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Research Article

Simple Syntheses of Two New Benzo-Fused Macrocycles Incorporating Chalcone Moiety

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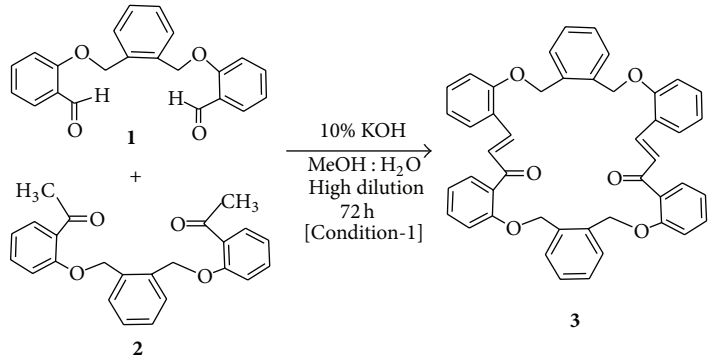
Simple syntheses of the benzo-fused 26-membered macrocyclic bischalcone (19*E*,43*E*)-2.11.27.36-tetroxaheptacyclo[44.4.0.0^{4,9}.0^{12,17}.0^{21,26}.0^{29,34}.0^{37,42}]pentaconta-1(46),4(9),5,7,12(17),13,15,19,21,23,25,29,31,33,37,39,41,43,47,49-icosaene-18,45-dione (**3**) and the benzo-fused 13-membered macrocyclic chalcone (19*E*)-2.11-dioxatetracyclo[19.4.0.0^{4,9}.0^{12,17}]pentacosa-1(25),4(9),5,7,12(17),13,15,19,21,23-decaen-18-one (**5**) using very common starting materials and reagents are described. The compounds are new and they have been characterized from their analytical and spectral data.

1. Introduction

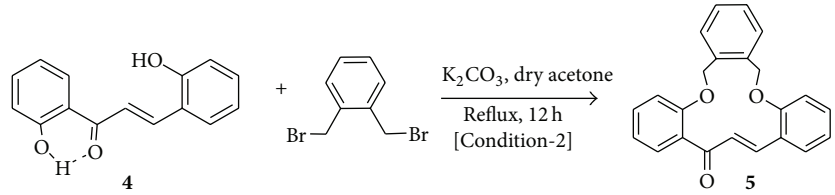
Chalcones (1,3-diphenyl-2-propen-1-ones) [1] are known to possess a range of important biological activities, such as antibacterial [2], antifungal [3], antileishmanial [4], antimalarial [4], antifilarial [5] anti-inflammatory [6–8], antiprotozoal (antileishmanial and antipanosomal) [9], antimicrobial [10–13], larvicidal [14], anticonvulsant [15], anti-HIV [16], antitumor [17], and anticancer [18] activities, and they could be readily transformed into varieties of other compounds, many of which are biologically active heterocycles [19, 20]. Owing to such biological activities of chalcones, the chemical literature shows the synthesis of a wide range of chalcones and their analogues [4, 8–13, 21–23]. Again, since macrocyclic compounds are well-known for their ability to show the important property of molecular recognition, macrocyclic systems containing the chalcone moiety are expected to generate compounds having interesting biological and material properties [24, 25]. Our research on such compounds has been initiated through the synthesis of a number of macrocyclic bis- and monochalcones reported recently [26]. In continuation of that study we have synthesized a benzo-fused 26-membered macrocyclic bischalcone, namely, (19*E*,43*E*)-2.11.27.36-tetroxaheptacyclo [44.4.0.0^{4,9}.0^{12,17}.0^{21,26}.0^{29,34}.0^{37,42}] pentaconta-1(46),4(9),5,7,12(17),13,15,19,21,23,25,29,31,33,37,39,41,43,47,49-icosaene-18,45-dione (**3**), and a benzo-fused 13-membered macrocyclic monochalcone, namely, (19*E*)-2.11-dioxatetracyclo[19.4.0.0^{4,9}.0^{12,17}] pentacosa-1(25),4(9),5,7,12(17),13,15,19,21,23-decaen-18-one (**5**), by use of readily available starting materials. Herein we report the synthesis of these two hitherto unknown compounds.

2. Results and Discussion

Alkylation products of salicylaldehyde and *o*-hydroxyacetophenone by the use of 1,2-(bis-bromobenzyl)benzene as alkylating agent were first prepared. The resulting dialdehyde (**1**) and diketone (**2**), both new compounds, were then subjected to Claisen-Schmidt reaction under high dilution condition when the macrocyclic bischalcone **3** was obtained in moderate yield (Scheme 1). In order to achieve the synthesis of **5**, 2,2′-dihydroxychalcone (**4**) was first constructed from *o*-hydroxyacetophenone and salicylaldehyde by Claisen-Schmidt reaction. The reaction between **4** and 1,2-(bis-bromobenzyl)benzene was then done by following the typical procedure for alkylation of phenols (K_2CO_3/acetone, reflux, 12 h) (Scheme 2). This reaction gave **5** in very good yield and no trace of any macrocyclic bischalcone **7** (a possible product through bimolecular cyclization of the intermediate **6**) (Scheme 3).



