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ESTABLISHMENT OF AN EFFICIENT SYNTHETIC ROUTE TO 3,4:3',4'-BIS(3,6,9-TRIOXAUNDECANE-1,11-DIOXY)BENZIL

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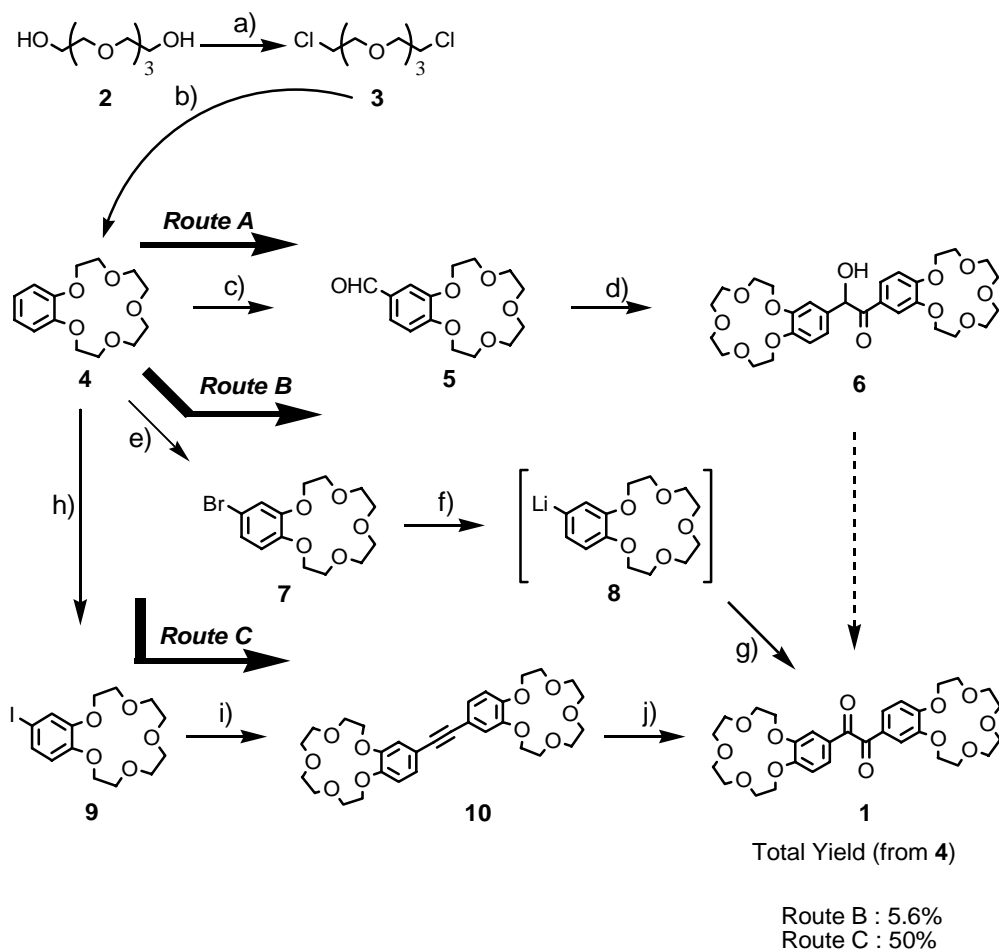
Abstract – 3,4:3',4'-Bis(3,6,9-trioxaundecane-1,11-dioxy)benzil (**1**) [bis(crown ether)benzil] was prepared by three different routes in which the third route C, including the method of Sonogashira-coupling, was the most efficient method with the overall yield of 50%. Further, the method of synthesizing the novel compound 3,4:3',4'-bis[3,4-(3,6,9-trioxaundecane-1,11-dioxy)]benzoin (**6**) [bis(crown ether)benzoin], which has not yet been prepared appropriately, was also provided.

INTRODUCTION

Although 3,4:3',4'-bis(3,6,9-trioxaundecane-1,11-dioxy)benzil (**1**) [bis(crown ether)benzil] is an essential intermediate for synthesis of heterocyclic compounds like imidazoles and pyrazines,¹ an appropriate synthetic method has not yet been known, other than a method developed by Huang *et al.* including ambiguity in characterization of the main product.² They claimed that 3,4:3',4'-bis[3,4-(3,6,9-trioxaundecane-1,11-dioxy)]benzoin (**6**) [bis(crown ether)benzoin] was obtained as the main product in 4.6% yield accompanied by bis(crown ether)benzil (**1**) in 1.3% yield by the condensation of 4'-formyl-benzo-15-crown-5 (**5**). We would like to report an efficient route to bis(crown ether)benzil (**1**), for which there has not been an practical and clear synthetic methods.

