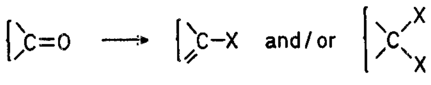
Halogenative Deoxygenation of Ketones; Vinyl Bromides and/or *gem*-Dibromides by Cleavage of 1,3-Benzodioxoles (Ketone Phenylene Acetals) with Boron Tribromide

Elio Napolitano*, Rita Fiaschi, Ettore Mastrorilli

Istituto di Chimica Organica, Facoltà di Farmacia, Via Bonanno 6, I-56100 Pisa, Italy

Representative ketones **1** have been converted in generally good yields to the respective 1,3-benzodioxoles **5** by *trans*-acetalization of ketone dimethyl acetals with 1,2-dihydroxybenzene, and cleaved with boron tribromide. 1,3-Benzodioxoles derived from α-unbranched aliphatic ketones gave in general a mixture of vinyl bromides and *gem*-dibromides; pure *gem*-dibromides could be selectively obtained in most of cases using a suitable reaction time. 1,3-Benzodioxoles derived from α-branched ketones gave complex mixtures and their cleavage appears to be of little synthetic significance. 1,3-Benzodioxoles of aromatic ketones gave vinyl bromides only. Aliphatic cyclic *gem*-dibromides **3** were converted to the respective vinyl bromides **2** by phase-transfer-catalysed dehydrobromination.

Halogenative deoxygenation of ketones (i.e. the regiospecific replacement of the carbonyl function by *gem*-dihalide or by vinyl halide functional group) has been generally realised by reaction with phosphorus pentachloride, in the case of X = Cl[1], or by reaction of an intermediate hydrazone[2] or vinylsilane[3,4] with iodine, in the case of X = J. Phosphorus pentabromide is generally not a good reagent for this transformation in the case of X = Br, because of its preferential attitude to effect α-oxidation of ketones[5]. To our best knowledge, reaction of an intermediate vinylsilane[3,4] with bromine is the only general method to bring about the conversion of **1** into **2** (X = Br); unfortunately, such an approach requires many steps, carefully controlled conditions, and the use of expensive reagents.



1 **2** **3**

X = halogen

Main methods for the preparation of **2** (X = Br) involve presently:
- controlled dehydrobromination of 1,2-dibromides[6];
- hydrobromination of carbon-carbon triple bonds mediated by a variety of reagents[7];
- Wittig olefination using bromo-substituted phosphoranes[7]; and
- decarboxylative dehydrobromination of α,β-dibromocarboxylic acids[8].

Concerning their limitation, the first and the second method are not regiospecific with respect to the location of the bromine atom, and regioselectivity is observed only in special cases; the second and the third ones are not suitable for cyclic substrates; the last method, although regiospecific and suitable in principle for cyclic substrates, lacks convenience because of the loss of one carbon atom.

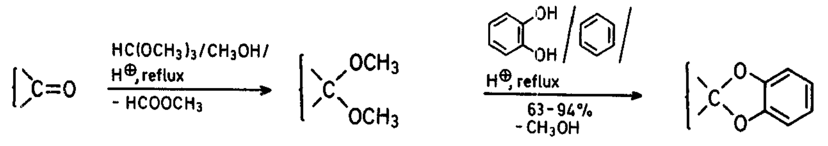
General methods of synthesis of **3** (X = Br) are:
- ionic addition of hydrogen bromide to vinyl bromides[9];
- reaction of diazoalkanes with bromine[10]; and
- reaction of α-bromocarboxamides with bromine[11].

Among these, the first suffers the same limitation of the synthesis of **2** previously outlined; the second involves the use of unstable intermediates and only few applications are known; the third is not convenient because of loss of one carbon atom from the original framework.

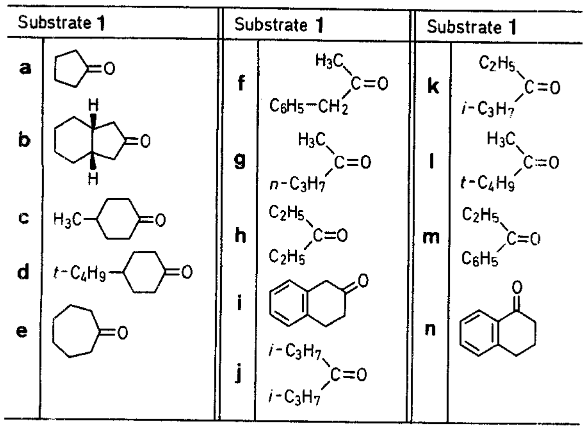
Our interest in a convenient and general method of synthesis of certain substituted cyclic *gem*-dibromides (to be used as sources of chiral non racemic cyclic vinyl bromides by enantioselective dehydrobromination promoted by chiral bases[12]), as well as the general utility of a new entry to vinyl bromides enabling the regiospecific location of the bromine atom led us to find simple conditions for the transformation described (X = Br).

