Synthesis of Secondary Bis- and Tris(amines) Derivatives through Staudinger/aza-Wittig Reactions

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Polyamines derivatives including putrescine, spermidine and spermine derivatives and their unsymmetrical derivatives have received a great deal of attention from synthetic organic chemists[1] because of their potential use in biological activities and their presence in a number of siderophores and other natural products.[2] The protonated polyamines can interact with nucleic acids, proteins, and phospholipids.[3] They can affect DNA conformation *in vitro* and *in vivo*, and thus influence many biological processes. The key interaction includes hydrogen bonding and hydrophobic interactions. Recently, due to their significant biological activities, a variety of artificially designed polyamines and their conjugates have been developed, and furthermore, these amines also have been used in supramolecular chemistry to construct mechanically interlocked molecules such as (pseudo)rotaxane with cyclodextrin[4] and cucurbit[6]uril.[5]

Secondary or tertiary amine derivatives were synthesized by *N*-alkylation reaction of primary amine with alkyl halides or reductive alkylation reaction of primary amine with carbonyl compounds.[1] Although the *N*-alkylation of amines is deceptively simple, this method has some drawback due to the formation of overalkylation products such as secondary amines, tertiary amines, and quaternary ammonium salts. There is also limitation due to stability of primary amine and availability and isolation problem for multi-amines derivatives. On the other hand, azides have proven to be useful as a kind of protecting group and precursor of amine compound in chemical synthesis.[6] Azide is easily accessible to prepare from the corresponding halide.[6,7] In continuation with our research on self-assembly (supramolecular chemistry) using polyamines derivatives, there is still a demand to develop a simple, convenient, and efficient method to approach amine compounds. In this paper, we describe a feasible route to synthesize polyamines derivatives via sequential Staudinger/aza-Wittig reaction using multi-azides compounds.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. ^{13}C NMR spectra were proton decoupled and recorded on a 75 or 125 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. Analytical thin layer chromatography was performed on silica plates with F_{254} indicator and the visualization was accomplished by UV lamp or using an iodine chamber. All chemicals were obtained from commercial sources and used as received, unless otherwise mentioned. 1,3,5-Tris(azidomethyl)benzene[8] was prepared according to previously reported procedure and the bis(azides), α,α'-diazido-*p*-xylene, 1,12-diazidododecane, and tetra(ethylene glycol) diazide were synthesized readily from α,α'-dichloro-*p*-xylene, 1,12-dibromododecane, and tetra(ethylene glycol) dimesylate and sodium azide.

General procedure for the perparation of polyamines derivatives (4). A solution of bis(azides) **1** (3.0 mmol) and arylaldehyde **3** (6.6 mmol) in anhydrous THF (15 mL) in the presence of triphenylphosphine (6.6 mmol) was stirred at room temperature. After 24-30 h, the reaction solution was diluted with MeOH (30 mL) and subsequently added $NaBH_4$ (6.6 mmol). Then the reaction was stirred overnight at room temperature. After evaporation, the residue was partitioned in CH_2Cl_2 and saturated Na_2CO_3 aqueous solution and extracted three to five times with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and filtered and the filtrate was concentrated. The crude product was dissolved with MeOH and treated with conc. HCl to make ammonium salts followed by crystallization adding THF. The generated solid was collected to afford the corresponding polyamines **4**.

4a: A white solid; 97% yield; m.p. 223-225 °C. ^{1}H NMR (500 MHz, D_2O) δ 4.32 (s, 4H), 4.34 (s, 4H), 7.53 (m, 10H), 7.57 (s, 4H); ^{13}C NMR (125 MHz, D_2O) δ 132.5, 131.0, 130.9, 130.3, 130.1, 129.7, 51.1, 50.4; MS (FAB): *m/z* = 318.22 [$M^+ - 2Cl^-$], 317.26 [$M^+ - H^+ - 2Cl^-$].

