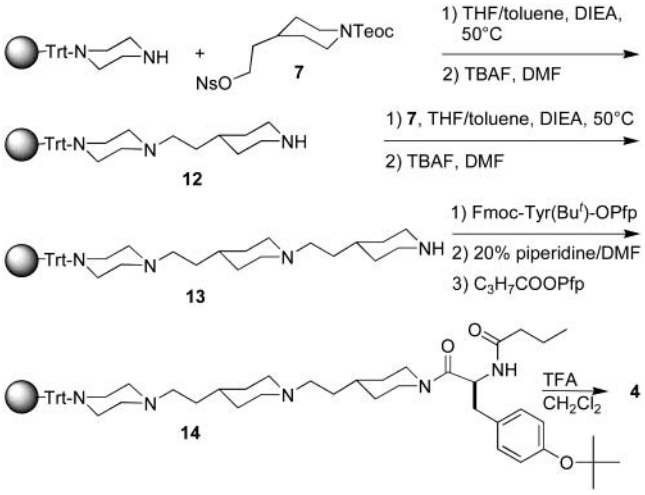
Scheme 3. Synthesis of **2**



Scheme 4. Synthesis of **4**



followed by N-acylation with pentafluorophenyl butanoate to give **11**. Finally, simultaneous cleavage from the resin and removal of the *O-tert*-butyl group were achieved by treatment with TFA/CH_2Cl_2 (1:1), and the product was purified by successive reversed-phase VLC and HPLC to afford **2** as the tris(TFA) salt in 28% overall yield.

Compound **3** was prepared by performing a sequence similar to that described above for the synthesis of **2**, starting from a commercially available trityl resin preloaded with piperazine. The product was isolated in 60% yield as the tris(TFA) salt by reversed-phase VLC and HPLC.

In the synthesis of compound **4**, two successive N-alkylation steps with nosylate **7** were necessary. To improve the overall yield, each treatment with **7** was repeated twice, first for 16 h and then for 2 h, before removal of the Teoc group. Introduction of the amino acid unit (Tyr), N-acylation, and cleavage from the resin were performed as in the syntheses of **2** and **3**. In initial attempts to obtain **4** using THF/CH_2Cl_2 in the N-alkylation step, only compound **3** was obtained in 80% yield. This result indicated that the required S_N2 reaction apparently was favored by the close proximity to the trityl linker. Consequently, the more hydrophobic THF/toluene mixture was applied in the N-alkylations (Scheme 4), and then the product **4** could be isolated in 26% overall yield as the tris(TFA) salt.

For comparison, the sequence shown in Scheme 4 was performed with the less reactive methanesulfonyl (mesyl) derivative of *N*-Teoc-2-(4-piperidyl)ethanol. In this case, only 19% of **3** was isolated, along with 29% of piperazine N-acylated with *N*-butyryltyrosine. Thus, a highly reactive sulfonate such as nosylate is necessary to achieve moderate yields in alkylations of secondary amines on solid support.

In the route presented here for the synthesis of these novel philanthotoxins, an alkylation approach to new tertiary amines on solid support was applied. Using this solid-phase strategy allowed a number of tedious purification steps of the highly polar intermediates to be avoided, and the final products **2**−**4** were obtained after single reversed-phase VLC and HPLC purification steps.

In the case of compound **4**, two sequential couplings proved to be feasible when an appropriate solvent mixture was selected. The present method is a useful alternative to a procedure previously reported by Zaragoza et al.,[17] which involves alkylation of secondary amines with alcohols employing (cyanomethyl)trialkylphosphonium iodide, a reagent that is not commercially available. For synthesis of N-monosubstituted piperazines on solid support, another somewhat more elaborate method consisting of amide bond formation followed by borane reduction has been reported by Salvino et al.[18] We have now demonstrated, that alkylation of resin-bound secondary amines using readily available nosylates represents an efficient and relatively mild synthetic protocol.

The novel philanthotoxins are currently undergoing extensive biological evaluation in electrophysiological iGluR and nAChR assays, the results of which will be published elsewhere.

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Supporting Information Available: Experimental procedures for the preparation and characterization of **2**−**4** and **7**−**9**, together with selected ^{1}H NMR, ESI-MS/MS, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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