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Synthesis and characterization of a novel derivative of azo calix [4]-arenes as a new potential for analgesic and antibacterial drug

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Abstract: Phenazopyridine hydrochloride is an important drug which is widely used as an analgesic and antibacterial drug with an antibiotic complement to cure urethras infection. Since the body environment is chiral, the chiral drugs show more effective interaction with their chiral receptors and so they show better efficiency compared with achiral drugs. In this research it is desirable to synthesis intrinsic chiral phenazopyridine derivatives by introducing a calix unit on these compounds, because of the multifunctional calix unit we hope that the antibacterial properties of this derivative to be likely increased.

Keywords: Phenazopyridine; Azo calix unit; Chiral drug; Antibacterial property.

Introduction

Recent development in calixarene chemistry has led to remarkable advances. These developments have been used as building blocks for host molecules with various applications in supramolecular chemistry [1, 2]. Functionalized calixarenes are fascinating objects for studying their supramolecular chemical properties from simple host-guest interaction [3] to applications as artificial sensor [4], synthetic acceptor for biological agents [5], antibody mimics [6] or building block units for molecular boxes [7], and potential as enzyme mimics [8]. In past two decades various methods have been achieved for functionalizing calixarenes and different derivatives of calixarenes have been synthesized [9]. Azo derivatives because of their properties as binding sites for complexation or as chromophores containing azo goups and described binding properties for metal ions are interest [10]. In general by introducing azo goup on calix [n] arene their structure show chromogenic character and this will cause increasing their molecular diagnostics as material sensors [11]. Of these calixarenes have been studied calixarenes bridging phenylazo moieties on the upper rim [12, 13], lower rim [14], double azo calixarenes [15] and azocalixcrowns [16] which show color changes because of molecular or ionic interactions. *Nomura* and colleagues synthesized azo calix [6] arene derivatives, Azo coupling reaction of calix [4] arene compounds were reported by *Morita* and *Shinkai* [17, 18].

Numerous researches on azo calix compounds properties have been developed [19-21]. However to the best of our knowledge there is no report on influence of introducing these compounds on drugs such as phenazopyridine hydrochloride as an inherently chiral unit which can likely show increased antibacterial character than the original drug. Herein the synthesis of an azo calix [4] arene has been reported.

Results and Discussion

Much attention has been paid in recent years to diazo-coupling techniques and the design and synthesis of new azocalixarene dye with a high coupling ability and an electrophiles and even cations in views of environmental protection. Phenazopyridine Hydrochloride is an azo dye which serves as a urinary tract analgesic. As the exact mechanism of its action is

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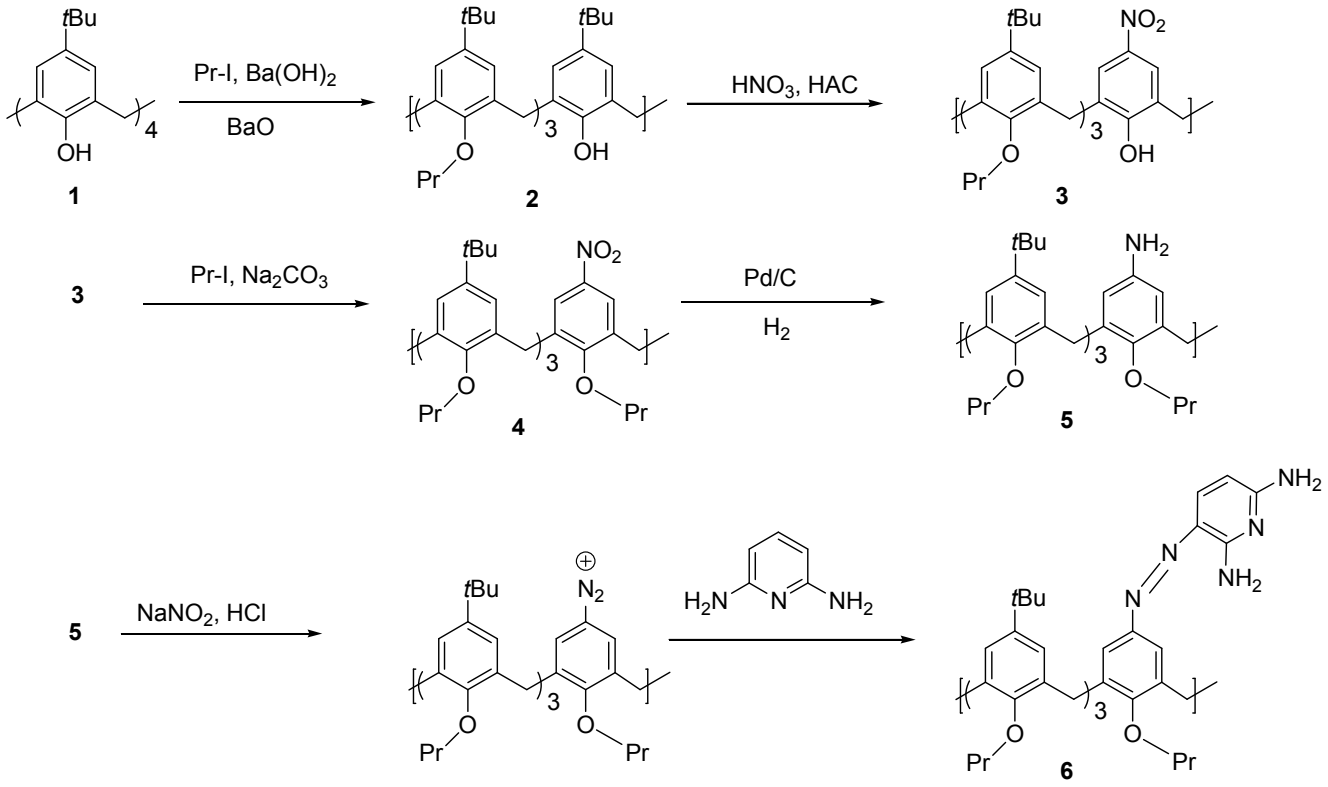

