Synthesis of 2,4,6,8,10-pentaaza[3.3.3]propellane substituted with different groups

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Abstract. Polyaza[3.3.3]propellanes have good symmetry and strong ring tension, which are suitable as the skeleton structure of functional materials such as high energy density materials. Based on the single benzyl derivative of 3,7,9,11-tetraoxo-2,4,6,8,10-pentaaza[3.3.3]propellane (compound **3**), a series of 2,4,6,8,10-pentaaza[3.3.3]propellane derivatives, such as **4a-c** and their reduced derivatives **5a-c**, were synthesized successfully.

1 Introduction

Tricyclic propellanes are a kind of polycyclic compounds in which three ring systems share a single bond (Figure 1) [1-5]. They have high reactivity and exist in many natural products [6-13]. Since the propellanes were firstly reported by Ginsburg [14] in 1965, they have

aroused the interest of many chemists [15-17]. Nitrocyclopropellanes, a class of heterocyclic propellanes, can be easily transformed to N-substituted compounds due to the high reactivity of nitrogen atoms, and they have attracted the attention of many researchers [18-20].

Figure. 1 The structure of propellanes.

Because aza[3.3.3]propellanes have good symmetry and compact skeleton, they have good compactness. In 1966, Altman [2] et al first synthesized monoaza[3.3.3]propellane and diaza[3.3.3] propellane, which enabled researchers to start the design and synthesis of azapropellanes. Combined with the influence of space tension on enthalpy of formation, detonation rate and work ability, they are ideal structures of energy-containing compounds. The secondary amine in the azapropellanes structure provides an active reaction site for the further introduction of energetic groups, and further reactions to obtain nitrogen-substituted compounds [21].

Recently, Burnett [18] reported the synthesis of 3,7,9,11-tetraoxo-2,4,6,8,10-pentaaza[3.3.3] propellane

with monosubstituted alkyl groups. Kim [22] synthesized 2,4,6,8,10-pentaaza[3.3.3] propellanes substituted with same groups (Scheme 1) by the condensation of 3,7,9,11-tetraoxo-2,4,6,8,10-pentaaza[3.3.3]propellane with benzylamine in 2014. However, 2,4,6,8,10-pentaaza[3.3.3] propellane derivatives substituted with different groups have never been reported. In order to study the debenzilation of pentaaza[3.3.3]propellane, we need derivatives substituted with different groups at nitrogen atoms. Therefore, we describe the preparation of N-substituted pentaazapropellanes with different substituents (Scheme 2).

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Scheme. 1 Synthesis of 2,4,6,8,10-pentaaza[3.3.3]propellane substituted with same groups.

Scheme 2. Synthesis of 2,4,6,8,10-pentaaza[3.3.3]propellane substituted with different groups.

2 Results and discussion

Compound **1** was prepared by bromination and urea condensation with diethyl tartrate as raw material according to the literature 22, but it was worth mentioning that the yield of compound **1** increased by 30% here. Compound **1** is difficult to dissolve in most organic solvents, however, when the amount of benzylamine used as a solvent and reactant was increased, compound **1** was successfully transformed to compound **2** in high yield.

Followed by benzylation, 10-benzyl derivative of 3,7,9,11-tetraoxo-2,4,6,8,10-pentaaza[3.3.3] propellane **3** was easy to be obtained by refluxing of dichloromethane

solution of benzylation mixture in the present of *p*-toluenesulfonic acid.

With single benzyl derivatives in hand, 3,7,9,11-tetraoxo-2,4,6,8,10-pentabenzyl-2,4,6,8,10-pentaaza[3.3.3]propellane **4a** was obtained by the reaction of **3** with BnBr in the present of NaH. Similarly, the other substituted derivatives of 3,7,9,11-tetraoxo-2,4,6,8,10-pentaaza[3.3.3]propellane (**4b**, **4c**) were provided by replacing benzyl bromide with 4-methylbromo-benzyl and 4-fluorobromobenzyl. During the synthesis of compound **4a**, it was found that the solvent plays a crucial role. And systematic research showed that when the amination was operated in a mixed solvent (DMSO: DMF = 1 : 4), the yield of total substituted products of nitrogen of **4** was the highest as shown in Table 1.

Table 1. Effect of solvent ratio of DMSO to DMF on the yield of compound **4a**.

