Rearrangement of 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-ones to phenolic derivatives

Faiz Ahmed Khan,* Jyotirmayee Dash, Dheeraj Jain and B. Prabhudas

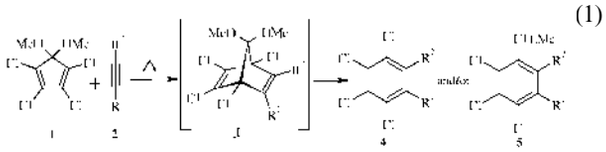
Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India.
E-mail: faiz@iitk.ac.in

Received (in Cambridge, UK) 7th September 2001, Accepted 17th October 2001
First published as an Advance Article on the web 15th November 2001

A simple Diels–Alder route leading to methyl 2,3,4-trihalo-5-hydroxybenzoates *via* thermal Grob-type rearrangement of easily accessible 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one with concomitant methyl halide elimination is described.

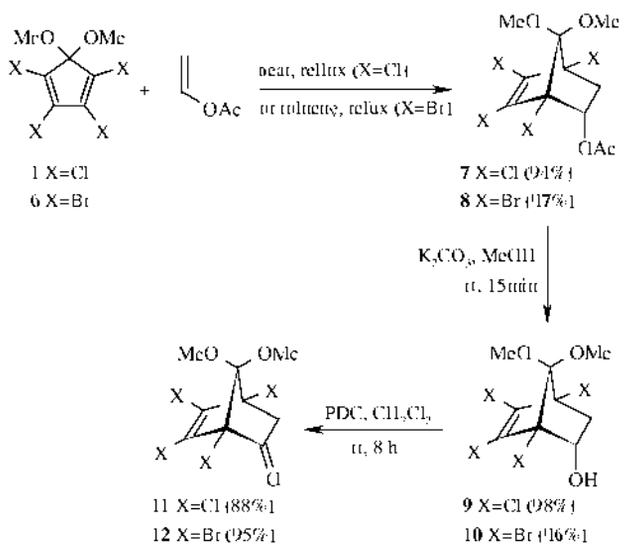
Benzene and its derivatives are extremely useful starting materials in the synthesis of target molecules of biological and industrial importance.[1] The Friedel–Crafts reaction is one of the fundamental methods[2] for the synthesis of polysubstituted benzenes *via* stepwise introduction of the substituents into the aromatic ring. The regioselective construction of substituted benzenes requires careful choice of reagents and generally starts from benzenoid precursors. Although cyclotrimerization of alkynes to benzenes was one of the important milestones in the year 1948 (Reppe), it was not until recently that transition-metal mediated/catalyzed approaches for the synthesis of polysubstituted benzene derivatives were considered an attractive alternative.[3] Another possible route to the preparation of substituted benzenes is *via* extrusion of carbon monoxide[4] or rearrangement[5] reaction of bicyclo[2.2.1]heptene derivatives. Thermal fragmentation of Diels–Alder adducts **3** derived from tetrachloro-5,5-dimethoxycyclopentadiene **1** and acetylenic dienophiles **2** to furnish aromatic products was extensively studied.[6] The norbornadiene derivatives **3** are unstable and undergo aromatization at the temperature at which they are formed, either by extrusion of dimethoxycarbene to give tetrachlorobenzenes **4** or by retaining the bridge carbon to yield aromatic esters **5** [equation (1)]. We herein report a rearrangement of the title compounds **11** and **12** to substituted phenols **13** and **14** [equation (2); see below] and suggest a plausible mechanism for the fragmentation.

