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QUADRUPLE PHOTOCYCLIZATION REACTION LEADING TO THE CYCLOPHANES CONTAINING TWO BENZO[1,2-*b*:5,4-*b'*]DIFURAN RINGS

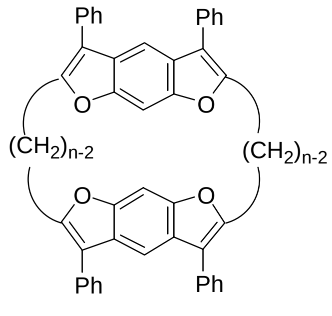
Kwanghee Koh Park* and Hongsan Lim

Department of Chemistry, Chungnam National University
Taejon 305-764, South Korea
khkoh@cnu.ac.kr

Abstract-Irradiation of the macrocycles (**4a-b**) having two 1,5-dibenzoyl-2,4-dialkoxybenzene moieties with 350 nm mercury lamp followed by dehydration afforded two benzo[1,2-*b*:5,4-*b'*]difuran ring-containing cyclophanes (**1a-b**) *via* quadruple photocyclization reaction forming four dihydrofuranol ring systems in one pot.

INTRODUCTION

Benzo[*b*]furan nucleus is present in numerous examples of natural products and many of the natural benzo[*b*]furans have physiological properties, and thus their chemical syntheses have been attracting active interests.[1-6] The cyclization of a suitably substituted benzene is the most often employed pathway for the synthesis of benzo[*b*]furans.[1-6] Either chemical reagents such as acid, base, or palladium catalysts,[1-3] or photocyclization technique[4-6] have been utilized for the cyclization. On the other hand, the synthesis of benzo[1,2-*b*:5,4-*b'*]difuran nucleus has rarely been described.[7-10] The reported synthetic routes are either *via* the formation of one benzo-fused furan ring from 5-formyl (or acetyl)-6-hydroxy-benzo[*b*]furan or *via* the formation of two benzo-fused furan rings from 4,6-diacetylresorcinols through the condensation with appropriate α-halocarbonyl compound.[7,8] The other synthetic methods are for the preparation of 2,3,5,6-tetraarylbenzodifuran derivatives either *via* photocyclization of 1,3-bis(benzyloxy)-4,6-dibenzoylbenzenes[9] or by acid-catalyzed cyclocondensation of resorcinol with *p*-benzyloxy-benzoin.[10] These methods have limited scope for the synthesis of benzo[1,2-*b*:5,4-*b'*]difuran derivatives. We have been interested in the synthesis of various furan ring derivatives *via* photocyclization technique,[6] and found recently that photochemical cyclization of 1,5-dibenzoyl-2,4-dialkoxybenzene, followed by dehydration, provides facile access to benzo[1,2-*b*:5,4-*b'*]difuran ring systems.[11] This photochemical procedure is quite remarkable due to its simplicity and immediate applicability to the synthesis of various cyclophanes containing those ring systems.[6,11] Cyclophanes, macrocycles containing aromatic groups, becoming central class of materials in supramolecular chemistry, and different types of cyclophanes having a variety of structures have been designed and synthesized.[12,13] However, most synthetic routes to cyclophanes are based on attaching appropriate side chains to preformed aromatic rings followed by connection of the side chains forming macrocycles.[12-14] Here, we describe a simple synthetic route to cyclophanes (**1a-b**) containing two benzo[1,2-*b*:5,4-*b'*]difuran rings. The cyclophanes were prepared through simultaneous formation of four dihydrofuranol rings from the appropriately preformed macrocycles (**4a-b**) *via* a quadruple photocyclization step.