Enty	V _{DMSO} : V _{DMF}	Yield
1	1:0	41%
2	1:1	56%
3	1:2	64%
4	1:3	75%
5	1:4	81%
6	1:5	77%
7	1:6	63%
8	0:1	71%

In order to reduce the carbonyl group of compounds **4**, we tried different reducing agents such as 10% Pd/C, LiAlH₄, NaBH₄ and red aluminum. As a result, it was found that **5a-c** were obtained by reduction of compounds **4a-c** with lithium aluminum hydride (LAH) in THF.

3 Experimental

3.1 Synthesis of glycoluric diethyl ester (1)

Diethyl tartrate (50 mmol, 10.30 g) and NBS (125 mmol, 22.25 g) were added to a 250 mL round bottom flask, then 80 mL 1,2-dichloroethane was added as a solvent, stirred and refluxed under argon. After 4 hours, the solution was cooled to room temperature, adding anhydrous sodium sulfite to the solution. The mixture was distilled to remove the solvent under reduced pressure, adding 40 mL ethyl acetate to dilute the mixture. The solid was filtered out, and brown organic phase was removed in vacuum distillation to give a white oily liquid. A solution of this oily liquid, trifluoroacetic acid (218 mmol, 16.5 mL) and urea (100 mmol, 6.00 g) in 80 mL toluene, were refluxed under argon atmosphere. After 6 hours, the solvent was removed in vacuum distillation and the concentrated solution was stirred for 3 hours in 100 mL ethanol. The mixture was filtered to give a white powder solid **1** (85%).

m.p. 294 - 296 °C; ¹H NMR (400 MHz, DMSO-*d*₆, 25 °C) δ 8.03 (s, 4H), 4.10 (q, 4H, *J* = 8.0 Hz), 1.18 (t, 6H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆, 25 °C) δ 167.47 (s), 159.67, 78.00, 62.13, 13.92; IR (KBr, *v*/cm⁻¹) 3231, 1754, 1698, 1488, 1391, 1268, 1173, 1078, 1031, 860, 767; HRMS (ESI⁺): calcd. for C₁₀H₁₅N₄O₆ [M+H]⁺ 287.0992, found 287.1001.

3.2 N, N'-Dibenzyl glycolide diamide (2)

Glycoluric diethyl ester **1** (20 mmol, 5.72 g) was added in a round bottom flask containing 60 mL benzylamine, and the mixture was refluxed under argon atmosphere. When the reaction was completed, 100 mL ethanol was added to the resulting mixture. The mixture was stirred at room temperature for 30 minutes to obtain compound **2**. (98%).

m. p. >300 °C; ¹H NMR (400 MHz, DMSO-*d*₆, 25 °C) δ 8.22 (s, 2H), 7.64 (s, 4H), 7.27 (t, *J* = 11.7 Hz, 10H), 4.13 (d, *J* = 5.0 Hz, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆, 25 °C) δ 167.36, 161.16, 139.17, 128.54, 128.07, 127.22, 79.62, 43.44; IR (KBr, *v*/cm⁻¹) 3343, 3297, 2928, 1719, 1697, 1529, 1454, 1360, 1161; HRMS (ESI⁺): calcd. for C₂₀H₂₁N₆O₄ [M+H]⁺ 409.1624, found 409.1626.

3.3 3,7,9,11-Tetraoxo-10-benzyl-2,4,6,8,10-pentaaza[3.3.3] propellane (3)

A mixture of compound **2** (10 mmol, 4.08 g), *p*-TsOH (30 mmol, 5.17 g) and 60 mL 1,2-dichloroethane was refluxed under argon atmosphere. When the reaction was

completed, the solvent was removed under reduced pressure. The residue was stirred in 100 mL ethanol for 3 hours. The white solid was collected by filtration and washed three times with ethanol. The solid was dried under vacuum to obtain compound **3** (97%).

m. p. >300 °C; ¹H NMR (400 MHz, DMSO-*d*₆, 25 °C) δ 8.76 (s, 4H), 7.44 - 7.14 (m, 5H), 4.65 (s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆, 25 °C) δ 170.82, 159.37, 135.72, 129.27, 128.38, 127.82, 74.33, 42.07; IR (KBr, *v*/cm⁻¹) 3246, 2920, 1723, 1682; HRMS (ESI⁺): calcd for C₁₃H₁₁N₅O₄ [M+H]⁺ 302.0884, found 302.0871.