(1)



Results and discussion

As part of our ongoing research program directed towards the selective utilization of halogens of tetrahalo-7,7-dimethoxy-norbornene derivatives[7] **7** and **8**, we prepared the tetrahalodimethoxy-2-oxo compounds **11** and **12**. They were easily obtained *via* the sequence depicted in Scheme 1. A Diels–Alder reaction between tetrachloro-5,5-dimethoxycyclopentadiene[8] **1** and vinyl acetate gave the *endo*-acetate adduct **7** in high yield.[9] Similarly the tetrabromo derivative **8** was prepared in almost quantitative yield by refluxing the tetrabromo-dimethoxycyclopentadiene **6** and vinyl acetate in toluene. The



Scheme 1

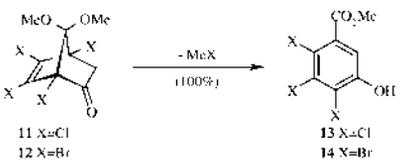
acetate group was hydrolyzed using K_2CO_3 in MeOH and the resulting secondary alcohols **9** and **10** were oxidized with pyridinium dichromate (PDC) in dichloromethane to furnish the corresponding 2-oxo compounds **11** and **12** in excellent yield (Scheme 1).

The *endo*-acetate adduct **7** has been widely used for applications requiring 7-oxo as well as 2-oxo derivatives.[10,11] However, in each case the hydrolysis of the 7-ketal or oxidation of the 2-hydroxy group (of **9**) was performed only after complete reductive dehalogenation, since the carbonyl group would be expected to react in the reductive dehalogenation step. That means tetrahalo ketones **11** and **12** have remained unexplored so far.

Tetrabromodimethoxynorborn-5-en-2-one **12** was made for the first time following the sequence shown in Scheme 1. After silica gel purification, product **12** was crystallized in hexane to give a white crystalline solid (mp 72–73 °C). The solid, upon storage for 2 days at room temperature, underwent transformation into a hard, powdery solid (mp 193–194 °C). The IR spectrum clearly showed the presence of a hydroxy group (3200 cm^{-1}) and an ester (1700 cm^{-1}). Based on ^1H and ^{13}C NMR data the compound was characterized as a phenolic ester derivative **14** [equation (2)]. The rearrangement of **12** was spontaneous when it was heated to 90 °C. The phenolic derivative **14** yielded methyl ether **15** upon treatment

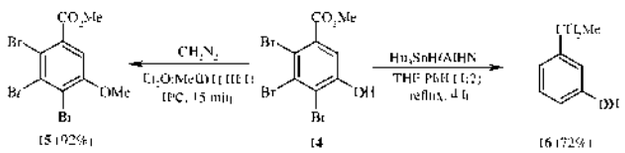
 DOI: 10.1039/b108152g

This journal is © The Royal Society of Chemistry 2001



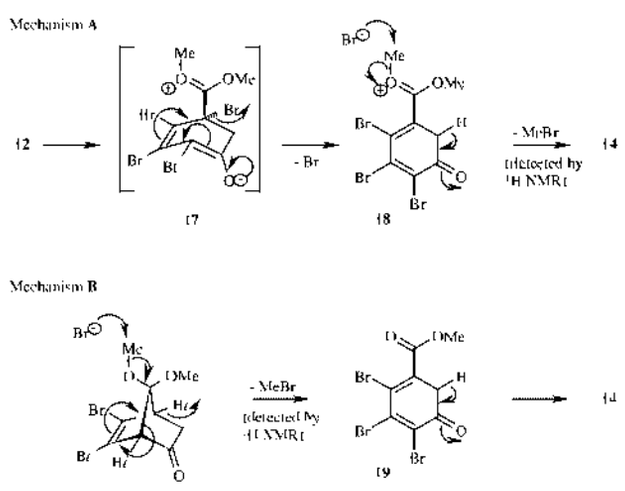
(2)

with ethereal diazomethane (Scheme 2). The structure of compound **14** was further confirmed by converting it into a known compound **16** (Scheme 2). Tributyltin hydride reduction of the tribromo phenol **14** resulted in hydrodebromination giving methyl *m*-hydroxybenzoate **16** (mp 66–68 °C; lit.,[12] 69–71 °C).