RESULTS AND DISCUSSION

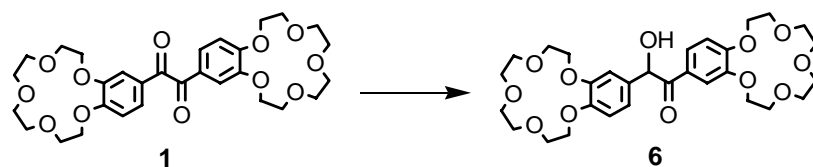
Initially, we attempted to synthesize bis(crown ether)benzoin (**6**) by the method of route A (shown in Scheme 1), starting from formylation of benzo-15-crown-5 (**4**) which was prepared according to the method of Pedersen *et al.*³ through two steps (starting from **2** → **3** → **4**) in total 42% yield, gave 4'-formyl- benzo-15-crown-5 (**5**) in 82% yield according to the method of Wada *et al.*,⁴ followed by the condensation of it according to the method of Huang *et al.*² to give bis(crown ether)benzoin (**6**), but the data of mp and chemical shifts of the main product was different from those of bis(crown ether)benzoin (**6**) mentioned in the reference.² The main product was confirmed to be small amount of the corresponding benzil (**1**) by HNMR analysis. So we tested another method (route B, shown in Scheme 1), using 1,4-dimethylpiperazine-2,3-dione (DMPD), which is known as an excellent benzil-precursor. 4'-bromobenzo-15-crown-5 (**7**) was prepared according to the method of Okano *et al.*⁵ through the bromination of benzo-15-crown-5 (**4**) in 80% yield. After the lithiation of 4'-bromobenzo-15-crown-5 (**7**), using DMPD, according to the method of Mueller-Westerhoff *et al.*,⁶ we obtained bis(crown ether)benzil



Scheme 1. Reaction conditions: a) SOCl₂, pyridine, benzene, reflux, 81%. b) catechol, NaOH, H₂O, BuOH, reflux, 52%. c) HMTA, CF₃COOH, NaOH/H₂O, 100°C, reflux, 82%. d) NaCN (10 eq.), EtOH/H₂O, reflux, 18%. e) Dioxane-bromine (1/1), THF, 0°C, 80%. f) BuLi/hexane, THF, -97°C. g) DMPD/THF, HCl/H₂O, -97°C to rt, 7.0%. h) I₂, HIO₄, AcOH, H₂SO₄, H₂O, 70°C, 68%. i) C₂H₂, [PdCl₂(PPh₃)₂], CuI, Et₂NH, reflux, 86%. j) PdCl₂, DMSO, 140°C, 86%.

(**1**) in 7.0% yield, but the yield was low. Then we attempted the method of route C (shown in Scheme 1): first, the iodination of benzo-15-crown-5 (**4**) gave 4'-iodobenzo-15-crown-5 (**9**) in 68% yield using the method of Shaw *et al.*,⁷ second, the Sonogashira coupling (the method of Kikugawa *et al.*)⁸ of 4'-iodobenzo-15-crown-5 (**9**) gave 1,2-bis[3,4-(3,6,9-trioxaundecane-1,11-dioxy)phenyl]ethyne (**10**) [bis(crown ether)tolan] in 86% yield, finally, the oxidation of bis(crown ether)tolan (**10**) gave bis(crown ether)benzil (**1**) in 86% yield according to the method of Chi *et al.*⁹ The overall yield of the route C was 50%, which was the most efficient in the routes tested.

After the success in synthesizing bis(crown ether)benzil (**1**), in order to confirm the structure of bis(crown ether)benzoin (**6**) which was mentioned by Huang *et al.*,² we synthesized bis(crown ether)benzoin (**6**) through the reduction of bis(crown ether)benzil (**1**) in 85% yield according to the method of Toda *et al* (shown in Scheme 2).¹⁰



Scheme 2. Reaction conditions: Zn/ZnCl₂, EtOH, reflux, 85%.

We compared our data of bis(crown ether)benzoin (**6**) with that of Huang *et al.* in the reference and found our data of mp and ¹H NMR were very different from those of the reference,² so we thought bis(crown ether)benzoin (**6**) itself was unstable, easy to be oxidized to bis(crown ether)benzil (**1**), therefore, according to the method of Huang *et al.*,² we did not get bis(crown ether)benzoin (**6**) mentioned by Huang *et al.*² Judging from the mp (181-182°C) shown by Huang *et al.*,² their product seems to be bis(crown ether)benzil (**1**) because we recorded 180-181°C for **1**.