Scheme 1: Synthesis of the macrocyclic bischalcone **3**.



Scheme 2: Synthesis of the macrocyclic monochalcone **5**.

The new compounds **3** and **5** were characterized from their analytical and spectral data which are presented in the Experimental Section as well as in the Supplementary File in the Supplementary Material available online at http://dx.doi.org/10.1155/2014/485014.

3. Experimental

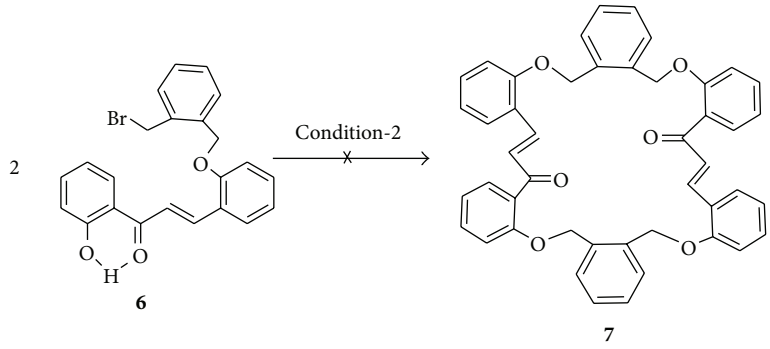
Melting points were taken in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX II) in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AV-300 (300 MHz) spectrometer. Analytical samples were routinely dried *in vacuo* at room temperature. Microanalytical data were recorded on a Perkin-Elmer 2400 Series II C, H, N analyzer. ESIMS(+) mass spectrum of **3** was measured with a Waters Micromass Q-Tof micro instrument. Column chromatography was performed with silica gel (100–200 mesh) and TLC with silica gel G made of SRL Pvt. Ltd. Petroleum ether used had the boiling range of 60–80°C.[1] H and ^{13}C NMR and mass spectra of different compounds can be found in the Supplementary Material.

3.1. 1,2-Bis(bromomethyl)benzene. This compound was prepared from *o*-xylene by benzylic bromination with NBS [NBS (2.2 equiv.), $(PhCOO)_2$ (trace), refluxed in CCl_4, 12 h, yield: 83%), m.p. 94°C (lit. [27] 92–96°C); ^{1}H NMR ($CDCl_3$): δ 4.66 (br. s, 4H, $-C\underline{H}_2$-Br), 7.29–7.31 (m, 2H, Ar-H), 7.33–7.38 (m, 2H, Ar-H).

*3.2. 1,2-Bis(2-formylphenoxymethyl)benzene (**1**).* A mixture of salicylaldehyde (2 mmol) and 1,2-bis(bromomethyl)benzene (1 mmol) was refluxed in methanolic KOH (5%, 25 mL) for 7 h. Removal of methanol by distillation and addition of water followed by extraction with ethyl acetate gave crude alkylation product **1**, which was purified by rapid column chromatography followed by crystallization from $CHCl_3$-petroleum ether (yield: 66%). The physical and spectral data of **1** were as follows: colourless needles, m.p. 118–120°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.31 (br. s, 4H, 2 × $-OCH_2-$), 7.05 (dt, 4H, J = 7.2 and 1.5 Hz), 7.42–7.45 (m, 2H, ArH), 7.50–7.57 (m, 4H), 7.82 (dd, 2H, J = 7.8 and 1.8 Hz), and 10.45 (br. s, 2H, 2 × $-C\underline{H}O$).

*3.3. 1,2-Bis(2-acetylphenoxymethyl)benzene (**2**).* A mixture of *o*-hydroxyacetophenone (2 mmol), 1,2-bis(bromomethyl) benzene (1 mmol) and anhydrous K_2CO_3 (3 g.) was refluxed in dry acetone for 12 h. Usual work-up followed by purification of the resulting crude material by column chromatography over silica gel afforded pure **2** (yield: 78%). The physical and spectral data of **2** were as follows: colourless needles ($CHCl_3$-petroleum ether), m.p. 74°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 6H, 2 × $-COCH_3$), 5.27 (br. s, 4H, $-OCH_2$), 7.03 (dt, 4H, J = 8.4 and 1.8 Hz), 7.40–7.46 (m, 4H), 7.54 (dt, 2H, J = 8.4 and 1.8 Hz), and 7.71 (dd, 2H, J = 7.8 and 1.8 Hz).

