Lewis Acid-Promoted Favorskii-Type Ring Contraction of Some Cyclic α-Bromo Ketones and Their Acetals

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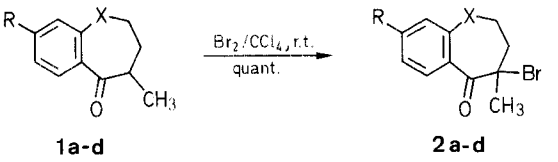
The α-bromo cycloalkyl aryl ketones **2a–d** on heating with zinc chloride in methanol furnished in moderate to good yields the ring-contracted products **3a–d** having *gem* methyl carbomethoxy function. The acetals of the related α-bromo ketones **7a–c**, lacking the methyl group on the halogen-bearing carbon atom, afforded in acceptable yields the ring-contracted esters **8a–c** when heated in protic solvent. The limitation of the present ring-contraction procedure has been discussed.

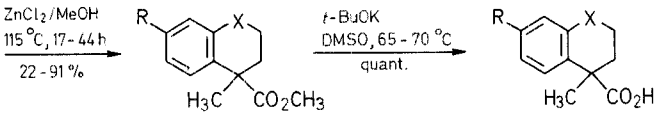
α-Arylalkanoic acids are well-known anti-inflammatory agents.[1] Various synthetic approaches[1] have been made for finding out a practicable method for the industrial production of this class of compounds. Thus α-haloalkyl aryl acetals are converted, *via* 1,2-aryl shift, into esters of 2-arylalkanoic acids by activation of the carbon-halogen bond through the use of silver salts,[2–4] Lewis acids,[5–7] peracids,[8–9] thallium nitrate,[10] and by protic solvents.[11] Moreover, α-bromoalkyl aryl ketones have very recently been transformed,[12] in a one pot reaction, into methyl esters of 2-arylalkanoic acids when heated in methanol with excess of zinc bromide. It has been demonstrated[5,12] that electron-donating substituent in the aryl group and alkyl substituent on the halogen-bearing carbon atom facilitate the 1,2-aryl shift. The function of zinc bromide in the transition state for aryl migration has also been discussed.[5]

As far as we know, the above simple procedure for 1,2-aryl shift has not been extended to the related cyclic α-halo ketones. In connection with our interest[13] in ring contraction reaction, we wish to report here the application of the above procedure[12] for the ring contraction of some cyclic α-bromo ketones of the types **2a–d** and **6a–c**.

The α-bromo ketones **2a–d** and **10** were prepared by the addition of bromine to a solution of the known α-methyl ketones **1a–d**[14] and 6-methoxy-2-methyl-1-tetralone[15] in carbon tetrachloride following the procedure reported[16] for the preparation of α-bromo ketone **2e** from **1e** (R = H, X = S). All the bromoketones **2a–e** were isolated as viscous oils, and they were fully characterized by their ^{1}H-NMR spectra (Table 1). Heating a mixture of concentrated solution of α-bromo ketone **2a** and anhydrous zinc chloride[17] in methanol at 115 °C for five hours, as described earlier,[12] afforded a ca 1 : 1 mixture (from IR) of the desired ring-contracted product **3a** and the unchanged bromoketone **2a**. Further treatment of this mixture as above for 12 h