As shown above, we have achieved success in establishing an efficient route to synthesize bis(crown ether)benzil (**1**) and also provided an appropriate route to synthesize bis(crown ether)benzoin (**6**) different from that of Huang *et al.*²

EXPERIMENTAL

General Procedure. All melting points were measured with a Yanagimoto micro melting point apparatus. IR spectra were recorded on a JASCO FT/IR-5000 spectrophotometer. UV-vis spectra were measured by a JASCO V-530 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Varian MERCURY (FT, 300 MHz) spectrometer or a Varian VXR-500 (FT, 500 MHz) spectrometer. Fast Atom Bombardment (FAB) mass spectra were recorded on a Micromass 70-SE. High Resolution Mass Spectra (HRMS) were recorded on a JEOL JMS-DX300 mass spectrometer coupled to JMA-3100 data analysis system.

4'-Iodobenzo-15-crown-5 (9). Benzo-15-crown-5 (**4**) (6.0 g, 22 mmol), I₂ (2.26 g, 8.9 mmol), and HIO₄ (1.02 g, 4.5 mmol) were added to the mixture of glacial AcOH (25 mL), water (5 mL) and concentrated H₂SO₄ (0.6 mL). The mixture was stirred at 70°C for 16 h under nitrogen, after cooled, diluted to 250 mL with water. The mixture was extracted with Et₂O, the ether extract being washed with aqueous Na₂S₂O₃ and then aqueous NaHCO₃. Et₂O was removed from the mixture by using rotary evaporator, and the product was extracted with hot hexane. After cooling, precipitated white crystals were filtered, and washed with hexane. We obtained 6.0 g (15 mmol, 68%) of 4'-iodobenzo-15-crown-5 (**9**) as colorless needles. mp 75-76°C; ¹H NMR (500 MHz, CDCl₃): δ = 7.20 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 4.11-4.08 (m, 4H), 3.91-3.88 (m, 4H), 3.82-3.70 (m, 8H); IR (KBr) ν_{max} 1255 (Ar-O-C), 1131 (C-O-C), 940 cm⁻¹ (Ar-I). [Lit.,⁷: 88%; mp 87-88°C (from light petroleum)]

1,2-Bis[3,4-(3,6,9-trioxaundecane-1,11-dioxy)phenyl]ethyne (10) [Bis(crown ether)tolan 10]. A solution of 4'-iodobenzo-15-crown-5 (**9**) (6.0 g, 15 mmol), [PdCl₂(PPh₃)₂] (102 mg, 0.15 mmol), and CuI (114 mg, 0.6 mmol) in Et₂NH (150 mL) was refluxed under nitrogen. Acetylene gas was passed through the mixture for 3 h under gentle reflux, then continue to reflux for 7h. After removal of Et₂NH under reduce pressure, the residue was purified by chromatography (silica gel, chloroform/methanol = 30/1). Obtained yellow crystals were recrystallized from AcOEt to give 3.63 g (6.5 mmol, 86%) of bis(crown ether)tolan (**10**) as colorless needles. mp 165-166°C; ¹H NMR (300 MHz, CDCl₃) δ = 7.08 (dd, *J* = 1.8, 8.4 Hz, 2H), 7.01 (d, *J* = 1.8 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.20-4.09 (m, 8H), 3.93-3.87 (m, 8H), 3.80-3.76 (m, 16H); ¹³C NMR (75 MHz, CDCl₃): δ 149.2, 148.4, 124.9, 116.5, 115.8, 113.3, 87.9, 71.0, 71.0, 70.3, 70.3, 69.4, 69.4, 68.8, 68.7; IR (KBr) ν_{max} 1251 (Ar-O-C), 1137 cm⁻¹ (C-O-C). [Lit.,⁸: 98%; mp 125.4-127.0°C. ¹H NMR (CDCl₃): δ = 3.6-4.3 (-OCH₂CH₂O-, m, 32H), 6.6-7.2 (aromatic protons, m, 6H)]

3,4:3',4'-Bis(3,6,9-trioxaundecane-1,11-dioxy)benzil (1) [Bis(crown ether)benzil] [from 4'-bromobenzo-15-crown-5 (7)]. 4'-Bromobenzo-15-crown-5 (**7**) (1.5 g, 4.3 mmol) was dissolved in 30 mL of dry THF under nitrogen and the temperature was lowered to -97 °C by a liquid nitrogen-methanol bath. Butyllithium (4.3 mmol, 0.93 mL of 1.60 M hexane solution) was added slowly by syringe. After stirring for 30 min at the same temperature, DMPD (0.31 g, 2.2 mmol) dissolved in 80 ml of THF was added gradually to the solution. After stirring for 1 h at the same temperature, the mixture was allowed to warm gradually to rt over a period of 5 h. And then the mixture was hydrolyzed with 10% HCl. THF was removed by using rotary evaporator and the resulting mixture was extracted with CH₂Cl₂. CH₂Cl₂ was removed by using rotary evaporator and then AcOEt was added to the residue, white crystals were precipitated. The crystals were filtered and washed with AcOEt. We obtained 90 mg (0.15 mmol, 7%) of bis(crown ether)benzil (**1**) as colorless needles.

