December 2006 Volume 2 Issue 5-6

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 2(5-6), 2006 [92-96]

Synthesis Of Ethylene Glycol Bis(2-Formylphenoxy) Derivatives

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Received: 29th October, 2006
Accepted: 13th November, 2006

Web Publication Date : 28th December, 2006

ABSTRACT

A new types of ethylene glycol bis (2-formylphenoxy) derivatives have been developed in two simple steps from reaction of 2-hydroxy benzaldehyde **(2)** with tetraethylene glycol dibromide **(1)** gave the compounds **(3a-c)** in good yield.

KEYWORDS

Ethylene glycol bis(2-formylphenoxy); Salicylaldehyde; Ethylene glycol dibromide derivatives.

INTRODUCTION

Stilbene-based compounds have over the years attracted the attention of many researchers due to their wide ranging biological activities. One of the most relevant and extensively studied stilbenes is resveratrol (trans-3,4-,5-trihydroxystilbene, (Figure 1), a phytoalexin present in grapes and other foods, which is capable of acting as a cancer chemopreventive agent[1,2]. Indeed, several *in vitro* and *in vivo* studies have shown that resveratrol inhibits cellular events associated with cancer initiation, promotion, and progression[3]. Moreover, resveratrol has powerful growth inhibitory effects on resveratrol has powerful growth inhibitory effects on various cancer cell lines, including:leukemia, colonic cancer, breast and prostate cancer cells[4-6]. Recently, resveratrol has also been shown to induce apoptosis in different cancer cell lines[7-9], although the mechanism by which this occurs remains a controversial issue[10,11]. Resveratrol is bioavailable following oral administration and it remains intact in a wide range of target organs[12,13].

Others application of this compounds are used for synthesis of new class crownethers. Crown ethers for example aza-crown ethers show good coordination properties with transition metal and heavy metal ions[14,15] and their complexes have been shown to be of great importance in host-guest chemistry, for example in membrane transportation ionopheres[16,17]. Many macrocyclic azacrown ethers and their corre-

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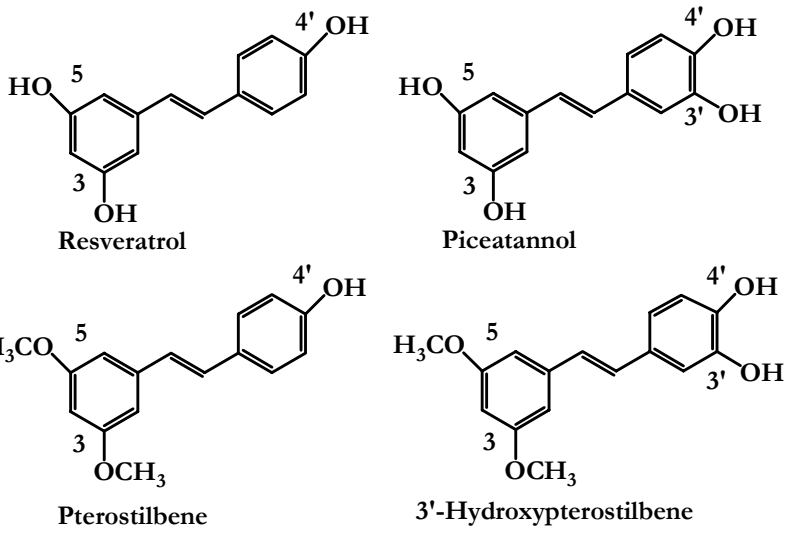

Figure 1: Chemical structure of trans-resveratrol, piceatannol, pterostilbene and 3- hydroxypterostilbene

sponding amides find wide application in chemistry, biology, microanalysis, metal separation, and molecular recognition[18-20].

