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Calix[4]quinone. Part 1: Synthesis of 5-hydroxycalix[4]arene by calix[4]quinone monoketal route

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Abstract—The oxidation of calix[4]arene tribenzoate **1** with chlorine dioxide yielded the corresponding calix[4]monoquinone tribenzoate **2**. Reaction of monoquinone **2** with ethylene glycol under acidic conditions produced the protected monoketal derivative **3**. The basic hydrolysis of the benzoate, followed by an acidic cleavage of ketal moieties and a metal hydride reduction of the quinones or vice versa, converted **3** to the title compound, 5-hydroxycalix[4]arene (**7**). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Chlorine dioxide, which is a yellowish gas at room temperature (boiling point 11°C), is widely used as an aqueous solution in water treatment and pulping industries. One of the main reasons for this is, because of its bleaching ability which leads to extensive destruction of certain harmful chemical compounds, especially phenols. In 1955, Logan et al.[1] reported that chlorine dioxide had an oxidative ability to convert phenols and hydroquinones to the corresponding 1,4-benzoquinones. Thirty years later, L. Rosik[2] treated calix[4]arene with chlorine dioxide in a phosphate-buffered solution, and the corresponding oxidative product, calix[4]-quinone, was collected in good yield. This result not only provided a new synthetic route for calixarene chemistry, but also introduced a new member into the calixarene family. The oxidative ability of chlorine dioxide towards calixarenes was then carefully re-examined by Gutsche and coworkers,[3] and subsequently, using an alternative oxidizing reagent (thallium trifluoroaceate) a variety of calix[4]arene derivatives were prepared by using calix[4]-quinones as synthetic intermediates.[4,5] In this paper, we report that by taking advantage of introducing an oxygen atom at the *para*-position of calixarenes in the chlorine dioxide oxidation reaction, the synthesis of *p*-monohydroxycalix[4]arene was achieved in a six-step synthetic route.

2. Results and discussion

It is well known that the cleavage of a phenolic ether linkage is difficult. Therefore, the calix[4]arene benzoates were selected for the synthesis of a *p*-hydroxy substituted calix[4]arenes in order to avoid ether linkage cleavage. When calix[4]arene tribenzoate **1**[6] was oxidized with chlorine dioxide in phosphate-buffered solution at room temperature, using a standard procedure described by L. Rosik,[2] the corresponding calix[4]monoquinone tribenzoate **2** was yielded as an orange-colored solid. The removal of benzoate moieties and the subsequent reduction of quinones (or vice versa) was an obvious and direct approach for the conversion of monoquinone **2** to the corresponding *p*-monohydroxycalix[4]arene. Unfortunately, both reaction routes failed to produce the corresponding products in the first step. For instance, the attempt to remove the benzoate moieties from monoquinone **2** in basic conditions resulted in a non-isolatable black tar, whereas, the original monoquinone **2** was recovered in acidic hydrolysis conditions. The attempt to reduce the quinone moieties of monoquinone **2** with metal hydrides yielded a colorless reaction mixture which redeveloped a yellowish color upon contact with atmosphere, and a non-isolable black tar also resulted from the further work-up procedure (Fig. 1).

Gutsche et al. reported in the literature that a nucleophile can be added to calixquinone in 1,2- or 1,4- fashion to produce *para*- or *meta*-substituted calixarene derivatives.[4] Thus, it was suspected that the hydroxide ion might behave not only in its usual role but also as a nucleophile in the basic hydrolysis of monoquinone **2**, so that an undesired black tar resulted. This assumption implied that the carbonyl moieties had to be masked with a ketal functionality to prevent any possibility of 1,2- or 1,4-addition. When monoquinone **2** was refluxed with ethylene glycol in the presence of *p*-TsOH in benzene,[7] instead of the expected fully protected quinone, the corresponding half-protected ketal derivative **3** was produced. This half-protected ketal derivative **3** was the only product even when the reaction conditions were altered, for example, a large excess of ethylene glycol and/or prolonged heating. The failure of