Scheme 2

Based on recent literature precedent[11] and in conjunction with the fact that **12** is a β-diketone ketal with a well poised push-pull system, a likely mechanism is proposed (mechanism **A**, Scheme 3). The carbonyl group at C^2 triggers a Grob-type



Scheme 3 Possible aromatization mechanisms for **12**.

fragmentation by pulling the electrons from the acetal group at C^7, resulting in regioselective cleavage of the C^1–C^7 bond. Bond reorganization results in the elimination of Br^- in **17**, which attacks the methyl group of oxonium ion in **18** resulting in the elimination of methyl bromide followed by aromatization to the phenolic derivative **14**. However, a competing concerted mechanism (**B**, Scheme 3) involving the attack of Br^- triggering the fragmentation followed by enolization of dienone **19** to furnish the product **14** could not be ruled out.[13] In a separate experiment, the gas evolved was trapped and identified as MeBr (MeCl, in the case of **11**) from its ^{1}H NMR spectrum which showed a peak at δ 2.66.

The tetrachloro-2-oxo compound **11** also underwent a similar rearrangement, upon storage at room temperature for 3–4 weeks, to provide the aromatic trichlorophenolic ester derivative **13**. The rearrangement was instantaneous and quantitative when **11** was heated to 110 °C.

In conclusion, we have observed a rearrangement of the title compounds **11** and **12** to highly substituted phenolic derivatives **13** and **14** in quantitative yield, thus providing a new entry to these useful compounds.

Experimental

Mps were recorded on a JSGW melting-point apparatus and are uncorrected. Methanol was refluxed and distilled over magnesium turnings and stored over 4 Å molecular sieves. Dry dicholoromethane was distilled from phosphorus pentaoxide and stored over 4 Å molecular sieves. IR spectra were recorded for samples either as a KBr pellet or neat on a Perkin-Elmer 1320 infrared spectrophotometer with NaCl optics. NMR spectra were measured in $CDCl_3$ solution with tetramethylsilane as internal standard on a JEOL spectrometer (400 MHz, ^{1}H NMR and 100 MHz, ^{13}C NMR). Insoluble compounds were made to dissolve by adding 3–4 drops of DMSO-d_6 to the $CDCl_3$ solution. Data are given in the δ-scale. TLC was performed on glass coated with silica gel (Acme). Column chromatography was carried out on Acme silica gel (100–200 mesh).

The Diels–Alder adducts **7** and **8** were prepared by refluxing the corresponding tetrahalocyclopentadiene with an excess of vinyl acetate following literature procedures.[9]

1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol 9

To a solution of the adduct **7** (700 mg, 2 mmol) in 5 ml of MeOH was added K_2CO_3 (276 mg, 2 mmol) and the mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with water and extracted thrice with ethyl acetate. The combined organic layer was washed once with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using 10% ethyl acetate–hexane as eluant to give **9** (604 mg, 98%). Although compound **9** is known,[9] we performed basic hydrolysis of the acetate **7** instead of acid-catalysed hydrolysis as reported; mp 60 °C; ^{1}H NMR δ 4.61 (dd, 1H, J = 7.8, 2.4 Hz, 2-H), 3.57 (s, 3H, OMe), 3.54 (s, 3H, OMe), 2.65 (dd, 1H, J = 12.2, 7.8 Hz, 3-H^{exo}), 2.33 (br s, OH), 1.75 (dd, 1H, J = 12.2, 2.2 Hz, 3-H^{endo}); ^{13}C NMR δ 130.74, 127.3, 112.0, 79.7, 77.4, 74.1, 52.5, 51.5, 44.1; IR (KBr) ν_{max} 3300, 2950, 1600, 1180, 1100 cm^{-1}.