Boron tribromide and boron trichloride are widely used reagents for the cleavage of phenolic ethers and, in particular, of the benzodioxole ring[13]. Because the by-products of these reactions are likely to be alkyl halides, we envisaged that compounds of general structure **5** could serve as precursors for **2** and/or **3** using boron tribromide as a reagent. The present paper concerns with the successful synthetic application of boron tribromide to a practical method for obtaining **2** and/or **3** from simple α-unbranched aromatic and aliphatic ketones.

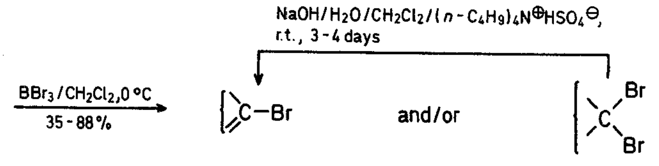
Although most of the compounds **5** (1,3-benzodioxoles) may be prepared by condensation of 1,2-dihydroxybenzene with ketones under usual conditions of formation of cyclic acetals (heating of the reagents in benzene in the presence of an acid catalyst under removal of water by azeotropic distillation or by reaction with a water scavenger such as trialkyl orthoformate), we have found that they are obtained in generally



1 4 5



better yields or as cleaner reaction products (particularly in the case of hindered, enolisable or volatile ketones) by condensation of 1,2-dihydroxybenzene with ketone dimethyl acetals 4.



2 3

Cleavage of 5 by boron tribromide is generally a rapid reaction, being complete in most cases by short exposure to a 10% excess of the reagent in dichloromethane at – 10°C, and it affords a mixture of compounds whose actual composition is dependent upon the substrate, the reaction time as well as the aging of the boron tribromide solution.

Acetals derived from α-unbranched aliphatic ketones (**5a–h**) are uniformly converted to **3a–h** after 8 h reaction at 0°C, using a freshly prepared solution of boron tribromide. With shorter reaction times or using old samples (perhaps partially hydrolysed) of boron tribromide, mixtures of **2a–h** and **3a–h**

Table. Ketones Phenylene Acetals **5**, Vinyl Bromides **2**, and *gem*-Dibromides **3** prepared

