Ring Opening of Aryl Cyclopropyl Ketones to 1-Acyl-1,1,3-tribromopropanes and Their Cyclization to 2-Aryl-3,3-dibromo-2-methoxy and -2-cyanotetrahydrofurans

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The reaction of aryl cyclopropyl ketones **1** with excess bromine gave 1-acyl-1,1,3-tribromopropanes **2**, which were cyclized to 2-aryl-3,3-dibromo-2-methoxytetrahydrofurans **3** on treatment with alkaline in aqueous methanol. 2-Aryl-3,3-dibromo-2-cyanotetrahydrofurans **5** were obtained by the reactions of **2** with sodium cyanide.

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The ring opening reactions of activated cyclopropanes by nucleophiles are now of interest because of the usefulness in organic synthesis (1). Cyclopropyl ketones belong to such reactive species and are cleaved by some nucleophiles (2). In the course of our work on the heterocyclic synthesis using cyclopropane derivatives (3) we treated aryl cyclopropyl ketones **1** with bromine and obtained 1-acyl-1,1,3-tribromopropanes **2** in good yields. Although **2** seems to be a useful starting material for heterocycles, its preparation and reaction have been scarcely described (4) in contrast to the convenient transformation of the related 1-benzoyl-1,3-dibromopropane into 1-(*t*-butyl)-2-benzoylazetidine (5). We report here the preparation of **2** and their cyclization to tetrahydrofurans **3** and **5** (6).

Treatment of **1a-e** (7) with excess bromine in chloroform at room temperature for 5-18 hours afforded **2a-e** in 48-83% yields (Scheme 1). The product **2a** was identical with the reported compound (4), and the structures of other products **2b-e** were revealed on the basis of the microanalysis and the spectral data (Table 1 and 2). Use of less than 5 equivalents of bromine sometimes resulted in the formation of the mixture of **2** and 1-acyl-1,3-dibromopropanes (5), and the most reliable method of exclusive ring opening to **2** was addition of 10 equivalents of bromine.

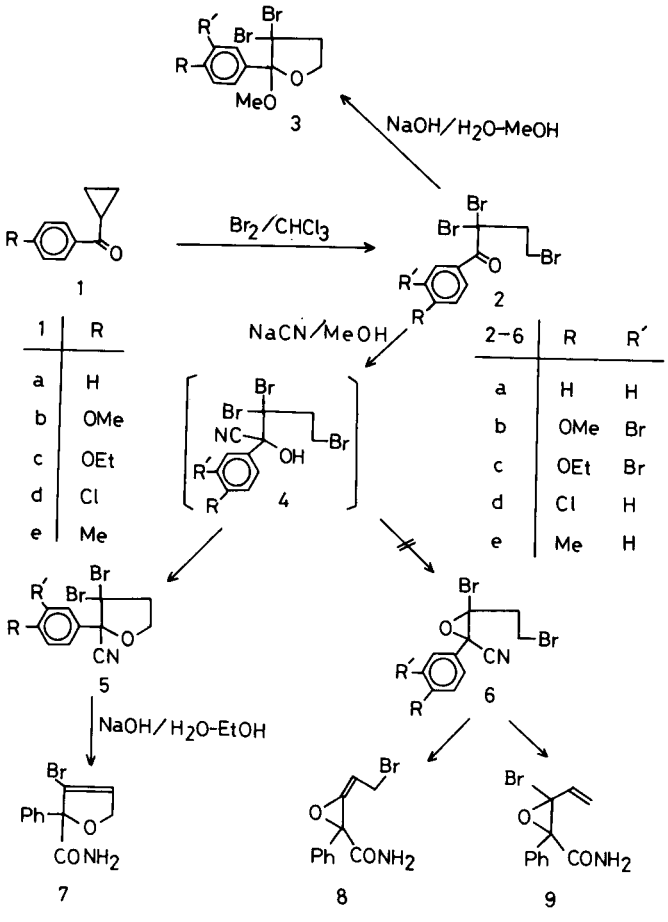
Cyclization of **2a-d** to 2-aryl-3,3-dibromo-2-methoxytetrahydrofurans (**3a-d**) was achieved readily in 35-75% yields on treatment with sodium hydroxide in aqueous methanol at room temperature. All the products **3a-d** were devoid of C=O absorptions in the ir spectra and showed singlet peaks due to methoxy groups at δ 3.1 ppm as well as two sets of multiplet of furan ring protons in the nmr spectra. The product **3a** was identical with the reported compound (4). In the cases of **2b** and **c** bromination occurred at the 3'-position of the aromatic rings as apparent from the nmr spectra and consideration of the orientation effect of alkoxy and carbonyl groups. The methyl deriva-