1,4,5,6-Tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol 10

Similar treatment of acetate **8** (1.40 g furnished the alcohol **10** (1.24 g, 96%) as a colourless solid, mp 72–74 °C; ^{1}H NMR δ 4.68 (m, 1H, 2-H), 3.60 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.67 (dd, 1H, J = 12.2, 7.8 Hz, 3-H^{exo}), 2.13 (d, 1H, J = 4.2 Hz, OH), 1.80 (dd, 1H, J = 12.2, 2.4 Hz, 3-H^{endo}); ^{13}C NMR δ 127.2, 122.8, 111.9, 79.1, 74.0, 67.7, 52.9, 51.6, 45.5; IR (KBr) ν_{max} 3400, 2950, 1560, 1420 cm^{-1} (Calc. for $C_9H_{10}Br_4O_3$: C, 22.25; H, 2.07. Found: C, 22.28; H 2.12%).

1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 11

To a solution of pyridine (1 ml, 12 mmol) in CH_2Cl_2 (16 ml) was added CrO_3 (600 mg, 6 mmol) and the mixture was stirred for 15 min. To this deep brown coloured mixture was added a solution of the alcohol **9** (308 mg, 1 mmol) in CH_2Cl_2 (3 ml) and the mixture was stirred for 12 h. The reaction mixture was decanted and the residue was washed with CH_2Cl_2. The combined organic layer was washed succesively with water (5 ml) and brine and then dried over Na_2SO_4. Silica gel column purification (5% ethyl acetate–hexane) afforded the pure ketone **11** (269 mg, 88%) as colourless crystals, mp 66–67 °C; ^{1}H NMR δ 3.63 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.80 (d, 1H, J = 16.5 Hz), 2.67 (d, 1H, J = 16.5 Hz); ^{13}C NMR δ 192.9 (C=O), 135.5, 124.4, 114.3, 82.9, 71.8, 53.2, 52.1, 42.5; IR (KBr) ν_{max} 2950, 1760, 1550, 1150 cm^{-1} (Calc. for $C_9H_8Cl_4O_3$: C, 35.33; H, 2.64. Found: C, 35.06; H, 2.71%).

1,4,5,6-Tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 12

To a solution of pyridine (0.7 ml, 8.55 mmol) in CH_2Cl_2 (11 ml) was added CrO_3 (425 mg, 4.25 mmol) and the mixture was stirred for 15 min. To this deep brown coloured mixture was added a solution of the alcohol **10** (345 mg, 0.71 mmol) in CH_2Cl_2 (3 ml) and the mixture was stirred for 8 h. The reaction mixture was decanted and the residue was washed with CH_2Cl_2. The combined organic layer was washed successively with water (5 ml) and brine and then dried over Na_2SO_4. Silica gel column purification (5% ethyl acetate–hexane) afforded the pure ketone **12** (327 mg, 95%) as colourless crystals; mp 72–73 °C (from hexane); ^{1}H NMR δ 3.66 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.80 (d, 1H, J = 16.6 Hz), 2.68 (d, 1H, J = 16.6 Hz); ^{13}C NMR δ 193.2 (C=O), 132.6, 119.3, 113.8, 78.2, 65.3, 53.4, 52.1, 43.2; IR (KBr) ν_{max} 2900, 1750, 1550, 1120 cm^{-1} (Calc. for $C_9H_8Br_4O_3$: C, 22.34; H, 1.67. Found: C, 22.61; H, 2.07%).

Methyl 2,3,4-trichloro-5-hydroxybenzoate 13

The neat ketone **11** (306 mg, 1 mmol) upon storage for 3–4 weeks at room temperature, or on heating to about 110 °C, furnished **13** (255 mg, 100%) with the evolution of a gaseous substance (MeCl, δ 3.02 in ^{1}H NMR spectrum, was detected when **11** was heated neat in a tightly stoppered NMR tube, cooled, and the contents dissolved in $CDCl_3$ for recording the spectrum). Compound **13** was a colourless solid, mp 168–174 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6 10 : 1) δ 10.59 (s, 1H, OH, D_2O exchangeable), 7.34 (s, 1H, 6H), 3.91 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$–DMSO-d_6 10 : 1) δ 165.1 (O–C=O), 152.8, 133.1, 129.9, 124.3, 121.7, 115.8, 52.5 (OMe); IR (KBr) ν_{max} 3000, 1680, 1570, 1300 cm^{-1} (Calc. for $C_8H_5Cl_3O_3$: C, 37.61; H 1.97. Found: C, 37.48; H, 1.34%).