Product No.	Yield [%]	b.p. [°C]/torr or m.p. [°C]	Molecular Formula[a] or Lit. data	I.R. (Neat/Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]
5a	76	60°/1	$C_{11}H_{12}O_2$ (176.2)	1330, 1230, 1080, 730	1.53–2.30 (m, 8H, CH_2); 6.76 (s, 4H_{arom})
5b	75	80°	$C_{15}H_{18}O_2$ (230.3)	1230, 730	1.50 (br. s, 8H); 2.18 (br. s, 6H); 6.80 (s, 4H_{arom})
5c	91	100°/1	$C_{13}H_{16}O_2$ (204.3)	1230, 730	0.98 (br. s, 3H, CH_3); 1.15–2.40 (m, 9H, ring H); 6.76 (s, 4H_{arom})
5d	94	100°	$C_{16}H_{22}O_2$ (246.3)	1230, 730	0.92 (s, 9H, CH_3); 1.00–2.33 (m, 9H, ring H); 6.75 (s, 4H_{arom})
5e	81	54°	$C_{13}H_{16}O_2$ (204.3)	1230, 740	1.68 (br. s, 8H, $OCCH_2(C\underline{H}_2)_4$); 1.95–2.31 (m, 4H, $OCCH_2$); 6.78 (s, 4H_{arom})
5f	85	150°/0.1	$C_{15}H_{14}O_2$ (226.3)	1230, 740	1.56 (s, 3H, CH_3); 3.15 (s, 2H, CH_2); 6.76 (s, 4H_{arom}); 7.30 (s, 5H_{arom})
5g	69	120/20	$C_{11}H_{14}O_2$ (178.2)	1230, 730	0.93 (t, J = 6 Hz, 3H, $CH_2CH_2C\underline{H}_3$); 1.20–2.10 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$); 1.59 (s, 3H, $CC\underline{H}_3$); 6.76 (s, 4H_{arom})
5h	71	110/20	$C_{11}H_{14}O_2$ (178.2)	1230, 730	0.96 (t, J = 7.5 Hz, 6H, $CH_2C\underline{H}_3$); 1.91 (q, J = 7.5 Hz, 4H, $C\underline{H}_2CH_3$); 6.76 (s, 4H_{arom})
5i	76	150/0.05	$C_{16}H_{14}O_2$ (238.3)	1230, 730	2.25 (t, J = 6.5 Hz, 2H, $ArCH_2C\underline{H}_2$); 3.10 (t, J = 6.5 Hz, 2H, $ArC\underline{H}_2CH_2$); 3.30 (s, 2H, $ArCH_2CO$); 6.78 (s, 4H_{arom}); 7.15 (s, 4H_{arom})
5j	70	70/0.05	55°/0.02[21]	1230, 1020, 730	1.00 (d, J = 6.8 Hz, 12H, $C\underline{H}_3CH$); 2.30 (heptet, J = 0.68 Hz, 2H, $CH_3C\underline{H}$); 6.75 (s, 4H_{arom})
5k	73	70°/0.1	$C_{12}H_{16}O_2$ (192.3)	1230, 730	0.95 (t, J = 7.5 Hz, 2H, $CH_2C\underline{H}_3$); 1.00 (d, J = 7.0 Hz, 6H, $CHC\underline{H}_3$); 1.91 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$); 2.05 (heptet, J = 7.5 Hz, 1H, $C\underline{H}CH_3$); 6.73 (s, 4H_{arom})
5l	75	30°	$C_{12}H_{16}O_2$ (192.3)	1230, 730	1.08 (s, 9H, $C(CH_3)_3$); 1.55 (s, 3H, CH_3); 6.80 (s, 4H_{arom})
5m	63	42°	$C_{15}H_{14}O_2$ (226.3)	1230, 740, 690	0.98 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$); 2.23 (q, J = 7.3 Hz, 2H, $C\underline{H}_2CH_3$); 6.80 (s, 4H_{arom})
5n	65	80°	$C_{16}H_{14}O_2$ (238.3)	1230, 730	1.80–2.45 (m, 4H, $ArC\underline{H}_2C\underline{H}_2CH_2$); 2.87 (t, J = 5.5 Hz, 2H, $ArCH_2CH_2C\underline{H}_2$); 6.86 (s, 4$H_{arom}$); 7.07–7.78 (m, 4$H_{arom}$)

Table. (Continued)