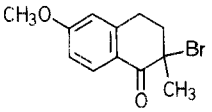


1a-d **2a-d**



3a-d **4a,b,d**

1–4	R	X	1–4	R	X
a	OCH_3	CH_2	**c**	OCH_3	O
b	H	CH_2	**d**	H	O



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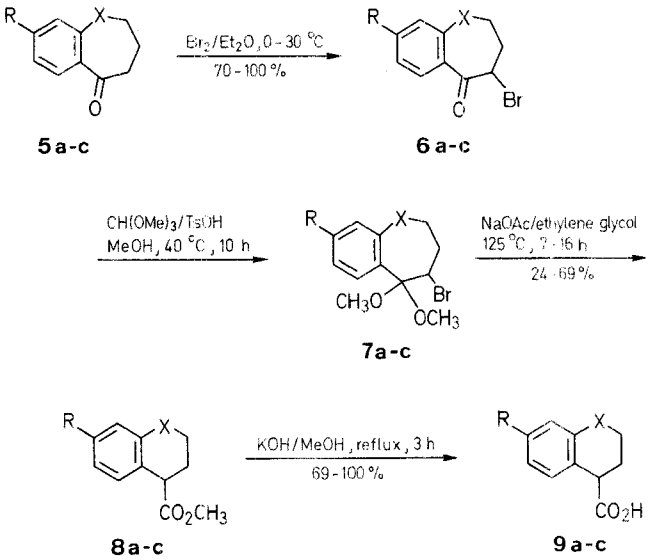
provided the desired ester **3a** in good yield (Table 2). Hydrolysis of this hindered ester **3a** with potassium *t*-butoxide[18] in dimethyl sulfoxide finally furnished the crystalline acid **4a** in near quantitative yield. The related bromoketone **2b**, lacking the methoxy group, required longer reaction time (Table 2) for an excellent yield of the ring-contracted ester **3b**. The bromoketones **2c–d** needed more forcing conditions (Table 2) for providing in moderate yields the ring-contracted products **3c–d**. The known homothiachromanone derivative **2e**[16] failed to give any trace of the expected ester **3e** even under forcing condition (20 h reflux). 2-Bromo-2-methyl-6-methoxy-1-tetralone (**10**) was practically recovered unchanged under the above ring contraction procedure. The α-bromoketone **6a**, lacking the methyl group at the migration terminus, was also recovered unchanged even under forcing condition (18 h reflux).

We next turned our attention for the preparation of the α-bromo acetals **7a–c** with a view to studying their ring contraction by the

procedure successfully exploited[3] in the case of the related acyclic system. The α-bromo ketones **6a–c** were prepared by the addition of bromine to an ethereal solution of the ketones **5a–c**[19] under ice-cold condition, and they were characterised by their spectral data (Table 1). These α-bromo ketones **6a–c** were converted to their acetals **7a–c** by the described procedure.[3] The crude acetals **7a–c** were directly rearranged by the known procedure[11] to the ring-contracted esters **8a–c**, and the results are tabulated in Table 2. Here again the α-bromo acetal **7c**, having no electron-donating group in the aromatic ring, gave, as expected, a poor yield of the ring-contracted ester **8c**. Usual mild



5–9	R	X
a	OCH_3	CH_2
b	OCH_3	O
c	H	O

alkaline hydrolysis of the esters **8a–c** furnished the crystalline acids **9a–c** in excellent yields. it may be mentioned here that the sterically hindered α-bromo ketones **2a, 2c** and **10** failed to provide the corresponding acetal derivative under the prescribed procedure.[3]

Lead tetraacetate-promoted[20] 1,2-aryl migration has been successfully utilized for the preparation of methyl aryl acetates from acetophenone and their derivatives. Tetrahydrosantonin is also known[21] to undergo Favorskii-type ring-contraction when treated with lead tetraacetate and boron trifluoride in the presence of alcohol. Attempted ring-contraction of the above cyclic ketones, **1a, 5a** and 2-methyl-6-methoxy-1-tetralone by the above procedure was not at all encouraging.

Though the ring contraction reaction reported here has some limitations, it provides an easy entry to a class of cyclic compounds **4a–d** having *gem*-methyl carboxy functions.

IR spectra were determined with a Perkin-Elmer 297-instrument and ^{1}H-NMR spectra were recorded with a Varian T-60 spectrometer unless otherwise stated.

2-Bromo-2-methyl-6-methoxy-1-tetralone (10); Typical Procedure:
To a stirred solution of 2-methyl-6-methoxy-1-tetralone (0.475 g, 2.5 mmol) in dry CCl_4 (10 mL) is added dropwise a solution of bromine (0.40 g, 2.5 mmol) in CCl_4 (10 mL) during 1 h at room temperature (30 °C). The mixture is left at this temperature for overnight. The solvent is removed under reduced pressure, and the residue is diluted with cold water (100 mL). The product is extracted with ether (3 × 30 mL) and the combined organic extract is washed successively with saturated $NaHCO_3$ solution (2 × 25 mL) and water (3 × 30 mL). Evaporation of the dried (Na_2SO_4) organic phase gives the bromoketone **10** which is purified by crystallization from ether/light petroleum ether (PE).

