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Facile synthesis of a selectively protected triazamacrocycle

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Abstract—1,7-Diaminoheptane was selectively homologated with the novel reagent *N*-(2-nitrobenzenesulfonyl)aziridine. A series of reactions then followed to afford a selectively protected 14-membered triazamacrocyclic ring.

Azamacrocycles and some of their *N*-substituted derivatives are of synthetic interest due to their unique binding properties with metal ions.[1] The addition of different pendant arms can enhance the selectivity of the azamacrocycle for a metal cation, or inorganic anion depending on the cavity size and on the nature of the substituents. *N*-substituted azamacrocycles have found biomedical applications in magnetic resonance imaging[1c] and in radioimmunotherapy.[1d] In addition, we have shown that substituted azamacrocycles are also potent inhibitors of HIV-1 replication.[2,3] However, methods for the regioselective *N*-functionalization of azamacrocycles are scarce.[4] Herein, we report the synthesis of a selectively protected 14-membered triazamacrocyclic ring **7**, which allows for functionalization at any of the three nitrogen atoms and is applicable to the synthesis of larger or smaller sized azamacrocyclic rings.

Treatment of 1,7-diaminoheptane **1** (5 equiv.) with 1.0 equiv. of *N*-(2-nitrobenzenesulfonyl)aziridine[5] in THF at room temperature resulted in a 12:1 ratio of the desired mono-alkylated product **2** (59% yield) to the corresponding bis-alkylated product (5% yield). To the best of our knowledge this is the first example of chain homologation of an amine by nucleophilic ring opening of *N*-(2-nitrobenzenesulfonyl)aziridine. Chemoselective carbamate formation at the primary amine was accomplished by the addition of *N*-*tert*-butoxycarbonyl anhydride (1 equiv.) to a solution of **2** in THF at −78°C to afford the corresponding carbamate in 63% yield after purification by flash column chromatography. Treatment of the resulting carbamate with diethylphosphoryl chloride[6] (DEPCl) resulted in protection of the secondary amine to afford compound **3** in 67% yield, which contains three different nitrogen-protecting groups. Selective deprotection of the *N*-*tert*-butoxycarbamate protecting group was achieved by stirring a solution of **3** in CH_2Cl_2 in the presence of TFA for 40 min at room temperature, thus liberating the primary amine **4** in a yield of 85%. This material readily underwent *N*-acylation with bromoacetyl bromide in the presence of Na_2CO_3 in THF at −15°C affording the amide **5** in 89% yield. Intramolecular *N*-alkylation was accomplished by employing high dilution conditions (0.006 M) in the presence of K_2CO_3 as base in CH_3CN at 60°C resulting in isolation of the macrocycle **6** in 90% yield.[7] With this compound in hand functionalization at any of the nitrogen atoms is possible. For instance, selective deprotection of the 2-nitrobenzenesulfonyl group was achieved using standard conditions[8] to afford **7** in 77% yield. *N*-Alkylation of the liberated secondary amine followed by protecting group removal afforded a biological target, which was evaluated for antiviral activity.[9] We have also shown[7] in a related example that the DEP protecting group can be selectively removed in the presence of a 2-nitrobenzenesulfonyl group. The amide function of **7** also serves as a protecting group and we have shown[7] that reduction to the corresponding amine in the presence of a 2-nitrobenzenesulfonamide protecting group can be achieved using BH_3·THF. Thus, it is possible using the combination of protecting groups illustrated (Scheme 1) to selectively functionalize at any nitrogen atom of the azamacrocyclic ring.

In conclusion, we have developed a method for the synthesis of selectively protected triazamacrocycles, which allows for functionalization at any ring nitrogen atom.

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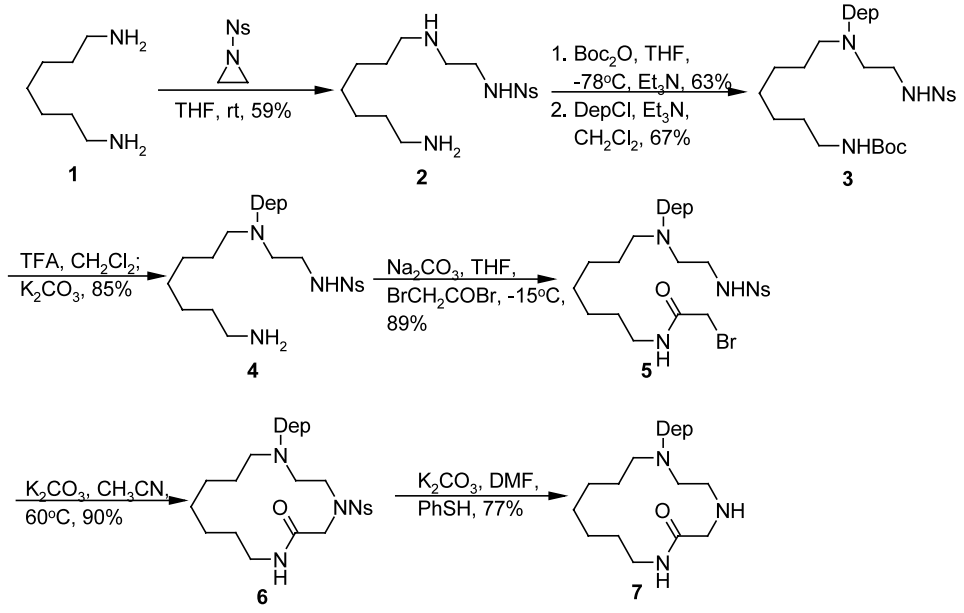