Product No.	Yield [%]	b.p. [°C]/torr or m.p. [°C]	Molecular Formula[a] or Lit. data	I.R. (Neat/Nujol) ν[cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ[ppm]
2a	60	130°/760	128–129/760[18]	–	–
2b	77	110°/1.5	$C_9H_{13}B_2$ (201.1)	1600, 790	1.45 (br. s, 8H, six membered ring CH_2); 2.08–2.78 (m, 3H, $BrCH_2CHCH$); 5.86 (bs, 1H, $=CH$)
2c	88	90°/20	$C_7H_4B_2$ (175.1)	1640, 930, 890, 800	0.96 (d, J = 5.0 Hz, 3H, CH_3); 1.10–2.28 (m, 5H, $=CHC\underline{H}_2C\underline{H}C\underline{H}_2$); 2.46 (m, 2H, $=CBrCH_2$); 6.00 (m, 1H, $=CH$)
2d	85	130°/1	$C_{10}H_{17}B_2$ (217.2)	1640, 1350	0.88 (s, 9H, CH_3); 1.10–2.21 (m, 5H, $=CHC\underline{H}_2C\underline{H}C\underline{H}_2$); 2.46 (m, 2H, $=CBrCH_2$); 6.06 (m, 1H, $=CH$)
2e	82	90/20	74–78°/19[18]	–	–
2i	35	85°/0.01	$C_{10}H_9Br$[b] (209.1)	1620, 750	2.84 (m, 4H, CH_2); 6.79 (s, 1H, $=CH$); 7.10 (m, 4H_{arom})
2m	73	150°/3	–[19,c]	–	–
2n	62	90°/0.05	81–84°/0.44[20]	1600, 940, 750	2.10–2.58 (m, 2H, $=CHC\underline{H}_2CH_2$); 2.83 (t, J = 7.5 Hz, 2H, $=CHCH_2C\underline{H}_2$); 6.45 (t, J = 4.5 Hz, 1H, $=C\underline{H}CH_2CH_2$); 6.95–7.73 (m, 4H_{arom})
3a	77	95°/1.5	$C_5H_8Br_2$ (227.9)	1170, 940	1.58–2.16 (m, 4H, $BrCCH_2-C\underline{H}_2$); 2.41–2.93 (m, 4H, $BrCC\underline{H}_2$)
3b	70	120°/0.05	$C_9H_{14}Br_2$ (282.0)	1180, 960	1.48 (br. s, 8H, six membered ring CH_2); 2.06–2.52 (br. s, 2H, CH); 2.56, 2.82, 2.92, 3.03, 3.15, 3.28 (m, 4H, $BrCCH_2$)
3c	85	100°/1	$C_7H_{12}Br_2$ (256.0)	950, 720	0.93 (m, 3H, CH_3); 1.08–2.05 (m, 5H, $CH_3-C\underline{H}C\underline{H}_2-$); 2.05–3.01 (m, 4H, $BrCCH_2$)
3d	82	150°/1	$C_{10}H_{18}Br_2$ (298.1)	1010, 990, 710	0.86 (s, 9H, CH_3); 1.05–3.05 (m, 9H, ring H)
3e	86	130°/2.5	$C_7H_{12}Br_2$ (256.0)	1160, 1000, 1140, 690	1.43–1.83 (m, 8H, $BrCCH_2C\underline{H}_2C\underline{H}_2$); 2.63–3.00 (m, 4H, $BrCC\underline{H}_2CH_2CH_2$)
3f	81	140°/1	$C_9H_{10}Br_2$ (278.0)	1050, 740, 700	2.48 (s, 3H, CH_3); 3.78 (s, 2H, CH_2); 7.41 (s, 5H_{arom})
3g	80	140°/760	$C_5H_{10}Br_2$ (230.0)	1110, 1090, 1020	1.00 (t, J = 7 Hz, 3H, $CH_2CH_2C\underline{H}_3$); 1.41–2.03 (m, 2H, $CH_2C\underline{H}_2CH_3$); 2.20–2.45 (m, 2H, $C\underline{H}_2CH_2CH_3$); 2.53 (s, 3H, CCH_3)
3h	83	135°/760	$C_5H_{10}Br_2$ (230.0)	1110, 1090, 1080	1.21 (t, J = 7 Hz, 3H, $CH_2C\underline{H}_3$); 2.41 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$)
3i	38	61°	$C_{10}H_{10}Br_2$ (290.0)	1030, 750, 730	2.58–3.27 (m, 4H, CH_2CH_2); 3.95 (s, 2H, CH_2); 6.92–7.30 (m, 4H_{arom})

[a] Satisfactory microanalyses obtained (C ± 0.3%, H ± 0.3%) except for unstable **3b**.

[b] 2-Bromo-3,4-dihydronaphthalene.

[c] Only the (*Z*)-isomer was obtained, as deduced from comparison with the reported ^{1}H-N.M.R. spectrum.

may result (particularly with five- and seven-membered cyclic derivatives). Vinyl bromides are obtained in the case of cyclic derivatives (**2a–e**) by phase tranfer catalysed dehydrobromination of **3a–e** in the system dichloromethane/33% sodium hydroxide /tetrabutylammonium hydrogen sulfate. Such a procedure does not apply to the open chain derivatives **3f–h**: in the first case, elimination does not stop at the stage of vinyl bromide and substantial amounts of 1-phenyl-1-propyne are also obtained; with **3g, h** only traces of elimination are observed even after 2 weeks. Compounds **2i** and **3i** were obtained as a mixture by working-up the reaction of **5i** with boron tribromide after 1 hour at 0 °C, and separation by flash chromatography.

Acetals derived from α-branched ketones **5j–l** give complex mixtures of compounds and the reaction sequence is not of practical value in these cases. From aromatic acetals **5m, n** only vinyl bromides **2m, n** (contaminated by small amounts of starting ketones **1m, n**) are obtained, and attempt to produce *gem*-dibromides by long reaction times only leads to decreased yields of **2m, n**.

Finally, all aliphatic cyclic vinyl bromides **2a–e** can be converted to the respective *gem*-dibromides **3** of good purity by reaction with a mixture of 33% hydrogen bromide in acetic acid and acetyl bromide.