The other bromoketones **2a–d** are also prepared by this procedure and are isolated as viscous oils which are purified by vacuum distillation. The characteristic spectral data are recorded in Table 1.

8-Methoxy-4-bromo-3,4-dihydro-1-benzoxepin-5(2*H*)-one (6b); Typical Procedure:
To an ice-cold (0–10 °C) and stirred solution of the ketone **5b**. (0.5 g, 2.6 mmol) in dry ether (20 mL) is added dropwise during 1 h a solution

Table 1. Physical and Spectral Data of the New Bromoketones **2a–d** and **6a–c**

Bromoketone	Yield (%)	m.p. (°C)[a] or b.p. (°C)/mbar[b]	Molecular Formula[c]	IR ($CHCl_3$) ν(cm^{-1})	^{1}H-NMR (CCl_4/TMS) δ, J(Hz)
2a	100	125–130/0.13	$C_{13}H_{15}BrO_2$ (283.3)	1675	1.90 (s, 3H); 1.95–2.37 (m, 4H); 2.72–3.03 (m, 2H); 3.73 (s, 3H); 6.50–6.68 (m, 2H); 7.25 (d, 1H, J = 8.5)[d,e]
2b	100	120–125/0.13	$C_{12}H_{13}BrO$ (253.2)	1685	1.93 (s, 3H); 1.95–2.33 (m, 4H); 2.51–2.95 (m, 2H); 6.80–7.40 (m, 4H)
2c	100	125–130/0.13	$C_{12}H_{13}BrO_3$ (285.2)	1670	1.95 (s, 3H); 2.10–2.87 (m, 2H); 3.77 (s, 3H); 4.00–4.46 (m, 2H); 6.26 (d, 1H, J = 3); 6.46 (dd, 1H, J = 8, 3); 7.45 (d, 1H, J = 8)
2d	100	115–120/0.13	$C_{11}H_{11}BrO_2$ (255.2)	1670	1.97 (s, 3H); 2.30–2.63 (m, 2H); 4.00–4.43 (m, 2H); 6.81–7.60 (m, 4H)
10	100	67–68 (ether/PE)[f]	$C_{12}H_{13}BrO_2$ (269.2)	1680	1.95 (s, 3H); 2.00–2.63 (m, 2H); 2.70–3.15 (m, 2H); 3.80 (s, 3H); 6.48–6.87 (m, 2H); 7.88 (d, 1H, J = 9)
6a	100	125–130/0.13	$C_{12}H_{13}BrO_2$ (269.2)	1675	1.65–2.41 (m, 4H); 2.66–3.13 (m, 2H); 3.76 (s, 3H); 4.66 (t, 1H, J = 5); 6.42–6.81 (m, 2H); 7.45 (d, 1H, J = 8.5)
6b	70	66–67 (ether/PE)[f]	$C_{11}H_{11}BrO_3$ (271.2)	1660	2.28–2.98 (m, 2H); 3.82 (s, 3H); 4.03–4.55 (m, 2H); 4.94 (t, 1H, J = 7); 6.58 (dd, 2H, J = 10, 2.5); 7.68 (d, 1H, J = 9)[d]
6c	81	125–130°/0.13	$C_{10}H_9BrO_2$ (241.2)	1675	2.20–3.30 (m, 2H); 4.03–4.40 (m, 2H); 4.78 (t, 1H, J = 7); 6.75–7.70 (m, 4H)

[a] Uncorrected, determined on a sulfuric acid bath.
[b] Bath temperature.
[c] Satisfactory microanalyses obtained: C ±0.24, H ±0.06.
[d] Measured in $CDCl_3$.
[e] 200 MHz spectrum.
[f] PE = Petroleum ether.