Herein this compounds as primary materials are used for synthesis of stilbene crown ether calixarenes. Shinkai and his colleagues synthesized an azobenzene containing crown ether to be used as a switchable alkali ion receptor[21]. The azobenzene moiety isomerized from the trans- to the cis-isomer upon irradiation, while the more sterically hindered cis-isomer converted back to the trans-isomer in the dark. The cis-isomer suitably bound K^+, Rb^+, and Cs^+ but the trans-isomer preferred to bind Li^+ and Na^+. An azobenzene-containing cryptand was also later synthesized by this group[22]. The switching of this cryptand from the trans- to the cis-isomer resulted in ring expansion that altered its binding. The p-tert-butylcalix[4]arene derivatives containing multiple benzaldehyde groups have been demonstrated preference from Na^+ to K^+. Owing to its pre-organized structure, calix[4]arene is currently a popular molecular platform for designing highly selective receptors[23]. Several isomerizable azobenzene crown ether calix[4]arenes have been prepared and studied[24-26].

Although the cis- and trans-isomers of these azobenzene derivatives display different selectivity in binding alkali metal ions, their thermal isomerization has prevented them from being good candidates for controllable molecular photo-switches.

RESULTS AND DISCUSSION

Unlike azobenzenes, the stilbene analogues have been found not to undergo thermal isomerization[27] and thus are more promising as switching units for molecular photoswitches. The p-tert-butylcalix[4] arene derivatives containing multiple benzaldehyde groups have been demonstrated to be useful for syntheses of several selective host molecules(Figure 2)[28,29].

The reaction of salicylaldehyde **(2)** with dibromides **(1)** in DMF using potassium carbonate as the base resulted in formation of dialdehydes **(3a-c)** in 80-85% yields.

During the course of our investigation to develop the new macromolecule ligands now we have reported the synthesis ethylene glycol-1,2-Bis(2-formylphenoxy) derivatives **(3a-c)**, from reaction of salicylaldehyde **(2)** with dibromides **(1)** in DMF using potassium carbonate as the base resulted in formation of dialdehyde ligands **(3a-c)** in 80-85% yields. The structures of **(3a-c)** were consistent with data derived from IR, ^{1}H NMR, ^{13}C NMR, MS and with elemental analyses (see SCHEME 1).

The reaction of salicylaldehyde**(2)** with dibromides**(1)** in DMF using potassium carbonate as the base resulted in formation of dialdehydes **(3a-c)** in 80-85% yields.

The structures of compounds **(3a-c)** were deduced from IR, ^{1}H NMR and ^{13}C NMR spectra and

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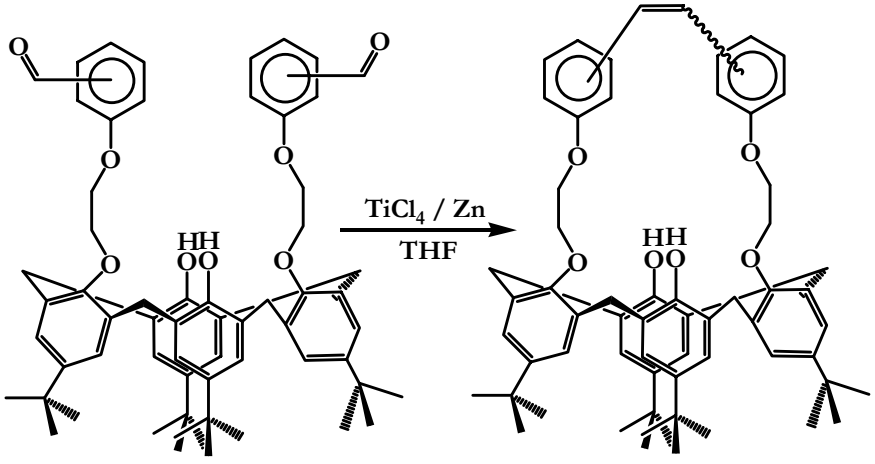
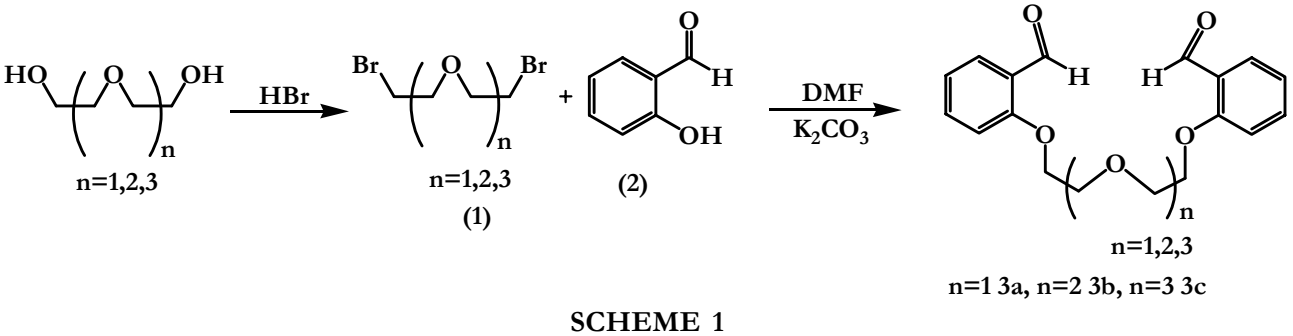