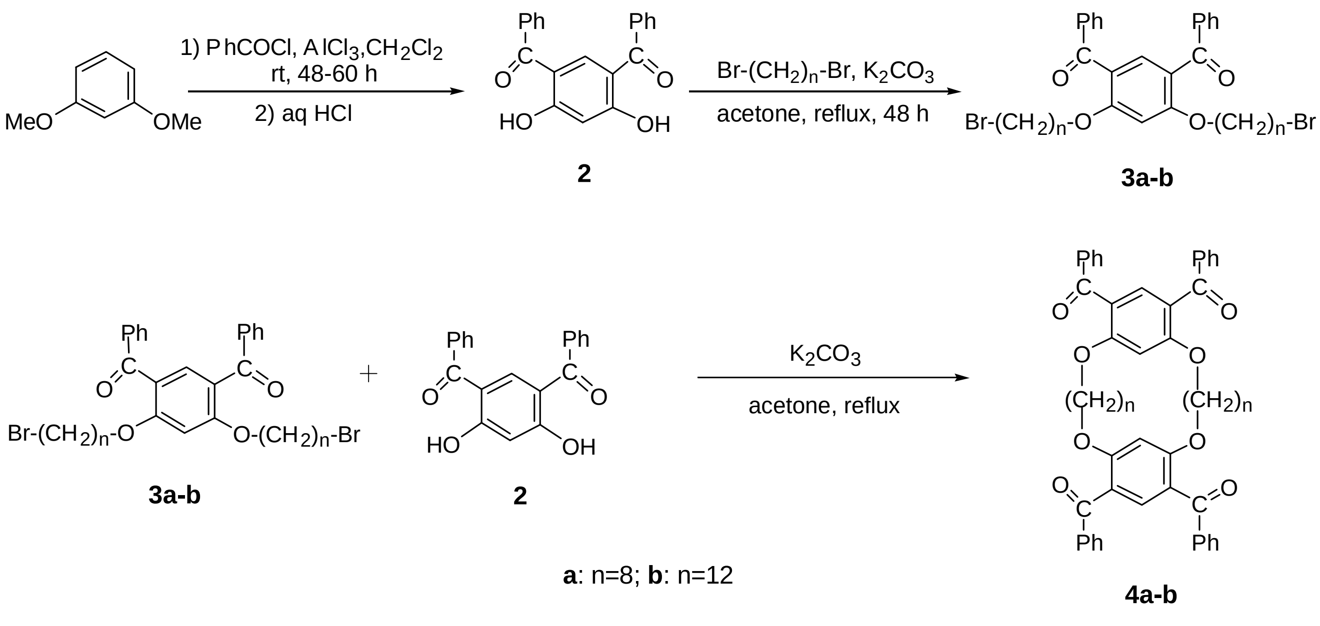
1a-b (a: n=8; b: n=12)

RESULTS AND DISCUSSION

For the synthesis of the cyclophanes (**1a-b**), we first prepared the macrocycles (**4a-b**), starting from 1,3-dimethoxybenzene (Scheme 1). Friedel-Crafts acylation of 1,3-dimethoxybenzene with benzoyl chloride followed by demethylation gave 1,5-dibenzoyl-2,4-dihydroxybenzene (**2**).[9,11] The reaction of the compound (**2**) with α,ω-dibromoalkanes in a 1:5 molar ratio in the presence of K_2CO_3 provided **3a-b** in