Scheme 1. Synthetic strategy

Experimental Section

Sodium nitrite was obtained from Kian Kaveh Company all the other compounds were obtained from Merck and were used without further purification. M.p.; Electrothermal-9100 apparatus. IR, Perkin Elmer spectrum GX. ^{1}H NMR and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in DMSO at 500 and 125 MHz, respectively.

*Procedure for the Preparation of Compounds**1-6***:
5,11,17,23-tetra tert.- butyl calix [4] arene **(1)**:

In a three-neck reaction flask 100g *para-tert*-butyl phenol, 24.8 ml formaldehyde solution 37% and 0.48g sodium hydroxide in 12ml were added and it was stirred with mechanical stirrer for 15 min in r.t. then it was heated in a thermal mantel up to 100-120 °C for 2 h. Then it was cooled to r.t. and obtained mixture (which is viscose yellow oil) was dissolved in 400 ml diphenyl ether and it was stirred in r.t. for 1 h. While the nitrogen or argon gas was passed intensively through the reaction mixture, it was heated to 120 °C. At this time the color of mixture changes from yellow to gay. When the water evaporation stopped, the containing was refluxed via a thermal mantel for 4 h. The mantel's temperature increased to 230 °C and after that it was cooled to r.t. for product reception 600 ml ethyl acetate was added to flask and it was stirred for 1 h. The vacuum filtered product was washed with 40 ml ethyl acetate two times, one time with 80 ml acetic acid, two times with 40 ml water and finally with 20 ml acetone, 65%. Yield, mp: 342-344 °C; ^{1}H-NMR (400 MHz, $CDCl_3$), 1.21[36H, s, $C(CH_3)_3$], 3.51, 4.25[8H, 2d, J=2.4Hz, $ArCH_2Ar$], 7.05[8H, s, ArH], 10.34[4H, s, OH].

5,11,17,23-tetra tert.- butyl– 2526,27-tri propoxy-28-hydroxy-calix [4] arene **(2)**:

20g (30.8 mmol) of **1** and 84 ml (852 mmol) propyl iodide in 400 ml dry DMF was dissolved. 34 g (108 mmol) barium hydroxide and 31.8 g (47.2 mmol) barium oxide was added to the mixture and it was stirred in r.t for 1 h. Then the reaction mixture was added in beaker containing 5ml water and it was

extracted with dichloromethane. After extraction the organic phase was evaporated via dried sodium sulfate and vacuum. The product was crystallized in methanol and dichloromethane. 63%. Yield, mp:194-196°C , ^{1}H-NMR (400 MHz ,$CDCl_3$) 0.81[18H, s, $C(CH_3)$], 0.96(3H, t, CH_3) , 1.1(6H, t, CH_3), 1.30 [9H, s, $C(CH_3)_3$], 1.32 [9H, s, $C(CH_3)_3$], 1.82-2.00 (2H, m, CH_2), 2.28-2.38 (4H, m, CH_2), 3.15, 4.29 (4H, 2d, J=12.6, $ArCH_2Ar$), 3.22, 4.33 (4H,2d, J=13.2 , $ArCH_2Ar$), 3. 3(4H, t, OCH_2), 3.81 (2H, t, OCH_2), 5.54 (1H, s, OH), 6.47 (2H, d, ArH), 6.48(2H, d, ArH), 7.03(2H, s, ArH), 7.10(2H, s, ArH).

5,11,17-tri tert.-butyl-23-nitro-25-hydroxy-26, 27,28-tri propoxy-calix [4] arene **(3)**:

10 g (12.9 mmol) of **2** was added to 50 ml of dichloromethane, 30 ml acetic acid glacial and 5 ml nitric acid 63% in -15 °C about 2 min. The obtained mixture was stirred in r.t for 5 min. and then were added to 250 ml water and washed with water several times. After drying and evaporation of organic phase. **3** were crystallized from ethanol. Yield 85%. mp:182-184°C, IR υ_{max} (KBr)/cm^{-1} 3456, 1592, 1472, 1334, 1201, 1006; ^{1}H-NMR(400 MHz ;$CDCl_3$) 0.83[18H, s, $C(CH_3)_3$], 0.95[3H, t, CH_3], 1.10[6H, t, CH_3], 1.35[9H, s, $C(CH_3)_3$], 1.93[4H, m, CH_2], 2.2[2H, m, CH_2], 3.19, 4.34[4H.2d, J=12.6Hz, $ArCH_2$ Ar], 3.75[2H, t, OCH_2], 3.81[4H, t, OCH_2], 3.39, 4.31[4H, 2d, J=13.9Hz, $ArCH_2Ar$], 6.45[2H, d, J=2.3Hz, ArH], 7.16[2H, s, ArH], 7.22[1H, s, OH], 8.06[2H, s, ArH].