Figure 2: Synthesis of stilbene crown ether calixarenes



SCHEME 1

mass spectra. For example in ^{1}H NMR spectrum of **(3c)** the signal due to the aldehyde group was observed at δ 10.5ppm as a singlet for aldehyde group and four groups of CH_2 of methylene moiety were showed in δ 3.65(q, 4H), 3.74(q, 4H), 3.91(t, 4H, J= 4.5Hz) and 4.25(t, 4H, J= 5Hz). The aromatic protons were appeared as a multiplet at d 6.8-7.8 ppm. The ^{13}C NMR spectrum of compound **(3c)** showed eleven distinct resonances in agreement with the 1,11-Bis (2-formylphenoxy)-3,6,8-trioxaundecane. The carbonyl groups of aldehyde showed same as one single signal in δ 189.9 ppm for two aldehyde groups. For more information the MS spectrum and elemental analysis(CHN) of this compound have confirmed it.

In conclusion we have prepared a new ethylene glycol bis (2-formylphenoxy) derivatives **(3a-c)** from reaction of salicylaldehyde **(2)** and dibromide **(1)** in good yield with a simple synthesis method. Moreover, synthetic versatility, no side reaction, ease of workup, and short reaction time can be considered as the advantage of this method.

EXPERIMENTAL

All materials and solvents used for synthesis were of analytical reagent grade. Silica gel 60 (Merck) was used for column chromatography. Preparative TLC aluminum plates covered with Silica gel 60 (Merck) were used. Also, the ^{1}H and ^{13}CNMR spectra, all in $CDCl_3$, were taken on BRUKER DRX-400 AVANCE instrument at 400.133, 100.625 MHz respectively. IR spectra of all compounds were measured on a Shimadzu IR-460 spectrometer. In addition, the mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 40eV. Elemental analyses for C, H and N were performed using a Thermofinigan Flash EA1112 analyzer. Tetraethyleneglycol, salicylaldehyde and anhydrous potassium carbonate were purchased from Fluka, (Buchs, Switzerland) and used without further purifications.

Syntheses of a series bis(2-formylphenoxy) oxadecane (3a-c)

General procedure

The synthesis of compounds **(1a-c)** were as in the literature[30]. A mixture of salicylaldehyde **(2)** (10mmol), dibromide **(1)** (5mmol) and K_2CO_3 (5g) was heated in DMF (40ml) at reflux for 3h. The mixture was poured into water and the product was extracted with $CHCl_3$. The organic layer was dried with anhydrous Na_2SO_4, distillation removed chloroform and left the crude product as a viscous oil, which was purified through silica gel 60 (230-400mesh) in glass columns (1.5-2 cm diameter). The crude product was purified by gradient column chromatography using CH_2Cl_2/methanol solvent system.