3.4 3,7,9,11-Tetraoxo-2,4,6,8,10-pentabenzyl-2,4,6,8,10-penta-aza[3.3.3]propellane (4a)

Compound **3** (10 mmol, 3.01 g) and BnBr (60 mmol, 10.26 g) were dissolved in a mixture of solvents (V_{DMSO} : V_{DMF} = 1 : 4) under argon atmosphere. The reaction temperature was cooled using an ice bath. After 5 minutes, NaH (50 mmol, 2.00 g) was added and the resulting mixture was stirred for 1 h. Then the reaction temperature was raised to room temperature and the reaction was continued for another 12 h. When the end of the reaction was detected, reaction mixture was cooled again and diluted with diethyl ether (30 mL). A solution of aq HCl was slowly added to the mixture to quench the unreacted hydride. The resulting mixture was added H₂O and extracted with ethyl acetate. The combined organic layers were dried with MgSO₄, filtered, and concentrated under reduced pressure. The residue oil was purified by silica gel column chromatography, to provide the compound **4a** as a white solid (81%).

m. p. 151-152 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 7.84-6.43 (m, 25H), 4.44 (s, 8H), 4.26 (s, 2H); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ 166.01 (s), 156.05 (s), 135.71 (s), 132.56 (s), 127.90 (s), 127.48 (d, *J* = 33.3 Hz), 126.56 (s), 125.99 (s), 74.39 (s), 44.65 (s), 41.62 (s); IR (KBr, *v*/cm⁻¹) 2925, 1718, 1690, 1446, 1146, 936, 694; HRMS (ESI⁺): calcd. for C₄₁H₃₆N₅O₄ [M+H]⁺ 662.2762, found 662.2779.

3.5 3,7,9,11-Tetraoxo-2,4,6,8-(4-methyl)benzyl-10-benzyl-2,4,6, 8,10-pentaaza[3.3.3] propellane (4b)

4-Me-bnBr was replace of BnBr, the synthesis of compound **4b** (76%) was the same as the compound **4a**

m.p. 172.4 - 172.9 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 7.37 - 6.69 (m, 21H), 4.41 (s, 8H), 4.25 (d, *J* = 14.7 Hz, 2H), 2.22 (s, 12H); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ 166.13 (s), 156.07 (s), 136.04 (s), 132.69 (d), 128.26 (s), 127.65 (d), 127.17 (s), 125.97 (s), 74.32(s), 44.38(s), 41.52(s), 20.09(d); IR (KBr, *v*/cm⁻¹) 3086.11, 2962.66, 2924.09, 1716.65, 1456.26, 1386.82, 1336.67, 1244.09, 1168.86, 1139.93, 1109.07, 991.41, 948.98, 916.19, 866.04, 729.09, 524.64; HRMS (ESI⁺): calcd. for C₄₅H₄₃N₅O₄ [M+H]⁺ 718.3388, found 718.3378.

3.6 3,7,9,11-Tetraoxo-2,4,6,8-(4-fluoro)benzyl-10-benzyl-2,4,6, 8,10-pentaaza[3.3.3]propellane(4c)

4-F-bnBr was replace of BnBr, the synthesis of compound **4c** (68%) was the same as the compound **4a**

m.p. 108.4 - 110.1 °C; ¹H NMR (400 MHz, DMSO, 25 °C) δ 7.55 - 6.49 (m, 21H), 5.06 - 4.11 (m, 10H). ¹³C NMR (100 MHz, DMSO, 25 °C) δ 167.19 (s), 162.99 (s), 160.57 (s), 157.26 (s), 134.79 (s), 133.58 (d), 129.53 - 128.96 (m), 128.33 (s), 115.58 (d), 115.41 - 115.23 (m), 75.16 (s), 44.82 (s); IR (KBr, ν/cm^{-1}) 3068.75, 2924.09, 1720.50, 1606.70, 1510.26, 1456.26, 1411.89, 1342.46, 1232.51, 1147.65, 1099.43, 947.05, 844.82, 815.89, 736.81, 698.23, 665.44, 526.57, 491.85; HRMS (ESI⁺): calcd. for C₄₁H₃₁F₄N₅O₄ [M+H]⁺ 734.2385, found 734.2374.