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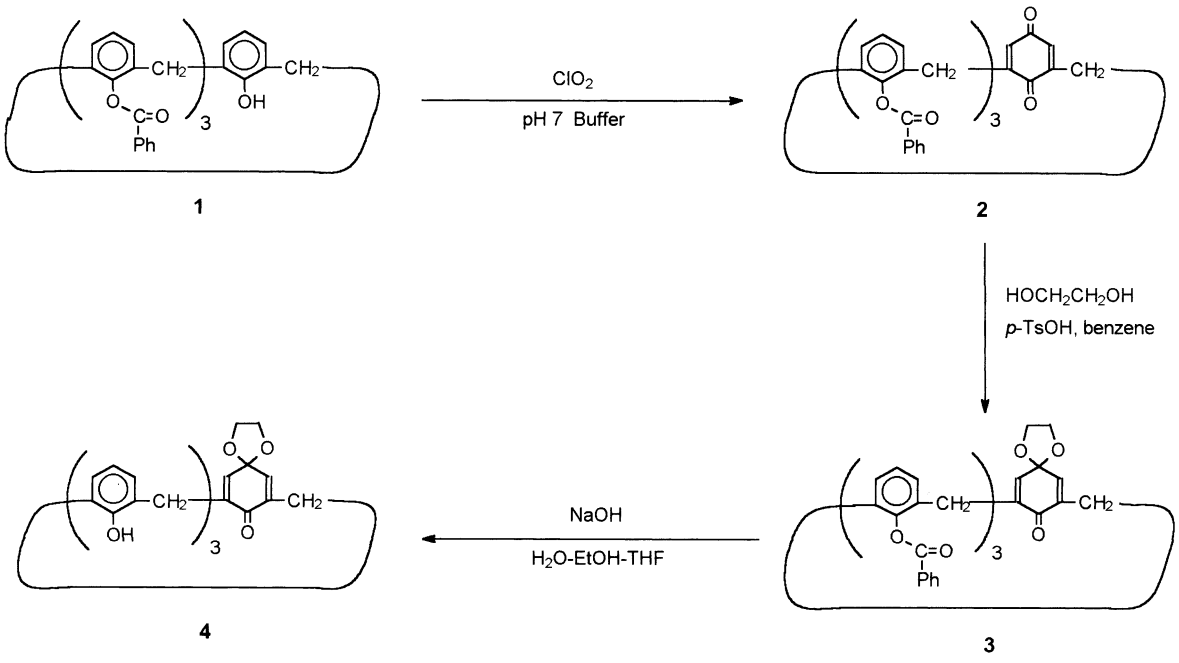

Figure 1.

generating the fully protected quinone was believed to be caused by steric hindrance, and therefore, the position of the masked carbonyl was assigned to be at the less hindered side, i.e the 'upper rim'. This observation is in agreement with the results previously reported by Gutsche et al.[3] This result also suggested that the two carbonyl groups were able to be distinguished in this ketal forming reaction, and consequently, a further conversion of the 'lower rim' free carbonyl group might provide a new synthetic route for the new class of calix[4]arenes.

After the 'upper rim' carbonyl groups were protected, the monoketal **3** was subjected to basic hydrolysis and metal hydride reduction as proposed for its parent compound **2**. Unlike its parent compound **2**, the benzoate moieties of monoketal **3** were easily removed in basic conditions[8] and calix[4]monoquinone monoketal **4** was produced as a light yellow solid. However, if the reaction mixture of this basic hydrolysis reaction was not handled properly, a brick-red solid **5** was observed during the acidification step. The ^{1}H NMR spectral analysis indicated that the amount of monoketal **4** decreased as the amount of neutralized acid used and/or the stirring period in acidic conditions were increased. For example, all trace of the expected hydrolysis