Table 2. Ring Contraction of the Bromo Ketones **2a–d** and the Bromo Acetals **7a–c** to the Esters **3a–d** and **8a–c**, and the Corresponding Acids **4a–d** and **9a–c** Respectively

Bromo-ketone/Acetal	Reaction Time (h)	Products	Yield (%)[a]	m.p. (°C)[b] or b.p. (°C)/mbar[c]	Molecular Formula[d]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
2a	17[e]	**3a**	61	135–140/0.1	$C_{14}H_{18}O_3$ (234.3)	1720	1.50 (s, 3H); 1.63–2.37 (m, 4H); 2.57–2.87 (m, 2H); 3.60 (s, 3H); 3.70 (s, 3H); 6.47–6.76 (m, 2H); 7.07 (d, 1H, J = 8)
		4a	59	106–107 (ether/PE)	$C_{13}H_{16}O_3$ (220.3)	1710	
2b	32[f]	**3b**	91	120–125/0.1		1725	1.45 (s, 3H); 1.66–2.37 (m, 4H); 2.70 (bt, 2H, J = 6); 3.51 (s, 3H); 6.80–7.26 (m, 4H)[g]
		4b	90	114–115 (ether/PE)	$C_{12}H_{14}O_2$ (190.2)	1710	
2c	32[e]	**3c**	44	140–145/0.1	$C_{13}H_{16}O_4$ (236.3)	1720	1.48 (s, 3H); 1.61–1.90 (m, 1H); 2.30–2.56 (m, 1H); 3.58 (s, 3H); 3.65 (s, 3H); 3.95–4.18 (m, 2H); 6.20–6.43 (m, 2H); 7.05 (d, 1H, J = 8)
2d	44[f]	**3d**	22	135–140/0.1	$C_{12}H_{14}O_3$ (206.2)	1720	1.57 (s, 3H); 1.68–2.00 (m, 1H); 2.16–2.64 (m, 1H); 3.65 (s, 3H); 4.00–4.40 (m, 2H); 6.74–7.40 (m, 4H)[h]
		4d	19	89–90 (ether/PE)	$C_{11}H_{12}O_3$ (192.2)	1710	
7a	7	**8a**	83	125–130/0.1	$C_{13}H_{16}O_3$ (220.3)	1725	1.50–2.10 (m, 4H); 2.50–2.86 (m, 2H); 3.43–3.75 (m, 1H); 3.60 (s, 3H); 3.66 (s, 3H); 6.40–6.65 (m, 2H); 7.95 (d, 1H, J = 9)[g]
		9a	69	83–84 (ether/PE)	$C_{12}H_{14}O_3$ (206.2)	1710	
7b	7	**8b**	59	140–150/0.1	$C_{12}H_{14}O_4$ (222.2)	1725	1.88–2.48 (m, 2H); 3.68 (s, 3H); 3.72 (s, 3H); 3.68–3.88 (m, 1H); 4.16–4.32 (m, 2H); 6.39 (d, 1H, J = 3); 6.50 (dd, 1H, J = 8 and 3); 7.12 (d, 1H, J = 8)[h]
		9b	68	67–69 (ether/PE)	$C_{11}H_{12}O_4$ (208.2)	1710	
7c	16	**8c**	24	110–115/0.1	$C_{11}H_{12}O_3$ (192.2)	1720	1.80–2.40 (m, 2H); 3.47–3.73 (m, 1H); 3.63 (s, 3H); 4.00–4.25 (m, 2H); 6.50–7.17 (m, 4H)
		9c	24	61–63 (ether/PE)	$C_{10}H_{10}O_3$ (178.2)	1710	

[a] Based on the bromoketones used.
[b] Uncorrected, determined on a sulfuric acid bath.
[c] Bath temperature.
[d] Satisfactory microanalyses obtained: C ±0.17, H ±0.27.
[e] After 5 h, the reaction mixture was worked up and the residue was again heated with fresh Zinc Chloride in methanol.
[f] After 20 h, the reaction mixture was worked up and the residue was again heated with fresh Zinc Chloride in methanol.
[g] Measured in CCl_4.
[h] 100 MHz spectrum.

of bromine (0.416 g, 2.6 mmol) in dry ether (20 mL). Each drop of the bromine solution is added after decolorization of the preceding one. After complete addition, the resulting mixture is stirred for 1 h at the above temperature, and then at room temperature (30 °C) for a further period of 1 h. The mixture is then diluted with cold water (100 mL), and the product is extracted with ether (3 × 50 mL). Processing of the organic extract as above gives the bromoketone **6b** as a solid and this is purified by crystallization.