3,4:3',4'-Bis(3,6,9-trioxaundecane-1,11-dioxy)benzil (1) [Bis(crown ether)benzil] [from bis(crown ether)tolan (10)]. A mixture of bis(crown ether)tolan (**10**) (5.30 g, 9.5 mmol) and Pd (II) Cl₂ (171.0 mg, 0.95 mmol) in DMSO (95 mL) was stirred at 120°C for 20 h. After cooled, the mixture was diluted with water and extracted with CHCl₃. After removal of CHCl₃ under reduce pressure, the residue was recrystallized from AcOEt to give 4.82 g (8.2 mmol, 86%) of bis(crown ether)benzil (**1**) as colorless needles. mp 180-181°C; ¹H NMR (500 MHz, CDCl₃): δ = 7.54 (d, *J* = 2.0 Hz, 2H), 7.44 (dd, *J* = 2.0, 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.20-4.18 (m, 8H), 3.94-3.90 (m, 8H), 3.78-3.72 (m, 16H); ¹³C NMR (75 MHz, CDCl₃): δ 193.4, 154.8, 149.1, 126.3, 126.3, 112.4, 111.6, 71.2, 71.2, 70.3, 70.2, 69.2, 69.1, 68.9, 68.3; MS (FAB) *m/z* 591 (M⁺+1); HRMS (FAB, NBA) Calcd for C₃₀H₃₉O₁₂ 591.2442 (M+H), Found 591.2412; IR (KBr) ν_{\max} 2930 (C-H), 1665 (C=O), 1597, 1516 (C=C) 1435 (CH₂), 1272 (Ar-O-C), 1141 cm⁻¹ (C-O-C); UV-vis (CHCl₃) λ_{\max} (log ϵ) 324 (4.26), 285 nm (4.24). [Lit.,²: 1.3%; mp 149.5-150.8°C; IR (KBr): 1663 (s; C=O), 1271, 1139 cm⁻¹ (C-O); ¹H NMR (90 MHz, CDCl₃): δ 7.55-6.80 (m, 6H), 4.23-3.77 (m, 32H); MS (70 eV) *m/z* 590 (M⁺); UV-vis (CHCl₃) λ_{\max} (log ϵ) 323 (4.24), 285 nm (4.22)]

3,4:3',4'-Bis[3,4-(3,6,9-trioxaundecane-1,11-dioxy)]benzoin (6) [Bis(crown ether)benzoin] [from bis(crown ether)benzil (1)]. A mixture of bis(crown ether)benzil (**1**) (1.3 g, 2.2 mmol), Zn powder (1.3 g, 19.9 mmol), ZnCl₂ (1.3 g, 9.5 mmol) and EtOH (13mL) were refluxed under nitrogen. After reaction for about 2h later, the mixture was cooled, and then added CHCl₃, filtered under reduced pressure to clear Zn powder. Then water was added, white precipitation appeared. After cooling in the freezer overnight, chloroform layer was separated, then water layer was extracted with CHCl₃. After CHCl₃ was removed by a rotary vacuum evaporator, we obtained dense yellow liquid, dried it with vacuum pump and got 1.1 g (1.9 mmol, 85%) of bis(crown ether)benzoin (**6**) as white crystals. mp 46-48°C; ¹H NMR (500MHz, CDCl₃): δ = 7.47 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.86 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 5.79 (s, 1H), 4.52 (s, 1H), 4.15 (m, 8H), 3.90 (m, 8H), 3.75 (m, 16H); MS (FAB) *m/z* 592 (M⁺); HRMS (FAB, NBA) Calcd for C₃₀H₄₁O₁₂ 593.2598 (M+H), Found 593.2547; IR (KBr): ν_{\max} 3464 (-OH), 2864 (C-H), 1673 (C=O), 1253 (Ar-O-C), 1133 (C-O-C), 1050 cm⁻¹ (Ar-O-C); UV-vis (CHCl₃) λ_{\max} (log ϵ) 315 (3.93), 283 nm (4.05). [Lit.,²: mp 181-182°C; IR (KBr): 3430 (s; OH), 1677 (s; C=O), 1271, 1136 cm⁻¹ (C-O); ¹H NMR (CDCl₃): δ = 1.88 (s; OH), 3.61-4.13 (m; 32-H of crown ring, -CH₃), 6.78-7.53 (m; 6-H of phenyl); UV (CHCl₃) λ_{\max} /nm 282 and 321; MS (70 eV) *m/z* 592 (M⁺)

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