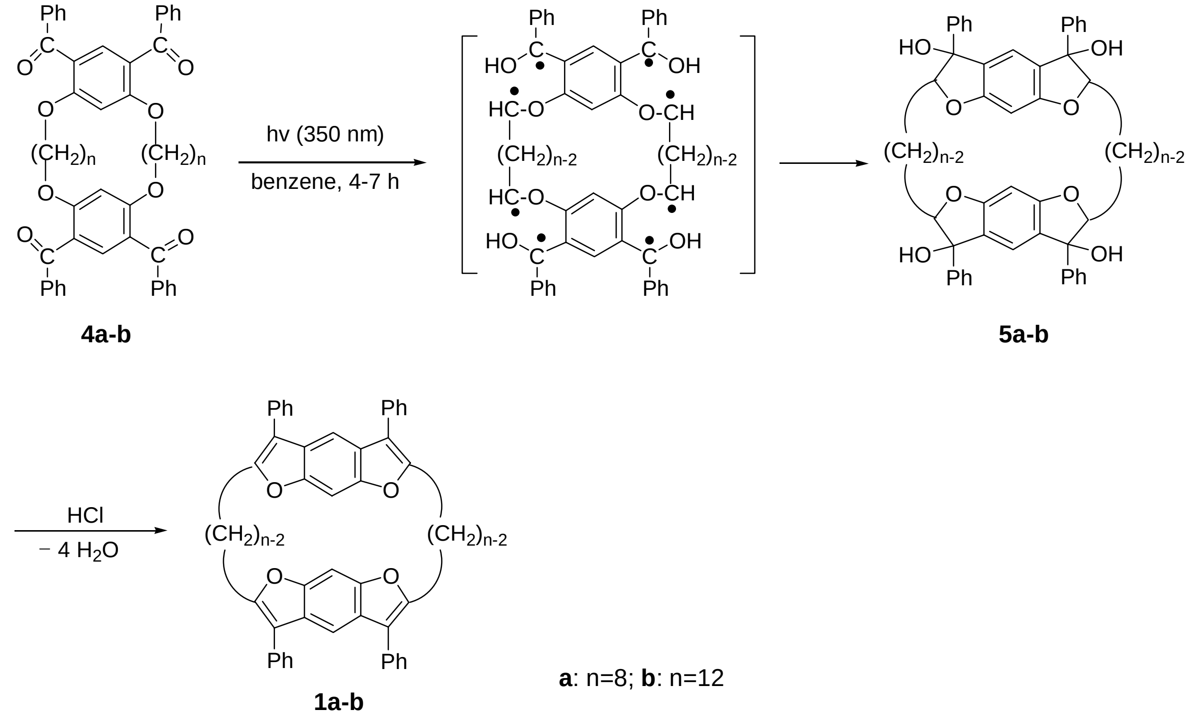
60-66 % yields.[11] 1,5-Dibenzoyl-2,4-bis(ω-bromoalkoxy)benzenes (**3a-b**) were then reacted with 1,5-dibenzoyl-2,4-dihydroxybenzene (**2**) in the presence of K_2CO_3 in refluxing acetone to afford the desired macrocycles (**4a**) and (**4b**) in 33% and 35 % yields, respectively. Attempts to prepare the macrocycles (**4a-b**) in one pot *via* 2:2 cyclization by reacting 1,5-dibenzoyl-2,4-dihydroxybenzene (**2**) with α,ω-dibromoalkanes in a 1: 1 molar ratio resulted in very low and inconsistent yields of the macrocycles (**4a-b**). The overall yields of **4a-b** obtained *via* two consecutive alkylation steps were moderate (20-23 %) and consistent.

Scheme 1



It is well known that *o*-alkoxy-substituted benzophenones photocyclize readily to benzo[*b*]furanols *via* intramolecular δ-hydrogen abstraction.[4-6] It was also found that the methodology can be successfully extended to 1,5-dibenzoyl-2,4-dialkoxybenzene derivatives leading to the formation of benzo[1,2-*b*:5,4-*b'*]difuran ring systems.[9,11] Since the macrocycles (**4a-b**) contain two 1,5-dibenzoyl-2,4-dialkoxybenzene moieties, we envisioned that the photoirradiation of the macrocycles (**4a-b**) followed by dehydration would produce a novel type of cyclophanes (**1a-b**) containing two benzo[1,2-*b*:5,4-*b'*]difuran rings, *via* quadruple photocyclization (Scheme 2). A suspension containing 0.5 mmol of the macrocycles (**4a-b**) in 500 mL of benzene was irradiated under nitrogen atmosphere with 350 nm mercury lamps. During irradiation the reaction mixture became a clear solution and after 4-7 h it showed virtually no starting material remaining. Without attempting isolation and separation of the bis(benzodifuranol) derivatives (**5a-b**), dehydration of the concentrated reaction mixtures with aq HCl afforded a new type of cyclophanes of bis(benzodifuran) derivatives (**1a**) and (**1b**) in 20 % and 15 % yields, respectively. The yields of **1a-b** are acceptable, if considered that four furan rings are formed in one step.