Table 1

Physical and IR Data of Compounds **2**, **3**, **5** and **7**

Compound	Yield %	Mp °C		Formula	Calcd. C	Calcd. H	Found C	Found H	IR (potassium bromide cm^{-1})			
2a	83	70-71							1660	1570	1430	1230
2b	57	100-102	(Methanol)	$C_{11}H_{10}Br_4O_2$	26.75	2.04	26.73	2.14	1655	1580	1260	1205
2c	79	80-82	(Methanol)	$C_{12}H_{12}Br_4O_2$	28.38	2.38	28.21	2.44	1675	1585	1265	1230
2d	48	61-63	(Methanol)	$C_{10}H_8Br_3ClO$	28.64	1.92	28.87	1.98	1655	1575	1240	1080
2e	51	60-62	(Methanol)	$C_{11}H_{11}Br_3O$	33.12	2.78	33.46	2.81	1665	1600	1240	1180
3a	60	68-70	(Cyclohexane)						1445	1270	1075	1040
3b	65	122-123	(Cyclohexane)	$C_{12}H_{13}Br_3O_3$	32.39	2.94	32.63	2.96	1600	1500	1255	1070
3c	75	68-72	(Cyclohexane	$C_{13}H_{15}Br_3O_3$	34.02	3.29	34.37	3.33	1590	1490	1260	1040
3d	35	88-90	(Cyclohexane)	$C_{11}H_{11}Br_2ClO_2$	35.66	2.99	35.85	3.05	1590	1485	1265	1040
5a	85	82-84	(Methanol)	$C_{10}H_9Br_2NO$	39.91	2.74	39.78	2.63	1495	1440	1240	1050
5b	97	130-132	(Methanol)	$C_{12}H_{10}Br_3NO_2$	32.76	2.29	32.69	2.32	1590	1495	1255	1050
5c	84	117-119	(Methanol)	$C_{13}H_{12}Br_3NO_2$	34.38	2.66	34.15	2.47	1590	1495	1250	1045
5d	83	104-107	(Methanol)	$C_{11}H_8Br_2ClO$	36.14	2.21	36.34	2.35	1590	1480	1435	1050
5e	75	86-89	(Methanol)	$C_{12}H_{11}Br_2NO$	41.77	3.21	41.57	3.36	1605	1510	1435	1060
7	32	128-129	(Chloroform-cyclohexane)	$C_{11}H_{10}BrNO_2$	49.27	3.76	49.43	3.64	3450	3150	3050	1680
									1615	1385	1060	

Scheme 1



tive **2e**, however, gave an unidentified oil somewhat different from **3a-d**.

2-Aryl-3,3-dibromo-2-cyanotetrahydrofurans **5a-e** were prepared in 75-97% yields via cyanohydrin intermediate **4**. Thus, **2** reacted easily with sodium cyanide in methanol at room temperature. The mass spectrum (M^+ m/e 331) and the microanalysis of the product from **2a** were in accord with both the structures **5a** and **6a**. The nmr spectra showed the presence of two adjacent methylene groups as A_2B_2 multiplets analogous to those of **2** and **3**. The cyano group, however, was not observed in the ir spectra probably due to the electron withdrawing bromine and oxygen atoms (8). Although the spectral data could not distinguish clearly between tetrahydrofuran **5a** and oxirane **6a** as the correct structure, we preferred **5a** to **6a** ultimately according to the experiment described below. The product from **2a** was treated with potassium hydroxide in refluxing aqueous ethanol. The ir spectrum of this reaction product exhibited C=O and NH absorptions at 3450, 3150, and 1680 cm^{-1}. Two singlets at δ 4.75 (1H), and 6.29 (2H) ppm in the nmr spectrum were ascribable to the olefinic and methylenic protons of the furan ring of 3-bromo-2-phenyl-2,5-dihydrofuran-2-carboxamide (**7**), respectively, rather than to those of the alternative two structures **8** and **9** derived from oxirane **6a**. The structure of **5a** was thus established.

Table 2

NMR Data of Compounds **2**, **3**, **5**, and **7** (Deuteriochloroform ppm)