Methyl 2,3,4-tribromo-5-hydroxybenzoate 14

The neat ketone **12** (387 mg, 0.8 mmol) upon storage for 2 days at room temperature, or on heating to about 90 °C, furnished **14** (311 mg, 100%) with the evolution of a gaseous substance (MeBr, δ 2.66 in the ^{1}H NMR spectrum, was detected when **12** was heated neat in a tightly stoppered NMR tube, cooled, and the contents dissolved in $CDCl_3$ for recording the spectrum, and had mp 193–194 °C; ^{1}H NMR δ 10.72 (s, 1H, OH, D_2O exchangeable), 7.23 (s, 1H, 6-H), 3.90 (s, 3H, OMe); ^{13}C NMR δ 166.1 (O–C=O), 154.6, 134.2, 129.8, 117.1, 115.5, 111.6, 52.5; IR (KBr) ν_{max} 3200, 1700, 1560, 1250 cm^{-1} (Calc. for $C_8H_5Br_3O_3$: C, 24.71; H, 1.30. Found: C, 24.68; H, 1.25%).

Methyl 2,3,4-tribromo-5-methoxybenzoate 15

To a solution of phenolic compound **14** (100 mg, 0.26 mmol) in diethyl ether at 0 °C was added an ethereal solution of diazomethane (excess) generated from *N*-nitrosomethylurea. After 15 min, the solvent ether was evaporated off and the crude was filtered through a small pad of silica gel (40% ethyl acetate–hexane) to furnish **15** (96 mg, 92%) as a colourless solid, mp 116–118 °C; ^{1}H NMR δ 7.13 (s, 1H, 6-H), 3.95 (s, 3H, OMe), 3.92 (s, 3H, OMe); ^{13}C NMR δ 166.4 (O–C=O), 156.0, 134.4, 131.1, 119.4, 114.8, 111.3 (CH), 57.0 (OMe), 53.0 (OMe); IR (KBr) ν_{max} 2950, 1725, 1560, 1220 cm^{-1} (Calc. for $C_9H_7Br_3O_3$: C, 26.83; H, 1.75. Found: C, 26.79; H, 1.69%).

Methyl 3-hydroxybenzoate 16

To a solution of tribromophenolic derivative **14** (100 mg, 0.26 mmol) in 6 ml of THF–benzene (1 : 2) were added Bu_3SnH (281 mg, 0.96 mmol) and AIBN (≈1 mg). The reaction mixture was refluxed for 4 h under argon. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (elution first with hexane to remove tin impurities, then 25% ethyl acetate–hexane) to yield **16** (29 mg, 72%) as a colourless solid, mp 66–68 °C (lit.[12] 69–71 °C).

Acknowledgements

This work was supported by the Indian National Science Academy (INSA) and Department of Science and Technology (DST), New Delhi, India. J. D. and B. P. thank CSIR for a research fellowship.