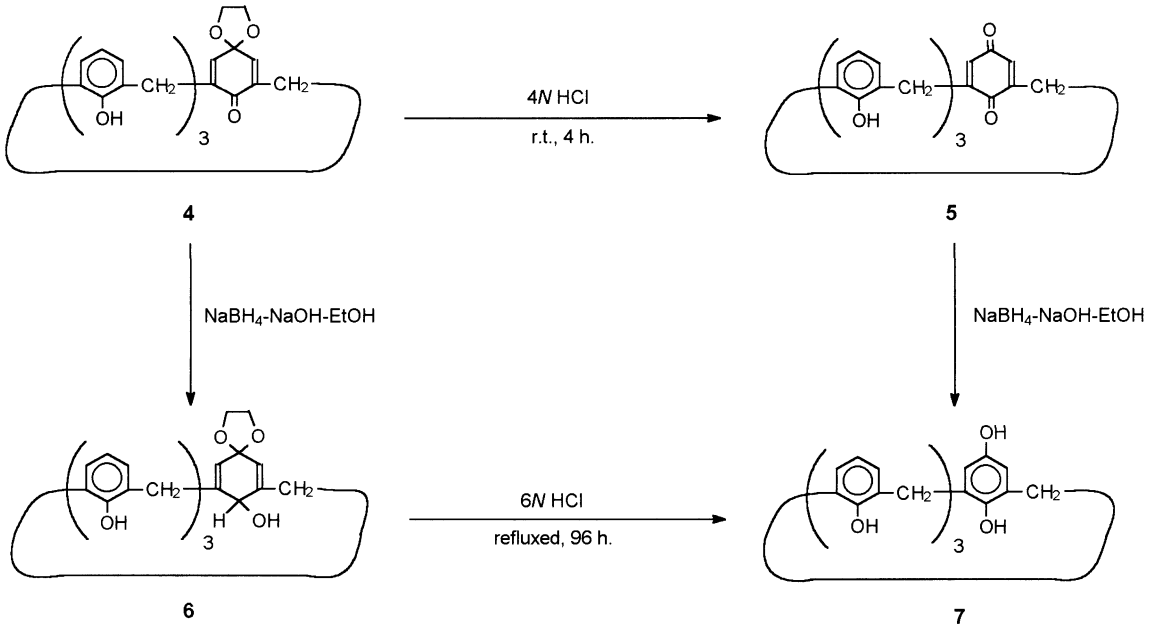

Figure 2.

product **4** disappeared and a brick-red solid **5** became the only product, if a large excess of 4N HCl was added to acidify the reaction mixture and then the resulting mixture was stirred at room temperature for an additional 4 h. This brick red solid **5** was also produced as the only product when a pure form of monoketal **4** was stirred in 4N HCl for 4 h at room temperature. All the spectral data indicated, as expected, that the compound **5** was calix[4]monoquinone, a product in which the ketal moieties had been totally removed from the monoketal **4** (Fig. 2).

In the metal hydride reduction of monoketal **3**, it was noticed that the free carbonyl group on the 'lower rim' was not affected by the metal hydrides ($NaBH_4$ or $LiAlH_4$) and the starting monoketal **3** was recovered quantitatively. These results indicated that the steric hindrance arose from the benzoate groups of monoketal **3** which prevented the occurrence of the metal hydride reduction. In order to verify the effect of steric hindrance, compound **4** which possessed no benzoate groups was subjected to the same reduction conditions. The studies indicated that the free ketone moieties of monoketal **4** were easily reduced by metal hydride and yielded compound **6** as a colorless solid. The formation of compound **6** suggested that the metal hydrides were able to attack the free carbonyl groups in the absence of the steric hindrance from three benzoate groups. Therefore, it is believed that other nucleophile should also have an easy access toward the free ketone moieties in monoketal **4**, and a variety of calix[4]arene's derivatives should be feasible from this new synthetic route. Further studies related to applying monoketal **4** as a synthetic intermediate for calixarene chemistry are under investigation in our laboratory.

Unlike the weak ketal linkage in compound **4**, the ketal moieties in compound **6** were unusually stable and reaction conditions of refluxing in 6N of HCl for 96 h were required to cleave all the ketal moieties from compound **6** to yield the title compound **7**, *p*-monohydroxycalix[4]arene. Compound **7** was moderately stable and was purified by recrystallization. As with the oxidizing character of hydroquinones, however, it gradually re-oxidized into a yellowish gray solid upon exposure to atmosphere and agreeable elemental analysis data were not possible.

Alternatively, the title compound **7** could be achieved from calix[4]monoquinone **5** by converting the quinone moieties into *p*-hydroquinone moieties with the metal hydride reduction. It was noticed that the removal of the ketal and then metal hydride reduction of the quinone was a better conversion pathway for calix[4]monoquinone monoketal **4** to the final product **7**. Further studies of this synthetic pathway for the other partial *p*-hydroxycalix[4]arenes, *p*-dihydroxycalix[4]arene and *p*-trihydroxycalix[4]arene, are still being studied in our laboratory.