Melting points were determined on a Kofler hot plate and are uncorrected. Boiling points are referred to the air bath temperature of bulb to bulb distillations using a Büchi GKR-50 apparatus and are uncorrected. ^{1}H-N.M.R. spectra were recorded on using a Varian EM360A spectrometer. I.R. spectra were measured as neat in the case of pure liquids or as Nujol mulls for solids using a Perkin-Elmer 197 Infrared Spectrophotometer. G.L.C. analyses were performed on a Perkin-Elmer Sigma 3B apparatus with a glass column (2 m × 2.5 mm) packed with 10% diethylene glycol succinate on silanised Chromosorb 80–100 mesh; compound **6b** decomposes under a variety of conditions. Commercial boron tribromide (Fluka) was used. Ketone **1b** (semicarbazone m.p. 212 °C, Lit.[14], m.p. 216 °C) was prepared by catalytic hydrogenation of bicyclo [4.3.0]6-nonen-8-one[15].

1,3-Benzodioxoles 5 (Ketone Phenylene Acetals); General Procedure:
A mixture of **1** (50 mmol), methyl orthoformate (6.4 g, 60 mmol), methanol (30 ml), and *p*-toluenesulfonic acid (50 mg) is gently heated while methyl formate formed in the reaction is distilled off through a short Vigreux column. The cooled reaction mixture is made basic by addition of few drops of a solution of sodium (0.5 g) in methanol (10 ml), and partitioned between ether (100 ml) and water (100 ml). The organic phase is washed with brine (50 ml) and dried with potassium carbonate. Evaporation of the solvent affords a good yield of dimethyl acetals **4**, which may be used in the following step without further purification.

A mixture of ketone dimethyl acetal **4** (50 mmol), 1,2-dihydroxybenzene (6.6 g, 60 mmol), and benzene (100 ml) is brought to reflux and part of the solvent (10 ml) is distilled through a short Vigreux column. Heating is discontinued, the temperature is lowered to 60 °C and *p*-toluenesulfonic acid (50 mg) is added. The distillation of the solvent is slowly continued until pure benzene is being collected. During this operation, addition of fresh benzene may be necessary to prevent the reaction mixture from becoming dry. Triethylamine (1 ml) is added to the cooled reaction mixture, which is then partitioned between ether (100 ml) and water (100 ml). The organic phase is washed with water (2 × 50 ml), with 10% sodium hydroxide (50 ml), with brine (50 ml), dried with potassium carbonate, and evaporated. Crude **5** thus obtained is purified by distillation or recrystallisation from methanol.

Cleavage of 5 with Boron Trifluoride; General Procedure:
To a magnetically stirred solution of **5** (10 mmol) in dichloromethane (20 ml) cooled in an ice-salt bath, is added dropwise 1 molar solution boron tribromide in dichloromethane (12 ml, 12 mmol). The reaction vessel is stoppered and the coloured solution stirred for 8 h at 0 °C in the case of **5a–h**[16], or for 1 h at 0 °C in the case of **5i, m, n**. The mixture is partitioned between hexane (80 ml) and ice-cold water (50 ml), and the mixture thoroughly shaken until most of the solid is dissolved. The organic phase is washed with water (2 × 50 ml), with 10% sodium hydroxide (50 ml), dried with magnesium sulfate, filtered through a short pad of aluminum oxide (activity I) to remove most of heavy coloured materials, and evaporated. Distillation of the residue affords **3a–h**, whose purity is more than 95%; an analytical sample is obtained by flash chromatography[17] on silica gel using hexane as eluent. Compound **5i** gives a mixture of **2i** and **3i**, which are separated by flash chromatography[17] as above. Compounds **5m, n** give **2m, n** contaminated by small amounts of ketones **1m, n** respectively; purification is performed by flash chromatography[17] (see above) and distillation.

Pure 2a–e by Dehydrobromination of 3a–e or Mixtures of 2a–e and 3a–e:
Compound **3a–e** (or a mixture of **2a–e** and **3a–e**) (500 mg) in dichloromethane (5 ml), 33% sodium hydroxide (10 ml), and tetrabutylammonium hydrogen sulfate (50 mg) are stirred until G.L.C. shows the disappearance of the starting material (3–4 days). The mixture is partitioned between ether (20 ml) and ice cold water (50 ml), the organic phase washed with water (2 × 10 ml), dried with magnesium sulfate, and distilled.

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* Correspondence author.

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