*3.4. (19E,43E)-2.11.27.36-Tetroxaheptacyclo[44.4.0.0^{4,9}.0^{12,17}.0^{21,26}.0^{29,34}.0^{37,42}]pentaconta-1(46),4(9),5,7,12(17),13,15,19,21,23,25,29,31,33,37, 39,41,43,47,49-icosaene-18,45-dione (**3**).* A mixture of the dialdehyde **1** (1 mmol) and the diketone **2** (1 mmol) was dissolved in a KOH solution (10%, 75 mL) in MeOH-H_2O (3 : 1) and the mixture was stirred at room temperature. A precipitate began to be formed after *ca.* 5 h of stirring. The stirring was continued for 72 h and then the solid was collected. The solid thus obtained was almost pure



Scheme 3: A possible way of formation of macrocyclic bischalcone from **6**.

and it was further purified by column chromatography over silica gel followed by crystallization from $CHCl_3$-petroleum ether (yield: 49%). The analytical and spectral data of the macrocyclic product **3** were as follows: light yellow cubes; m.p. 205–207°C; IR (KBr, cm^{-1}): 1598 (C=O), 1567, 1485, 1446, 1384 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.85 (s, 4H, –O–C$\underline{H}_2$–), 5.06 (s, 4H, –CH_2–O–), 6.77 (d, 4H, J = 7.2 Hz), 6.80 (t, 2H, J = 7.5 Hz), 6.97 (t, 4H, J = 7.8 Hz), 7.18–7.26 (m, 10H), 7.27 (d, 2H, J = 16.2 Hz, 2 × H-α), 7.38 (dt, 2H, J = 7.5 and 1.5 Hz), 7.47 (dd, 2H, J = 8.4 and 1.5 Hz), 7.70 (d, 2H, J = 16.2 Hz, 2 × H-β); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.23, 68.48, 112.47, 112.75, 121.04, 121.21, 123.98, 127.65, 128.10, 128.11, 128.48, 129.40, 129.60, 130.10, 130.21, 131.47, 132.23, 133.81, 134.42, 140.17, 156.42, 157.10, 194.64 (C=O); MS (TOF MS ES$^+$): m/z 707.18 $(M+Na)^+$, 685.19 $(M+H)^+$. Elemental analysis: Calcd. for $C_{46}H_{36}O_6$:C, 80.68; H, 5.30. Found: C, 80.56; H 5.42%.

*3.5. 2,2′-Dihydroxychalcone (**4**).* This chalcone was prepared by condensation of *o*-hydroxyacetophenone and salicylaldehyde with aqueous alkali, m.p. 162–164°C (lit. [28] 168°C).^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74 (br. s, 1H, 2-OH), 6.88 (br. d, 1H, J = 8.1 Hz), 6.94–7.07 (m, 3H), 7.32 (dt, 1H, J = 7.8 and 1.8 Hz), 7.52 (dt, 1H, J = 7.5 and 1.5 Hz), 7.63 (dd, 1H, J = 7.8 and 1.9 Hz), 7.87 (d, 1H, J = 15.6 Hz, H-α), 7.96 (dd, 1H, J = 8.1 and 1.5 Hz), 8.21 (d, 1H, J = 15.6 Hz, H-β), 12.92 (s, 1H, 2′-OH).

*3.6. (19E)-2.11-Dioxatetracyclo[19.4.0.0^{4,9}.0^{12,17}]pentacosa-1(25),4(9),5,7,12(17),13,15,19,21,23-decaen-18-one (**5**).* To a mixture of **4** (1 mmol) and 1,2-bis(bromomethyl)benzene (1 mmol) in dry acetone (25 mL), anhydrous K_2CO_3 (3 g) was added and the mixture was refluxed with stirring for 12 h. Usual work-up of the reaction mixture followed by chromatography of the crude product over silica gel using petroleum ether-ethyl acetate (90 : 10, v/v) gave pure **5** as light yellow crystals (yield: 57%), m.p. 160–162°C, IR (KBr) cm^{-1}: 3028, 2903, 1585, 1562, 1470, 1453, 1436, 1297, 1249, 1152, 1058, 960, 745. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.28 (s, 4H, 2 × $ArCH_2O$–), 7.01–7.10 (m, 2H), 7.11 (d, 1H, J = 16.5 Hz, H-α), 7.23–7.38 (m, 7H), 7.45–7.51 (m, 2H), 7.58 (dd, 1H, J = 7.5 and 1.8 Hz, proton *ortho* to C=O), 7.66 (d, 1H, J = 16.5 Hz, H-β), ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.65, 71.70, 113.51, 119.01, 121.67, 123.46, 128.43, 128.81, 129.19, 129.77, 129.79, 129.87, 130.68, 130.88, 131.89, 132.62, 135.18, 135.29, 141.56, 156.71, 156.97, 195.23. MS (TOF MS ES$^+$): m/z $(M+Na)^+$ 365.00. Elemental analysis: Calcd. for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.45; H, 5.44%.

4. Conclusion

Thus, we report very simple syntheses of two new benzo-fused macrocycles incorporating chalcone moiety by the use of very common starting materials. The compounds may find important applications.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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