3. Experimental

3.1. General

All reagents were obtained from Commercial Chemical Companies and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) and were uncorrected. ^{1}H NMR spectra were recorded on Burker DMX-300 WB and/or Burker DMX-500 SB spectrometer and chemical shifts were reported as δ values in ppm relative to TMS (δ=0.00) as an internal standard. IR were recorded on Perkin–Elmer Paragon 1000 FT-IR spectrometer, FAB-MS spectra were taken on a JOEL JMS-HX 102 spectrometer, and elemental analyses were taken on a Perkin–Elmer 240C analyzer. TLC analyses were carried out on Merck aluminum back silica gel 60 F_{254} plates (absorbant thickness 0.2 mm).

3.1.1. 25,26,27-Tribenzoyloxy-28-hydroxycalix[4]arene (1). A solution of 2.12 g (5.00 mmol) of calix[4]arene in 25 mL pyridine was cooled in an ice bath, and 5.0 mL (6.05g, 43.0 mmol) of benzoyl chloride was added. The mixture was stirred for 3 h, and was poured into 300 mL of water to induce a white solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to give 3.10 g (84%) of colorless, thin plate-like crystals: mp 268–270°C (lit.[6] mp 268–270°C). The spectral properties of this product was identical to the literature reported.[6]

3.1.2. 25,26,27-Tribenzoyloxy-28-calix[4]monoquinone (2). A slurry of 4.00 g (5.42 mmol) of **1** was dissolved in 100 mL of acetone, and 44 mL of concentrated buffer solution[9] was added. A portion of 76 mL of yellowish ClO_2 aqueous solution[10] was then added, and the reaction mixture was stirred at room temperature for 48 h. Organic solvent was removed by rotorvapor, and pale yellow solid were collected. The solid material was recrystallized from $CHCl_3$ and CH_3OH to give 2.81 g (69%) of light yellow crystals: mp 329–331°C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J=7.4 Hz, 4H, *o*-Ar′*H*), 7.76 (t, J=7.5 Hz, 2H, *p*-Ar′*H*), 7.66 (t, J=7.2 Hz, 1H, *p*-Ar′*H*), 7.56 (t, J=7.6 Hz, 4H, *m*-Ar′*H*), 7.52 (d, J=7.4 Hz, 2H, *o*-Ar′*H*), 7.46 (t, J=7.8 Hz, 2H, *m*-Ar′*H*), 7.11 (d, J=7.6 Hz, 2H, *m*-Ar*H*), 6.85 (d, J=7.5 Hz, 2H, *m*-Ar*H*), 6.71–6.74 (m, 3H, *p*-Ar*H*), 6.63 (d, J=7.4 Hz, 2H, *m*-Ar*H*), 6.28 (s, 2H, quinone-*H*), 3.70 (d, J=15.3 Hz, 2H, ArCH_2Ar), 3.61 (d, J=15.3 Hz, 2H, ArCH_2Ar), 3.51 (d, J=14.0 Hz, 2H, ArCH_2Ar), 3.70 (d, J=14.0 Hz, 2H, ArCH_2Ar); IR (KBr) cm^{-1} 1732 (s, C=O), 1656 (s, C=O); FAB-MS *m/z*: 751 (M^++1). Anal.[11] Calcd for $C_{49}H_{34}O_8$: C, 78.40; H, 4.53. Calcd for $C_{49}H_{34}O_8 \cdot H_2O$: C, 76.56; H, 4.69. Found: C, 76.78; H, 4.67.

3.1.3. 25,26,27-Tribenzoyloxy-28-calix[4]monoquinone-17-ethylene ketal (3). A slurry of 1.14 g (1.50 mmol) of **2**, 2.8 mL (3.10 g, 50.0 mmol) of ethylene glycol, and 0.11 g of *p*-TsOH in 70 mL of benzene was equipped with a Dean–Stark water trap and refluxed for 48 h. The solvent was removed, and the residue was treated with water to leave a pale yellow solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to afford 1.05 g (88%) of pale yellow crystals: mp 308–309°C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J=7.2 Hz, 4H, *o*-Ar′*H*), 7.74 (t, J=7.5 Hz, 2H, *p*-Ar′*H*), 7.66 (t, J=7.2 Hz, 1H, *p*-Ar′*H*), 7.55–7.58 (m, 6H, *m*-Ar′*H* and *o*-Ar′*H*), 7.46 (t, J=7.6 Hz, 2H, *m*-Ar′*H*), 7.14 (d, J=7.4 Hz, 2H, *m*-Ar*H*), 6.79 (d, J=7.5 Hz, 2H, *m*-Ar*H*), 6.69–6.73 (m, 3H,