3.7 2,4,6,8,10-Pentabenzyl-2,4,6,8,10-pentaaza[3.3.3]propellane (5a)

Compound **4a** was dissolved in 50 mL THF, cooling the solution to 0 °C with an ice bath. After 5 minutes, LAH (60 mmol, 2.28 g) was added slowly at low temperatures, under refluxing for 12 h. When the reaction was completed, the reaction mixture was cooled to 0 °C again. Ethyl acetate (6 mL) was slowly added to the reaction mixture and the resulting mixture was stirred for 30 minutes to quench the residual hydride. A solution of aq NaOH (10%, 12 mL) was added until the sludgy phase disappeared. After stirring for another 20 minutes, the mixture was filtered with EtOAc and the filtrate was evaporated. The yellow oil was purified by silica gel column chromatography to give white solid compound **5a** (2.57g, 85%).

m.p. 142 - 144 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 7.93 - 6.69 (m, 25H), 3.92 (d, J = 14.2 Hz, 6H), 3.80 - 3.62 (m, 6H), 3.30 (d, J = 2.0 Hz, 2H), 2.74 (s, 4H); ¹³C NMR (100 MHz, DMSO, 25 °C) δ 140.00 (s), 138.66 (s), 128.71 (s), 128.18 (s), 128.07 (s), 127.91 (s), 126.93 (s), 126.55 (s), 96.10 (s), 74.23 (s), 59.83 (s), 56.41 (s), 51.74 (s); IR (KBr, ν/cm^{-1}) 3061, 3024, 2900, 2800, 1602, 1493, 1453, 773, 698; HRMS (ESI⁺): calcd. for C₄₁H₄₃N₅ [M+H]⁺ 606.3591, found 606.3589.

3.8 2,4,6,8-(4-Methyl)benzyl-10-benzyl-2,4,6,8,10-pentaaza [3.3.3]propellane (5b)

4b was replace of **4a**, the synthesis of compound **5b** (78%) was the same as the compound **5a**.

m.p. 122.7 - 125.5 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 7.52 - 6.77 (m, 21H), 3.81 (d, J = 19.9, 8.6 Hz, 6H), 3.60 (d, J = 13.2 Hz, 6H), 3.19 (d, J = 3.5 Hz, 2H), 2.63 (s, 4H), 2.17 (d, J = 23.8 Hz, 12H); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ 135.87 (s), 135.12 (s), 127.85 (s), 127.26 (s), 126.93 (s), 126.00 (s), 95.09 (s), 73.46 (s), 58.94 (s), 55.52 (s), 50.51 (s), 20.04 (s); IR (KBr, ν/cm^{-1}) 3022.45, 2916.37, 2893.22, 2819.93, 2779.42, 2696.48, 1514.12, 1452.40, 1377.17, 1359.82, 1290.38, 1261.45, 1174.65, 1101.35, 1020.34, 877.61, 798.53, 742.59,

698.23, 476.42; HRMS (ESI⁺) calcd. for C₄₅H₅₁N₅ [M+H]⁺ 662.4217, found 662.4220.

3.9 2,4,6,8-(4-Fluoro)benzyl-10-benzyl-2,4,6,8,10-pentaaza [3.3.3] propellane (5c)

4c was replace of **4a**, the synthesis of compound **5c** (72%) was the same as the compound **5a**.

m.p. 111.2 - 113.0 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 7.46 - 6.66 (m, 22H), 3.75 (d, J = 13.8 Hz, 6H), 3.68 - 3.49 (m, 6H), 3.15 (d, J = 4.5 Hz, 2H), 2.61 (s, 4H); ¹³C NMR (100MHz, CDCl₃, 25 °C) δ 161.99 (s), 159.56 (s), 137.47 (s), 134.40 (d), 128.33 (d), 127.86 (s), 127.34 (s), 127.34 - 126.66 (m), 126.18 (s), 95.04 (s), 58.90 (s), 55.26 (s), 50.04 (s); IR (KBr, ν/cm^{-1}) 3035.96, 2912.51, 2806.43, 1602.85, 1508.33, 1452.40, 1375.25, 1220.94, 1151.50, 1091.71, 1014.56, 848.68, 821.68, 700.16; HRMS (ESI⁺): calcd. for C₄₁H₃₉F₄N₅ [M+H]⁺ 678.3214, found 678.3225.

4 Conclusion

In summary, the process route of 2,4,6,8,10-pentabenzyl-2,4,6,8,10-pentaaza[3.3.3]propellane **5a** was improved, and 2,4,6,8,10-pentaaza[3.3.3]propellane substituted with different groups, such as **5b** and **5c**, were synthesized based on the condensation of 3,7,9,11-tetraoxo-2,4,6,8-(4-methyl)benzyl-10-benzyl-2,4,6,8,10-pentaaza[3.3.3]propellane **4b** and 3,7,9,11-tetraoxo-2,4,6,8-(4-fluoro)benzyl-10-benzyl-2,4,6,8,10-pentaaza[3.3.3]propellane **4c**. The further studies of 2,4,6,8,10-pentaaza[3.3.3] propellanes substituted with different groups are in progress now.

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