2a	3.06-3.47 (m, 2H), 3.52-3.83 (m, 2H), 7.29-8.41 (m, 5H)
2b	3.05-3.49 (m, 2H), 3.53-3.83 (m, 2H), 3.95 (s, 3H), 6.90 (d, 1H, J = 9 Hz), 8.36 (dd, J = 2 and 9 Hz), 8.52 (d, 1H, J = 2 Hz)
2c	1.48 (t, 3H, J = 7 Hz), 3.02-3.32 (m, 2H), 3.51-3.82 (m, 2H), 4.18 (q, 2H, J = 7 Hz), 6.86 (d, 1H, J = 9 Hz), 8.31 (dd, 1H, J = 2 and 9 Hz), 8.52 (d, 1H, J = 2 Hz)
2d	3.04-3.32 (m, 2H), 3.54-3.82 (m, 2H), 7.19 (d, 2H, J = 9 Hz), 8.26 (d, 2H, J = 9 Hz)
2e	2.43 (s, 3H), 3.04-3.25 (m, 2H), 3.53-3.84 (m, 2H), 7.24 (d, 2H, J = 8 Hz), 8.21 (d, 2H, J = 8 Hz)
3a	2.83-3.72 (m, 2H), 3.10 (s, 3H), 3.90-4.52 (m, 2H), 7.28-7.83 (m, 5H)
3b	2.65-3.59 (m, 2H), 3.09 (s, 3H), 3.65-4.50 (m, 2H), 3.92 (s, 3H), 6.91 (d, 1H, J = 9 Hz), 7.65 (dd, 1H, J = 2 and 9 Hz), 7.90 (d, 1H, J = 2 Hz)
3c	1.50 (t, 3H, J = 7 Hz), 2.81-3.68 (m, 2H), 3.09 (s, 3H), 3.85-4.52 (m, 2H), 6.89 (d, 1H, J = 9 Hz), 7.56 (dd, 1H, J = 2 and 9 Hz), 7.88 (d, 1H, J = 2 Hz)
3d	2.77-3.71 (m, 2H), 3.11 (s, 3H), 3.89-4.52 (m, 2H), 7.37 (d, 2H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz)
5a	3.13-3.81 (m, 2H), 4.27-4.53 (m, 2H), 7.40-7.85 (m, 5H)
5b	3.23-3.54 (m, 2H), 3.93 (s, 3H), 4.23-4.54 (m, 2H), 6.92 (d, 1H, J = 9 Hz), 7.70 (dd, 1H, J = 2 and 9 Hz), 7.91 (d, 1H, J = 2 Hz)
5c	1.46 (t, 3H, J = 7 Hz), 3.19-3.50 (m, 2H), 3.92-4.55 (m, 4H), 6.84 (d, 1H, J = 9 Hz), 7.55-7.85 (m, 2H)
5d	3.14-3.77 (m, 2H), 4.26-4.51 (m, 2H), 7.34 (d, 2H, J = 8 Hz), 7.65 (d, 2H, J = 8 Hz)
5e	2.37 (s, 3H), 3.21-3.78 (m, 2H), 4.21-4.57 (m, 2H), 7.18 (d, 2H, J = 8 Hz), 7.61 (d, 2H, J = 8 Hz)
7	4.75 (s, 2H), 6.29 (s, 1H), 6.46 (broad s, 1H), 6.79 (broad s, 1H), 7.27-7.65 (m, 5H)

EXPERIMENTAL

Infrared spectra were recorded on a Hitachi model A 102 spectrometer and the nmr spectra obtained on a JEOL model JNM-PMX 60 spectrometer. Microanalyses were carried out on a Shimadzu model UM-3B apparatus.

1-Acyl-1,1,3-tribromopropanes (**2a-e**).

A General Procedure.

To a stirred solution of bromine (100 mmoles) in chloroform (50 ml) was added **1** (10 mmoles) and the mixture was stirred for 5-18 hours at

room temperature. After removal of the solvent *in vacuo* the residue was washed with a small amount of methanol and recrystallized to give white crystals.

2-Aryl-3,3-dibromo-2-methoxytetrahydrofurans (**3a-d**).

A General Procedure.

A mixture of **2** (1.0 mmole) and 25 ml of 2*M* sodium hydroxide in 50% aqueous methanol was stirred for 6-20 hours at room temperature. The precipitates were collected by filtration and recrystallized to give **3** as white crystals.

2-Aryl-3,3-dibromo-2-cyanotetrahydrofurans (**5a-e**).

A General Procedure.

A mixture of **2** (5.0 mmoles), sodium cyanide (5.0 mmoles) and methanol (25 ml) was stirred for 4 hours at room temperature. After removal of the resulting precipitates by filtration the filtrate was evaporated to dryness and the residue was recrystallized to give **5** as white crystals.

3-Bromo-2-phenyl-2,5-dihydrofuran-2-carboxamide (**7**).

A mixture of **5a** (990 mg, 3.0 mmoles) and 50 ml of 0.1 *M* potassium hydroxide in 90% aqueous ethanol was refluxed for 4 hours. After removal of the solvent water was added to the residue, and the mixture was extracted with ether. The residue obtained upon evaporation of ether was chromatographed on a silica gel. Elution with chloroform gave **7** as white crystals (260 mg, 32%).

REFERENCES AND NOTES

(1) S. Danishefsky, *Acc. Chem. Res.*, **12**, 66 (1979); D. Tunemoto and K. Kondo, *J. Synth. Org. Chem. Japan*, **35**, 1070 (1977).

(2) R. D. Miller and D. R. Mckean, *J. Org. Chem.*, **46**, 2412 (1981) and references cited therein.

(3) M. Takahashi, S. Watanabe, and T. Kasai, *Heterocycles*, **14**, 1921 (1980); M. Takahashi and S. Watanabe, *Chem. Letters*, 1213 (1979); M. Takahashi, N. Inaba, H. Kirihara, and S. Watanabe, *Bull. Chem. Soc. Japan*, **51**, 3312 (1978).

(4) A. Jovtscheff and S. L. Spassov, *Monats. Chem.*, **98**, 2326 (1967).

(5) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, **6**, 439 (1969).

(6) A review for tetrahydrofurans with manipulable functionality; J. E. Semple and M. M. Joullié, *Heterocycles*, **14**, 1825 (1980).

(7) W. J. Close, *J. Am. Chem. Soc.*, **79**, 1455 (1957).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd Ed, John Wiley and Sons, Inc., New York, NY, 1958, p 284; R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectroscopic Identification of Organic Compounds", 3rd Ed, John Wiley and Sons, Inc., New York, NY, 1974, p 105.