p-Ar*H*), 6.58 (d, *J*=7.3 Hz, 2H, *m*-Ar*H*), 6.14 (s, 2H, quinone-*H*), 3.90–3.91 (m, 2H, ketal-*H*), 3.74–3.76 (m, 2H, ketal-*H*), 3.63 (d, *J*=15.1 Hz, 2H, ArCH_2Ar), 3.57 (d, *J*=15.1 Hz, 2H, ArCH_2Ar), 3.30 (bs, 4H, ArCH_2Ar); IR (KBr) cm^{-1} 1738 (s, C=O), 1651 (s, C=O); FAB-MS *m/z*: 795 (M^++1). Anal. Calcd for $C_{51}H_{38}O_9$: C, 77.08; H, 4.79. Found: C, 77.36; H, 5.13.

3.1.4. 25,26,27-Trihydroxy-28-calix[4]monoquinone-17-ethylene ketal (4). A slurry of 1.60 g (2.00 mmol) of **3** was dissolved in 70 mL of THF, and a portion of 50 mL of ethanolic alkali solution (7.00 g of NaOH dissolved in 15 mL of water and 35 mL of ethanol) was added, and the reaction mixture was refluxed for 20 h. The reaction mixture was neutralized with diluted acid, and solvent was then removed to leave an oily residue. A large amount of water was added to induced an off white solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to afford 0.65 g (67%) of pale yellow crystals: mp 258–260°C; ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1H, ArO*H*), 9.06 (s, 2H, ArO*H*), 7.05 (d, *J*=7.5 Hz, 2H, *m*-Ar*H*), 6.97 (d, *J*=7.5 Hz, 2H, *m*-Ar*H*), 6.83 (d, *J*=7.5 Hz, 2H, *m*-Ar*H*), 6.64–6.73 (m, 3H, *p*-Ar*H*), 6.58 (s, 2H, quinone-*H*), 4.08 (s, 4H, ketal-*H*), 3.86 (bs, 4H, ArCH_2Ar), 3.58 (bs, 4H, ArCH_2Ar); IR (KBr) cm^{-1} 3384 (broad s, OH), 1628 (s, C=O); FAB-MS *m/z*: 483 (M^++1). Anal. Calcd for $C_{30}H_{26}O_6$: C, 74.69; H, 5.39. Found: C, 74.77; H, 5.39.

3.1.5. 25,26,27-Trihydroxy-28-calix[4]monoquinone (5). A portion of 40 mL of 4N HCl was added to a solution of 0.96 g (1.00 mmol) of **4** in 80 mL of THF, and the reaction mixture was stirred at room temperature for 4 h. The organic solvent was removed, and the residue was treated with water to leave a dark red solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to afford 0.75 g (86%) of dark red crystals: mp 256–258°C; ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H, ArO*H*), 8.80 (s, 2H, ArO*H*), 7.03–7.06 (m, 4H, *m*-Ar*H*), 6.87–6.88 (m, 2H, *m*-Ar*H*), 6.70–6.73 (m, 3H, *p*-Ar*H*), 6.68 (s, 2H, quinone-*H*), 3.87 (bs, 4H, ArCH_2Ar), 3.75 (bs, 4H, ArCH_2Ar); IR (KBr) cm^{-1} 3279 (broad s, OH) 1645 (s, C=O); FAB-MS *m/z*: 439 (M^++1). Anal. Calcd for $C_{28}H_{22}O_5$: C, 76.70; H, 5.06. Calcd for $C_{28}H_{22}O_5 \cdot CH_3OH$: C, 74.04; H, 5.53. Found: C, 74.50; H, 5.32.