4b: An orange solid; 94% yield; m.p. 215-217 °C. ^{1}H NMR (500 MHz, D_2O) δ 4.52 (s, 4H), 4.70 (s, 4H), 7.66 (s, 4H), 8.20 (d, J = 5.8 Hz, 4H), 8.93 (br, 4H); ^{13}C NMR (125 MHz, D_2O) δ 151.8, 142.5, 132.1, 131.5, 128.0, 51.7, 49.4; MS (FAB): *m/z* = 320.21 [$M^+ - 2H^+ - 4Cl^-$], 319.23 [$M^+ - 3H^+ - 4Cl^-$].

4c: A white solid; 98% yield; m.p. 222-224 °C. ^{1}H NMR

(500 MHz, D_2O) δ 1.29-1.37 (m, 16H), 1.70 (m, 4H), 3.07 (t, J = 7.7 Hz, 4H), 4.25 (s, 4H), 7.51-7.52 (m, 10H); ^{13}C NMR (125 MHz, D_2O) δ 131.2, 130.2, 130.0, 129.7, 51.3, 47.4, 29.0, 28.9, 28.5, 26.1, 25.7; MS (FAB): m/z = 382.22 [$M^+ - 2Cl^-$], 381.27 [$M^+ - H^+ - 2Cl^-$].

4d: A white solid; 96% yield; m.p. 204-206 °C. ^1H NMR (500 MHz, D_2O) δ 1.27-1.37 (m, 16H), 1.73 (m, 4H), 3.18 (t, J = 7.8 Hz, 4H), 4.57 (s, 4H), 8.12 (d, J = 5.8 Hz, 4H), 8.87 (d, J = 5.8 Hz, 4H); ^{13}C NMR (125 MHz, D_2O) δ 152.2, 142.5, 127.8, 49.6, 49.0, 29.0, 28.9, 28.6, 26.1, 25.9; MS (FAB): m/z = 384.28 [$M^+ - 2H^+ - 4Cl^-$], 383.27 [$M^+ - 3H^+ - 4Cl^-$].

4e: A white solid; 94% yield; m.p. 148-150 °C. ^1H NMR (500 MHz, D_2O) δ 3.29 (t, J = 4.6 Hz, 4H), 3.71 (s, 8H), 3.79 (t, J = 4.4 Hz, 4H), 4.27 (s, 4H), 7.50-7.51 (m, 10H); ^{13}C NMR (125 MHz, D_2O) δ 131.2, 130.2, 130.1, 129.7, 70.0, 69.8, 65.7, 51.3, 46.7; MS (FAB): m/z = 374.23 [$M^+ - 2Cl^-$], 373.26 [$M^+ - H^+ - 2Cl^-$].

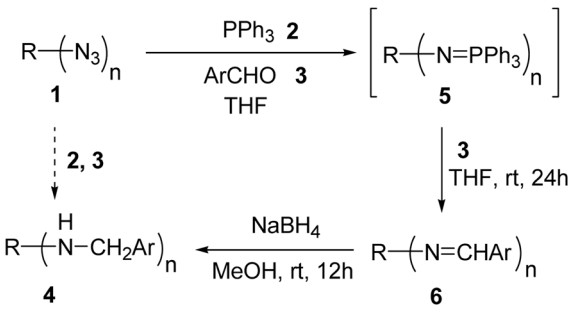
4f: A yellow solid; 90% yield; m.p. 155-157 °C. ^1H NMR (500 MHz, D_2O) δ 3.49 (t, J = 4.5 Hz, 4H), 3.77 (m, 8H), 3.90 (t, J = 4.3 Hz, 4H), 4.70 (s, 4H), 8.22 (d, J = 5.6 Hz, 4H), 8.94 (br, 4H); ^{13}C NMR (125 MHz, D_2O) δ 151.8, 142.5, 127.9, 70.0, 65.7, 49.7, 48.2; MS (FAB): m/z = 377.23 [$M^+ - H^+ - 4Cl^-$], 376.14 [$M^+ - 2H^+ - 4Cl^-$], 375.21 [$M^+ - 3H^+ - 4Cl^-$].