5,11,17-tri tert.- butyl -23 - nitro – 25 , 26, 27,28-tetra propoxy-calix [4] arene **(4)**:

To solution of 7 g (9.16 mmol) **3** in 400 ml acetonitrile were added 9.6 g (81.6 mmol) sodium carbonate and 8.4 ml (92 mmol) propyl iodide. The mixture was refluxed for 240 hr., after evaporation of solvent, the residue was stirred in 200 ml dichloromethane and 200 ml water for 16 hr. then the organic phase was separated and evaporated. After recrystallization in dichloromethane-ethanol **4** was obtained as white crystals. 80% yield. mp : 214-216 °C, υ_{max} (KBr)/Cm^{-1} 2962, 1523, 1482, 1342, 1208; ^{1}H-NMR(500 MHz; $CDCl_3$) 0.68[9H, s, $C(CH_3)_3$], 0.97[6H, t, CH_3], 1.14[6H, t, CH_3], 1.41[18H, s, $C(CH_3)_3$], 1.94[4H, m, CH_2], 2.1[4H, m, CH_2], 3.18, 4.46[4H, 2d, J=13.5Hz, $ArCH_2Ar$] , 3.21, 4.50[4H, 2d, J=12.9Hz, $ArCH_2Ar$], 3.74[2H, t, OCH_2], 3.78[2H, t, OCH_2], 3.89, 4.08 [4H, m, OCH_2], 6.26[2H, s, ArH], 7.17[2H, d, J=2.3Hz, ArH], 7.20[2H, d, J=2.4Hz, ArH], 7.30[2H, s, ArH].

5,11,17-tri tert.-butyl-23- amino - 25,26, 27,28-tetra propoxy-calix [4] arene **(5)**:

1 g of **4** was dissolved in methanol and Pd/C (0.2 g, 10 weight-%) was added and then the hydrogenation was carried out for 24 h, the reaction was monitored by TLC. After reaction complication, the obtained mixture was filtered and solvent was evaporated. The product was obtained by 50% yield. mp:185-187 °C, υ_{max} (KBr)/Cm^{-1} 3511, 2961, 1606, ^{1}H-NMR (500 MHz; Cycle $_3$) 0.83[9H, s, $C(CH_3)_3$], 0.95[6H, t, CH_3], 1.11 [6H, 2t, CH_3], 1.35[18H, s, $C(CH_3)_3$], 1.93[4H, m, CH_2], 2.08[4H, m, CH_2], 3.3, 4.48[4H, 2d J=12.6Hz, $ArCH_2Ar$], 3.55[2H, t, OCH_2], 3.69[4H, t, OCH_2], 3.14, 4.36[4H, 2d, J=13.9Hz, $ArCH_2Ar$], 5.73[2H,S, NH_2], 6.32[2H,S.ArH], 7.04[2H, d, ArH], 7.1[2H, d, ArH], 7.3[2H, s, ArH].

5,11,17-tri tert.-butyl-23-diazo-2′,6′-diaminopyridine-25,26,27,28-tetra propoxy-calix [4] arene **(6)**:

To the Solution of 22 mM **5** in THF were added 0.5 ml water and 25 ml hydrochloride acid was added to in -5 °C. then sodium nitrite (3.6 mm in water) was added to progressively in half an hour. The obtained solution was stirred well for an hour. The reaction mixture was orange. After this 0.2 g 2,6-diamino pyridine in 2ml water was added to progressively in half an hour, and was heated further one hour. The residue was filtered and washed with water to remove the excess amount of 2,6-diamino pyridine. The product was dried in a dark place to avoid possible photo destructions. mp: >230 °C, υ_{max} (KBr)/Cm^{-1} 3450, 2961, 1482, 1202, ^{1}H-NMR (500 MHz; $CDCl_3$) 0.61 [9H, s, $C(CH_3)_3$], 1.32 [18H, s, $C(CH_3)$], 0.96 [6H, t, CH_3], 1.09 [3H, t, CH_3], 1.49 [3H, t, CH_3], 1.92 [4H, m, CH_2], 2.03 [4H, M, CH_2], 3.14, 4.43 [4H, 2d, J=12.5 Hz, $ArCH_2Ar$], 3.16, 4.47 [4H, 2d, J=12.5 Hz, $ArCH_2Ar$], 3.65 [4H, m, OCH_2], 3.98 [4H, t, OCH_2], 6.29 [2H, S, ArH], 6.41 [2H, S, ArH], 6.85 [H,d, ArH], 6.95 [H, d, ArH], 7.15 [4H, Br, NH_2].

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