The other bromoketones **6a, c**, prepared by this procedure, are isolated as viscous oil and these are purified through vacuum distillation. All these bromoketones are characterized by their spectral data (Table 1).

Ring Contraction of the Bromo Ketones (2a–d) and (6a–c): 1-Methyl-1-methoxycarbonyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (3a), and the Corresponding Carboxylic acid (4a); Typical Procedure:

Anhydrous zinc chloride (2.4 g, 0.02 mol) is added at room temperature under nitrogen and with stirring to methanol (10 mL). The resulting solution is heated at 115 °C and a solution of the crude α-bromo ketone 2a, (0.5 g, 2 mmol) in methanol (2.5 mL) is added. The mixture is kept under nitrogen and with stirring at 115 °C for 5 h. It is cooled to room temperature, poured into water (150 mL), and extracted with a mixture of ether/CH_2Cl_2 (3 × 40 mL). The combined organic extract is washed with water (2 × 40 mL) and dried (Na_2SO_4). Evaporation of the solvent gives a residue as a mixture of the ester **3a** and the unchanged bromoketone **2a**. This mixture is again treated with zinc chloride as above for 12 h for completion of the reaction. Usual work-up as above furnishes mainly the ester **3a**, (0.43 g) contaminated with a small amount of **2a**. To a solution of this product (0.43 g) in dry DMSO (15 mL) is added dry powdered *t*-BuOK (1.5 g) and the resulting mixture is stirred at 65–70 °C for 1.5 h. It is cooled, poured into water (150 mL), and the neutral material, if any, is extracted with ether/CH_2Cl_2 (2 × 25 mL). The aqueous alkaline solution is acidified with dilute HCl and the separated acid is extracted with ether/CH_2Cl_2 (3 × 40 mL). The combined extract is washed with water (2 × 30 mL) and dried (Na_2SO_4). Evaporation of the solvent gives an acid; yield: 0.36 g (93%), which on esterification with diazomethane furnishes the pure ester **3a**; yield: 0.25 g (61%), b.p. 135–140 °C (bath)/0.13 mbar (Table 2).

Hydrolysis of the above ester **3a**, (0.25 g) with *t*-BuOK in DMSO as above gives the carboxylic acid **4a** (0.23 g, quantitative); m.p. 106–107 °C (ether/PE).

1-Carboxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (9a) from the Acetal (7a); Typical Procedure:

A mixture of the crude α-bromo ketone **6a**, (0.19 g, 0.7 mmol), trimethyl orthoformate (0.15 mL, 1.4 mmol), methanol (1 mL) and *p*-toluenesulfonic acid (0.005 g) is stirred at 40 °C for 10 h under nitrogen. The reaction mixture is cooled, poured into saturated aqueous Na_2CO_3 (50 mL), and extracted with ether (3 × 20 mL). Work-up of the extract as given in the literature[3] furnishes the crude α-bromo acetal **7a**; yield: 0.2 g (90%) showing no IR band in the carbonyl region.

A mixture of the above crude acetal (0.2 g, 0.63 mmol), sodium acetate (0.07 g) and ethylene glycol (2 mL) is heated at 125 °C for 7 h according to the reported procedure.[11] Work-up[11] of the reaction mixture provides the ester **8a** (0.2 g). This ester (0.2 g) is directly hydrolysed by heating under reflux for 3 h with a 5% solution of methanolic KOH (5 mL). After removal of methanol, the residue is diluted with water, and the neutral material, if any, is extracted with ether (2 × 25 mL). The aqueous alkaline solution is acidified with dil. HCl and the separated acid is extracted with ether (3 × 25 mL). The combined ether extract is washed with water (2 × 25 mL) and dried (Na_2SO_4). Removal of the solvent affords the crystalline acid **9a**; yield: 0.12 g (69%); m.p. 83–84 °C (ether/PE) (Lit.[22] m.p. 89 °C). This acid on esterification with diazomethane gives the methyl ester **8a** in quantitative yield.

In the rearrangement of the α-bromo acetals **7b–c**, the crude acids first isolated are further purified by esterification with diazomethane to furnish the pure esters **8b–c**. Usual alkaline hydrolysis of these esters affords the crystalline acids **9b–c** in practically quantitative yields.

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