4g: A white solid; 93% yield; m.p. 203-205 °C. ^1H NMR (500 MHz, D_2O) δ 4.33 (s, 6H), 4.37 (s, 6H), 7.50-7.51 (m, 15H), 7.60 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 133.3, 132.8, 130.8, 130.3, 130.2, 129.7, 51.3, 50.2; MS (FAB): m/z = 437.04 [$M^+ - H^+ - 3Cl^-$], 436.09 [$M^+ - 2H^+ - 3Cl^-$].

4h: An orange solid; 84% yield; m.p. 165-167 °C. ^1H NMR (300 MHz, D_2O) δ 4.51 (s, 2H), 4.56 (s, 4H), 4.67 (s, 2H), 4.71 (s, 4H), 7.64 (m, 1H), 7.84 (m, 2H), 8.20 (m, 6H), 8.89 (br, 6H); ^{13}C NMR (75 MHz, D_2O) δ 151.7, 142.3, 133.9, 132.6, 127.9, 51.4, 49.5; MS (FAB): m/z = 440.62 [$M^+ - 4H^+ - 6Cl^-$], 439.88 [$M^+ - 5H^+ - 6Cl^-$], 438.98 [$M^+ - 6H^+ - 6Cl^-$].

Results and Discussion

Staudinger/aza-Wittig reactions are a powerful tool in organic synthetic strategies directed towards the construction of nitrogen-containing heterocycles.[9] To the best of our knowledge, there is no report to synthesize acyclic polyamines using Staudinger/aza-Wittig reactions. Our strategies in the synthesis of bis-linear and tripodal amines derivatives are *in situ* Staudinger/aza-Wittig reactions using an azido group and aldehyde in the presence of triphenylphosphine and followed by the reduction of imine intermediates. Before the adaptation of multi-azides reaction, we have investigated a simple Staudinger/aza-Wittig reaction using benzyl azide and benzaldehyde. From the reaction of benzyl azide and benzaldehyde in THF (0.2 M) in the presence of triphenylphosphine, the disappearance of benzyl azide, benzaldehyde, and triphenylphosphine and the appearance of triphenylphosphine oxide and new spot were observed from TLC analysis within 12 h. The resultant imine product



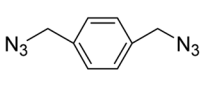
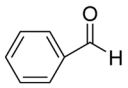
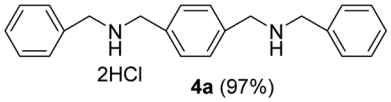
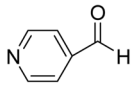
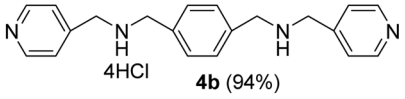
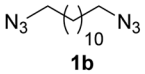
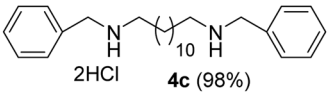
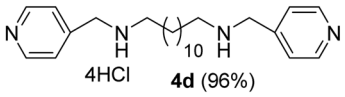
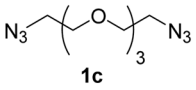
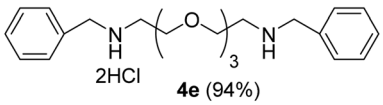
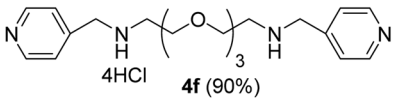
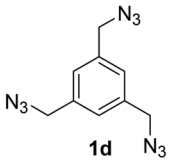
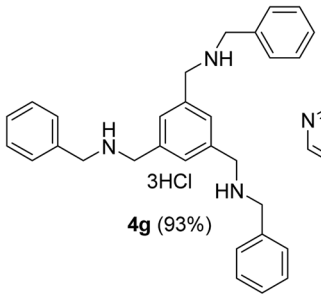
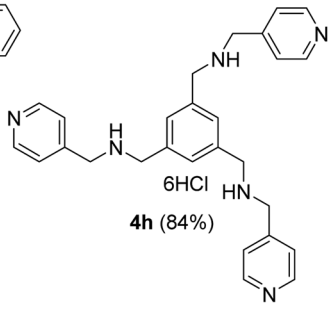
Scheme 1

was identified by ^1H-NMR spectroscopy which showed the characteristic imine peak at 8.4 ppm (Ph-C*H*=N-). This process can be achieved by the conversion of the azide into an imonophosphorane (the Staudinger reaction) followed by *in-situ* aza-Wittig reaction with aldehyde.