3.1.6. 28-Hydro-25,26,27,28-tetrahydroxycalix[4]monoquinone-17-ethylene ketal (6). A solution of 0.24 g (0.50 mmol) of **4** in 40 mL of ethanol was cooled in an ice bath, and 0.40 g (10.5 mmol) of $NaBH_4$ and two drops of 10N ehtanolic alkali solution was added. The reaction mixture was stirred in ice bath temperature for 20 h, acetone was added to removed the excess reducing agent, and conc. H_2SO_4 was added to neutralize the reaction mixture. The solvent was removed, and the residue was recrystallized from $CHCl_3$ and *n*-hexane to afford 0.14 g (58%) of colorless crystals: mp 274–276°C; ^{1}H NMR ($CDCl_3$) δ 10.10 (s, 4H, ArO*H* and CHO*H*), 7.01–7.06 (m, 6H, *m*-Ar*H*), 6.68–6.74 (m, 3H, *p*-Ar*H*), 6.60 (s, 2H, quinone-*H*), 4.25 (bs, 4H, ArCH_2Ar), 3.81–3.93 (m, 5H, ketal-*H* and C*H*OH), 3.55 (bs, 4H, ArCH_2Ar); IR (KBr) cm^{-1} 3162 (v. broad s, OH); FAB-MS *m/z*: 484 (M^+). Anal. Calcd for $C_{30}H_{28}O_6$: C, 74.38; H, 5.79. Calcd for $C_{30}H_{28}O_6 \cdot H_2O$: C, 71.71; H, 5.98. Found: C, 71.35; H, 5.61.

3.1.7. 5,25,26,27,28-Pentahydroxycalix[4]arene (7). *Method A: Metal hydride reduction of 25,26,27-trihydroxy-28-calix[4]monoquinone* (**5**). A solution of 0.44 g (1.00 mmol) of **5** in 40 mL of ethanol was cooled in an ice bath, and 0.40 g (10.5 mmol) of $NaBH_4$ and two drops of 10N ethanolic alkali solution was added. The reaction mixture was stirred in ice bath temperature for 20 h, acetone was added to removed the excess reducing agent, and conc. H_2SO_4 was added to neutralize the reaction mixture. The solvent was removed, and the residue was recrystallized from $CHCl_3$ and *n*-hexane to afford 0.23 g (58%) of colorless crystals: mp 310–312°C; ^{1}H NMR ($CDCl_3$) δ 10.09 (bs, 5H, ArO*H*), 7.00–7.06 (m, 6H, *m*-Ar*H*), 6.70–6.73 (m, 3H, *p*-Ar*H*), 6.50 (s, 2H, quinone-*H*), 4.20 (bs, 4H, ArCH_2Ar), 3.52 (bs, 2H, ArCH_2Ar), 3.46 (bs, 2H, ArCH_2Ar); IR (KBr) cm^{-1} 3198 (broad s, OH); FAB-MS *m/z*: 440 (M^+). Anal. Calcd for $C_{28}H_{24}O_5$: C, 76.36; H, 5.45. Calcd for $C_{28}H_{24}O_5 \cdot H_2O$: C, 73.36; H, 5.68. Found: C, 73.65; H, 5.65.

Method B: Acidic hydrolysis of 28-hydro-25,26,27,28-tetrahydroxycalix[4]monoquinone-17-ethylene ketal (**6**). A portion of 20 mL of 6N HCl was added to a solution of 0.48 g (1.00 mmol) of **6** in 40 mL of THF, and the reaction mixture was refluxed for 96 h. The organic solvent was removed, and the residue was treated with water to leave an off white solid. The solid material was collected and recrystallized from $CHCl_3$ and *n*-hexane to afford 0.18 g (41%) of colorless solid which is identical with the product produced by method A.

Acknowledgements

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9. Concentrated aqueous buffer solution was obtained by dissolving 4.36 g of $Na_2HPO_4 \cdot 2H_2O$ and 2.42 g of $NaH_2PO_4 \cdot 2H_2O$ in 100 mL of deionized water. A pH 7 buffer

solution was afforded when this concentrated solution was diluted five times in volume.

10. Aqueous chlorine dioxide solution was prepared by mixing equal volume of sodium chlorite dihydrate solution ($NaClO_2$, 31.60 g, 0.25 mol in 500 mL of deionized water) and sodium persulfate solution ($Na_2S_2O_8$, 29.70 g, 0.25 mol in 500 mL of deionized water). The solution was then stored in a brown bottle at 0°C prior being used.
11. All the new compounds, which were submitted to Elemental Analysis (EA), were dried at 120°C under vacuum for 48 h prior to the analysis. If the analysis value was different from the calculated value, the sample was dried at 140°C under vacuum for 48 h prior to another analysis.