Scheme 2



The structures of the compounds (**4a-b**) and (**1a-b**) were characterized by ^{1}H and ^{13}C NMR spectra, mass spectra, and elemental analysis. The number of ^{1}H and ^{13}C NMR peaks confirmed the symmetrical nature of the compounds. The numbers of the peaks observed in their ^{13}C NMR spectra, 13 peaks for **4a** and **1a** and 15 peaks for **4b** and **1b**, exactly match the expected numbers based on the symmetry of the compounds. The actual carbon numbers present in the compounds are 56 for **4a** and **1a** and 64 for **4b** and **1b**. The formation of the cyclophanes (**1a-b**) from the photoirradiation of the precursor macrocycles (**4a-b**) followed by dehydration indicates clearly that the simultaneous formation of four furan ring systems in one pot is feasible *via* quadruple photocyclization reaction.

In summary, we described quadruple photocyclization reaction leading to the simultaneous formation of four dihydrofuranol ring systems in one pot. By this technique, we could prepare new type of cyclophanes

(**1a-b**) containing two benzo[1,2-*b*:5,4-*b'*]difuran rings. The schemes described here could be easily applied to the syntheses of various other types of two benzodifuran ring-containing macrocycles having different tethering groups. This facile access to new cyclophanes is noteworthy as the cyclophanes have a wide range of applicability in various fields, and synthesis of heteroaromatic ring-containing cyclophanes are less frequently reported compared to carbocyclic ring-containing cyclophanes.[12,13]

EXPERIMENTAL SECTION

1,5-Dibenzoyl-2,4-dihydroxybenzene (**2**) and 1,5-dibenzoyl-2,4-dialkoxybenzenes (**3a-b**) were prepared by the procedure described in an earlier report,[11] and all the other reagents were purchased from Aldrich Chemical Co. and used as received. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, using tetramethylsilane as an internal standard in $CDCl_3$. NMR measurements and elemental analyses were performed at the Central Research Facilities of Chungnam National University. Mass spectra were taken at Korea Basic Science Institute.

Preparation of the precursor macrocycles (4a-b).

A solution of 1,5-dibenzoyl-2,4-dialkoxybenzenes (**3a-b**) (2.85 mmol) in acetone (100 mL) was added very slowly to the suspension of 1,5-dibenzoyl-2,4-dihydroxybenzene (**2**) (1.00 g, 3.14 mmol) and K_2CO_3 (1.95 g, 14.1 mmol) in acetone (50 mL) at reflux and reflux was continued for 48-72 h. Then water was added to the concentrated reaction mixture and the mixture was extracted with dichloromethane. Purification by silica gel column chromatography (eluent: 20:1 dichloromethane-ethyl acetate) followed by solvent removal gave the desired macrocycles (**4a**) and (**4b**) as white solids in 33% and 35 % yields, respectively.

4a: mp 198-199 °C; ^{1}H NMR δ 1.24 (br s, 16H, 2 x $-O(CH_2)_2\mathit{(CH_2)_4}(CH_2)_2O-$), 1.54 (quintet, 8H, J =7 Hz, 2 x $-OCH_2\mathit{CH_2}(CH_2)_4\mathit{CH_2}CH_2O$), 3.96 (t, 8H, J =7 Hz, 2 x $-O\mathit{CH_2}(CH_2)_6\mathit{CH_2}O-$), 6.51 (s, 2H, 2 x Ar-H *ortho* to both $–O(CH_2)_8-$), 7.41 (t, 8H, J = 8 Hz, 4 x Ar-H *meta* to C=O in C_6H_5CO-), 7.53 (tt, 4H, J = 8, 1 Hz, 4 x Ar-H *para* to C=O in C_6H_5CO-), 7.62 (s, 2H, 2 x Ar-H *ortho* to both C_6H_5CO-), 7.75-7.78 (m, 8H, 4 x Ar-H *ortho* to C=O in C_6H_5CO-); ^{13}C NMR δ 25.00, 27.84, 28.35, 68.53, 97.13, 121.21, 128.08, 129.49, 132.52, 133.44, 138.60, 161.01, 194.95; MS (positive ion FAB) 857.3 (MH^+). Anal. Calcd for $C_{56}H_{56}O_8$: C, 78.48; H, 6.59. Found: C, 78.40; H, 6.37.