Scheme 1. [10]

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10. Experimental procedure for the synthesis of compound **2** and characterization data for compounds **2**–**7**: To a stirred solution of 1,7-diaminoheptane (33.4 g, 256.30 mmol) in anhydrous THF (220 mL) at room temperature was added dropwise *N*-(2-nitrobenzenesulfonyl)aziridine (11.7 g, 51.30 mmol) in anhydrous THF (80 mL). After the addition was complete the mixture was stirred for 20 min at room temperature and concentrated in vacuo to afford crude product as a yellow oil. The oil was purified by silica gel chromatography using MeOH/NH_4OH/CH_2Cl_2 (1:1:18) as eluant to give compound **2** (10.9 g, 59% yield based on the aziridine) as a yellow oil. The bis-alkylated product (1.5 g, 5%) was also isolated as a yellow oil. Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27–1.42 (m, 10H), 2.09 (br s, 4H), 2.47 (t, $J=7.1$ Hz, 2H), 2.67 (t, $J=6.9$ Hz, 2H), 2.73–2.77 (m, 2H), 3.14 (t, $J=6.0$ Hz, 2H), 7.71–7.77 (m, 2H), 7.84–7.89 (m, 1H), 8.12–8.16 (m, 1H); exact mass m/z calcd for $C_{15}H_{26}N_4O_4S$ 358.1, found 359.2 $[M+H]^+$; Compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.25 (m, 8H), 1.28 (t, $J=7.2$ Hz, 6H), 1.41 (br s, 11H), 2.85–2.93 (m, 2H), 3.03–3.09 (m, 2H), 3.18–3.21 (m, 4H), 3.91–4.08 (m, 4H), 4.59 (br s, 1H), 6.22 (br s, 1H), 7.68–7.74 (m, 2H), 7.77–7.82 (m, 1H), 8.05–8.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.48 (2C, $^3J_{PC}=7.5$ Hz), 26.97, 28.80 (3C), 29.30, 29.47, 30.33, 40.87, 42.86 (2C), 45.83 (d, $^2J_{PC}=5.2$ Hz), 47.03 (d, $^2J_{PC}=3.6$ Hz), 62.99 (2C, d, $^2J_{PC}=5.7$ Hz), 79.37, 125.54, 131.15, 132.96, 133.91, 134.01, 148.48, 156.41, exact mass m/z calcd for $C_{24}H_{43}N_4O_9PS$ 594.2, found 595.3 $[M+H]^+$; Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28–1.33 (m, 12H), 1.42–1.51 (m, 4H), 2.60–2.67 (m, 5H), 2.87–2.96 (m, 2H), 3.20–3.22 (m, 4H), 4.00–4.07 (m, 4H), 7.70–7.73 (m, 2H), 7.81–7.82 (m, 1H), 8.09–8.12 (m, 1H); exact mass m/z calcd for $C_{19}H_{35}N_4O_7SP$ 494.2, found 495.2 $[M+H]^+$; Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.56 (m, 16H), 2.90–2.98 (m, 2H), 3.21–3.31 (m, 6H), 3.88 (s, 2H), 3.95–4.09 (m, 4H), 6.12 (br s, 1H), 6.60 (br s, 1H), 7.71–7.76 (m, 2H), 7.82–7.86 (m, 1H), 8.10–8.13 (m, 1H); exact mass m/z calcd for $C_{21}H_{36}^{81}BrN_4O_8PS$ 616.1, found 617.1 $[M+H]^+$; Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.70 (m, 16H), 2.90–2.99 (m, 2H), 3.19–3.47 (m, 6H), 3.93–4.04 (m, 6H), 6.30 (t, $J=6.0$ Hz, 1H), 7.65–7.69 (m, 1H), 7.72–7.77 (m, 2H), 8.16–8.19 (m, 1H); exact mass m/z calcd for $C_{21}H_{35}N_4O_8PS$ 534.1, found 535.2 $[M+H]^+$; Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (dt, $J=7.2$, 0.6 Hz, 6H), 1.39–1.60 (m, 11H), 2.70 (t, $J=7.4$ Hz, 2H), 2.93–3.01 (m, 2H), 3.18–3.26 (m, 2H), 3.30 (s, 2H), 3.33–3.36 (m, 2H), 3.93–4.05 (m, 4H), 7.41 (br s, H), exact mass m/z calcd for $C_{15}H_{32}N_3O_4P$ 349.1, found 350.2 $[M+H]^+$.