References

1 T. Bach, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 729.
2 J. March, *Advanced Organic Chemistry*, Wiley, New York, 4th edn., 1992, Ch. 11, p. 501.
3 S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901.
4 E. T. McBee, W. R. Diveley and J. E. Burch, *J. Am. Chem. Soc.*, 1955, **77**, 385; R. K. McCulloch, A. R. Rye and D. Wege, *Aust. J. Chem.*, 1974, **27**, 1929; A. Roedig, H.-H. Bauer, G. Bonse and R. Ganns, *Chem. Ber.*, 1974, **107**, 558; J. J. Gajewski and G. C. Paul, *J. Org. Chem.*, 1990, **55**, 4575.
5 P. E. Hoch, *J. Org. Chem.*, 1961, **26**, 2066; K. Mackenzie, *J. Chem. Soc.*, 1962, 457; P. Kniel, *Helv. Chim. Acta*, 1963, **46**, 492; P. Kniel, *Helv. Chim. Acta*, 1965, **48**, 837; R. E. Winkler, *Helv. Chim. Acta*, 1967, **50**, 2497; U. O'Connor and W. Rosen, *J. Org. Chem.*, 1980, **45**, 1824; R. H. Mitchell, M. Chaudhary, T. Kamada, P. D. Slowey and R. V. Williams, *Tetrahedron*, 1986, **42**, 1741.
6 R. W. Hoffmann, *Angew. Chem.*, 1971, **83**, 595; J. Diekmann, *J. Org. Chem.*, 1963, **28**, 2880; D. M. Lemal, E. P. Gosselink and S. D. McGregor, *J. Am. Chem. Soc.*, 1966, **88**, 582; R. K. Lustgarten and H. G. Richey, Jr., *J. Am. Chem. Soc.*, 1974, **96**, 6393; D. Seyferth and A. B. Evnin, *J. Am. Chem. Soc.*, 1967, **89**, 1468; L. A. Paquette, R. E. Moerck, B. Harirchian and P. D. Magnus, *J. Am. Chem. Soc.*, 1978, **100**, 1597; K. Mackenzie, *J. Chem. Soc.*, 1964, 5710; A. Haas and H.-U. Krächter, *Chem. Ber.*, 1988, **121**, 1833; R. G. Hall and S. Trippett, *Tetrahedron Lett.*, 1982, **23**, 2603; U. Annen, M. Regitz and H. Kluge, *Chem. Ber.*, 1990, **123**, 935; D. E. Sunko, Z. Lovric and H. Vančik, *J. Chem. Soc., Chem. Commun.*, 1985, 1589.
7 F. A. Khan and B. Prabhudas, *Tetrahedron Lett.*, 1999, **40**, 9289; F. A. Khan, B. Prabhudas, J. Dash and N. Sahu, *J. Am. Chem. Soc.*, 2000, **122**, 9558.
8 For a recent review on applications of Diels–Alder adducts of **1**, see F. A. Khan, B. Prabhudas and J. Dash, *J. Prakt. Chem.*, 2000, **342**, 512.
9 M. E. Jung and J. P. Hudspetch, *J. Am. Chem. Soc.*, 1977, **99**, 5508; B. Berger, C. G. Rabiller, K. Königsberger, K. Faber and H. Griengl, *Tetrahedron: Asymmetry*, 1990, **1**, 541; L. A. Paquette, K. S. Learn, J. L. Romine and H.-S. Lin, *J. Am. Chem. Soc.*, 1988, **110**, 879.
10 P. W. M. Sgarbi and D. L. Clive, *Chem. Commun.*, 1997, 2157; D. L. J. Clive, S. Sun, X. He, J. Zhang and V. Gagliardrini, *Tetrahedron Lett.*, 1999, **40**, 4605; D. L. J. Clive, S. Sun, V. Gagliardrini and M. K. Sano, *Tetrahedron Lett.*, 2000, **41**, 6259; M. E. Jung and S. M. Kaas, *Tetrahedron Lett.*, 1989, **30**, 641.
11 G. Mehta, N. Mohal and S. Lakshminath, *Tetrahedron Lett.*, 2000, **41**, 3505; G. Mehta and S. Lakshminath, *Tetrahedron Lett.*, 2000, **41**, 3509.
12 E. Frerot, C. Marquis and P. Vogel, *Tetrahedron Lett.*, 1996, **37**, 2023.
13 We thank one of the referees for this suggestion.