4b: mp 183-185 °C; ^{1}H NMR δ 1.10-1.23 (m, 32H, 2 x -$O(CH_2)_2$*$(CH_2)_8$*$(CH_2)_2O$-), 1.50 (quintet, 8H, J =7 Hz, 2 x -OCH_2*CH_2*$(CH_2)_8$*CH_2*CH_2O), 3.94 (t, 8H, J =7 Hz, 2 x -O*CH_2*$(CH_2)_{10}$*CH_2*O-), 6.48 (s, 2H, 2 x Ar-H *ortho* to both –$O(CH_2)_{12}$-), 7.41 (t, 8H, J = 8 Hz, 4 x Ar-H *meta* to C=O in C_6H_5CO-), 7.52 (t, 4H, J = 8 Hz, 4 x Ar-H *para* to C=O in C_6H_5CO-), 7.65 (s, 2H, 2 x Ar-H *ortho* to both C_6H_5CO-), 7.76 (d, 8H, J = 8 Hz, 4 x Ar-H *ortho* to C=O in C_6H_5CO-); ^{13}C NMR δ 25.18, 28.24; 28.53; 29.10; 29.19; 68.52; 96.71; 121.16; 128.05; 129.43; 132.42; 133.37; 138.82; 161.22; 195.11; MS (positive ion FAB) 969.4 (MH^+). Anal. Calcd for $C_{64}H_{72}O_8$: C, 79.31; H, 7.49. Found: C, 79.17; H, 7.51.

Photocyclization-dehydration reactions of 4a-b to 1a-b.

A suspension containing 0.5 mmol of the macrocycles (**4a-b**) in 500 mL of benzene was placed in a Pyrex glass vessel, purged with nitrogen for 1 h and then irradiated under nitrogen with 350 nm mercury lamps using RPR-100 photochemical reactor (Southern New England Ultraviolet Company). After 4-7 h of irradiation, the reaction mixture was concentrated and the residue was dissolved in 10 mL of acetone. The acetone solution was treated with a few drops of 1 M HCl and stirred for 2-3 h. To this, water was added and the mixture was extracted with dichloromethane. The concentrated organic layers were purified by silica gel column chromatography eluting with 1:1 hexane-dichloromethane. Solvent removal afforded the two benzodifuran ring-containing cyclophanes (**1a**) and (**1b**) as white solids in 20 % and 15 % yields, respectively.

1a: mp 309-310 °C (decomp); ^{1}H NMR δ 1.31-1.37 (m, 8H, 2 x -$(CH_2)_2$*$(CH_2)_2$*$(CH_2)_2$-), 1.73-1.81 (m, 8H, 2 x -CH_2*CH_2*$(CH_2)_2$*CH_2*CH_2-), 2.83 (t, 8H, J = 7 Hz, 2 x -*CH_2*$(CH_2)_4$*CH_2*-), 7.30-7.53 (m, 24H, Ar-H); ^{13}C NMR δ 26.23, 27.46; 27.93; 93.96; 107.69; 116.94; 125.37; 126.82; 128.70; 129.18; 133.21; 152.06; 155.11; MS (positive ion FAB) 785.3 (MH^+). Anal. Calcd for $C_{56}H_{48}O_4$: C, 85.68; H, 6.16. Found: C, 85.66; H, 6.29.

1b: mp 177-178 °C; ^{1}H NMR δ 1.10-1.32 (m, 24H, 2 x -$(CH_2)_2$*$(CH_2)_6$*$(CH_2)_2$-), 1.73 (quintet, 8H, J = 7Hz, 2 x -CH_2*CH_2*$(CH_2)_6$*CH_2*CH_2-), 2.81 (t, 8H, J = 7 Hz, 2 x -*CH_2*$(CH_2)_8$*CH_2*-), 7.30-7.57 (m, 24H, Ar-H);

^{13}C NMR δ 26.73, 28.10; 28.66; 29.10; 29.32; 93.97; 108.01; 117.12; 125.69; 127.08; 128.95; 129.42; 133.40; 152.28; 155.43; MS (positive ion FAB) 897.4 (MH$^+$). Anal. Calcd for $C_{64}H_{64}O_4$: C, 85.68; H, 7.19. Found: C, 85.77; H, 7.28.

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