With this basic result, we began our study by establishing the validity of the chemistry in the synthesis of polyamines derivatives, as shown in Scheme 1. Thus, the Staudinger reaction[10] between the phosphine **2** and the multi-azides **1** gave the iminophosphoranes **5**, which were then made to undergo *in-situ* aza-Wittig reaction[11] with aldehydes **3** to give the imines **6**. The reduction of the imines **6** with sodium borohydride gave the polyamines derivatives **6**, generally in excellent yields as shown in the Table 1.

The Table 1 shows the multi-azides and aldehydes that were used in our study, together with the isolated yields of the polyamines. The reaction of bis(azides), α,α'-diazido-*p*-xylene **1a**, with benzaldehyde **3a** and 4-pyridinecarboxaldehyde **3b** in the presence of PPh_3 (2.2 equiv) in anhydrous THF (0.2 M) followed by reduction with $NaBH_4$ afforded the desired products **4a** and **4b** in yields of 97% and 94%, respectively. The desired amine product was then conveniently isolated in hydrochloric acid form from the usual aqueous workup followed by the crystallization. This result represents a significant advancement in the synthesis of polyamines derivative, since we can bypass the use of polyamines compound as a starting material. To probe the viability of our approach, we applied this method into the synthesis of α,ω-diamino-linear derivatives. The reaction of 1,12-diazidododecane **1b** with benzaldehyde and 4-pyridinecarboxaldehyde in the presence of PPh_3 followed by reduction with $NaBH_4$ afforded the desired products **4c** and **4d** in yields of 98% and 96%, respectively. Also, treatment of tetra(ethylene glycol) diazide **1c** and benzaldehyde and 4-pyridinecarboxaldehyde with PPh_3 in anhydrous THF followed by reduction with $NaBH_4$ led efficiently to the desired products **4e** and **4f** in yields of 94% and 90%,, respectively. Encouraged by these results, we then decided to investigate a tripodal system based on same strategy. Reaction of 1,3,5-tris(azidomethyl)benzene **1d** with benzaldehyde and 4-pyridinecarboxaldehyde with PPh_3 (3.3 equiv) in anhydrous THF followed by reduction with $NaBH_4$ afforded the desired products **4g** and **4h** in yields of 93% and 84%, respectively. Currently, we are studying the formation of rotaxanes from these polyamines with curcurbituril and/or

Table 1. Synthesis of secondary polyamines derivatives from multi-azides and aldehyde

Entry	Starting materials		Products (%)
1	 **1a**	 **3a**	 2HCl **4a** (97%)
2	**1a**	 **3b**	 4HCl **4b** (94%)
3	 **1b**	**3a**	 2HCl **4c** (98%)
4	**1b**	**3b**	 4HCl **4d** (96%)
5	 **1c**	**3a**	 2HCl **4e** (94%)
6	**1c**	**3b**	 4HCl **4f** (90%)
7	 **1d**	**3a**	 3HCl **4g** (93%)
8		**3b**	 6HCl **4h** (84%)

cyclodextrins and the applications of this protocol for poly-functionalized azides such as dendritic materials, which will be detailed elsewhere.

In summary, we have developed a method for the one-pot synthesis of secondary polyamines derivatives from multi-azides and aldehyde in the presence of triphenylphosphine. Compatibility with diverse functional groups would make the present protocol useful in organic synthesis. Further studies on the development of methodologies for the polymer supported synthesis of polyamines based upon Staudinger/ aza-Wittig chemistry are underway.

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