1,5-Bis(2-formylphenoxy)-3-oxadecane(3a)

It was obtained from **(2)** and **(1)** following the above procedure as yellow organic oil in 80% yield. IR (film) (υ_{max} cm^{-1}): 3300, 3070, 2960, 2940, 1604, 1520, 1349, 1280, 1130, 936, 849, 746 (cm^{-1}). ^{1}HNMR ($CDCl_3$, 400 MHz): δ 4.01(t, 4H, J =4.46 Hz); 4.3(t, 4H, J =4.32 Hz); 6.82-6.97(m), 7.5(t, 2H, Ph); 7.82 (d, 2H, Ph); 10.5 (s, 2H, CH=O).; ^{13}CNMR ($CDCl_3$, 400 MHz): δ 68.2, (s, $2CH_2$), 69.0(s, $2CH_2$), 112.8, 121.o3, 121.5, 122.7, 125.1, 128.5, 136.1, 161.1, 189.7(C=O). MS(m/z): 314(M^+), 267, 122. Anal.Calcd. for $C_{18}H_{18}O5$:C 68.78, H 5.73, Found: C 68.50, H 5.42.

1,8-Bis(2-formylphenoxy)-3,6-dioxadecane(3b)

Yellow organic oil in 85% yield. IR(film) (υ_{max} cm^{-1}): 3335, 3060, 2940, 2940, 1604, 1520, 1349, 1280, 1130, 936, 849, 746(cm^{-1}). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77(s, 4H, 2 CH_2); 3.93(t, 4H, J =4.6Hz), 4.26(t, 4H, J =3.7Hz, 2 CH_2), 6.8-7.1(m, 4H oh Ph), 7.5(t, 2H, J=0.2, Ph); 7.82 (d, 2H, J= 6.8, Ph); 10.5(s, 2H, CH=O).; ^{13}C NMR ($CDCl_3$, 400 MHz): δ 68.2, (s, $2CH_2$), 69.0(s, $2CH_2$), 69.6(s, $2CH_2$), 112.8, 121.03, 125.2, 128.3, 135.9, 161.1, 189.9(C=O). MS(m/z): 358(M^+), 267, 122, 77. Anal.Calcd. for $C_{20}H_{22}O6$: C 67.04, H 6.14, Found: C 67.40, H 5.86.

1,11-Bis (2-formylphenoxy)-3,6,8-trioxaundecane (3c)

Yellow organic oil in 82% yield. IR (film) (υ_{max} cm^{-1}): 3320, 3080(CH=O), 2950, 2944, 1604, 1520, 1349, 1280, 1130, 936, 849, 746(cm^{-1}). ^{1}HNMR ($CDCl_3$, 400MHz): δ 3.68(q, 4H, $2CH_2$); 3.74(q, 4H), 3.91(t, 4H, J =4.5Hz, 2 CH_2), 4.25(t, 4H, J=5 Hz, 2 CH_2), 6.80-7.02(m, 4H of Ph), 7.53(t, 2H, J =7.3Hz, Ph); 7.83(dd, 2H, J_1=6.8, J_2=1.65Hz, 2H, Ph); 10.5(s, 2H, CH=O).; ^{13}CNMR($CDCl_3$, 400MHz): δ 67.8, (s, $2CH_2$), 68.0(s, $2CH_2$), 69.2, (s, $2CH_2$), 69.6 (s, $2CH_2$), 112.8, 121.03, 125.4, 128.3, 135.9, 161.1, 189.9 (C=O). MS(m/z): 402(M^+), 267, 122, 77. Anal.Calcd. for $C_{22}H_{26}O7$:C 65.67, H 6.47, Found: C 65.01, H 5.84.

ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Young Research Club of Islamic Azad University from Zahedan.

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