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SELECTIVE CLEAVAGE OF UNSYMMETRICAL 2,2-SPIRO-1,3-DIOXOLANES I

KETALIZATION OF 5-BROMO-3-METHOXYCARBONYL-4,5,6,7-TETRAHYDROBENZO[b]FURAN-4-ONE AND ITS ANALOGS

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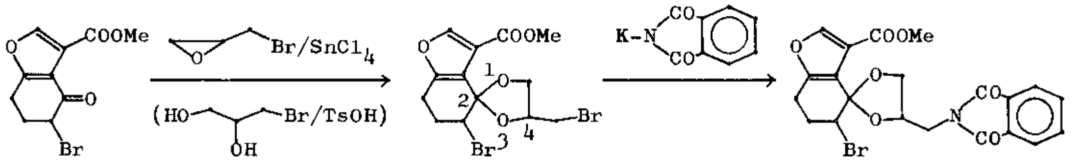
Abstract Reaction of 2-bromocyclohexanones fused with an aromatic or heteroaromatic ring (1-4) with epibromohydrin or 3-bromo-1,2-propanediol gave two (a and b) or four (a, b, c, and d) isomers of the corresponding 2,2-spiro-4-bromomethyl-1,3-dioxolanes 5-8, respectively. The stereochemistry of the reactions is discussed.

The stereochemistry of 1,3-dioxolane has recently received much attention. Yandovskii and Temnikova[1] reported that the reaction of benzaldehyde with p-substituted β,β-dimethylstyrene oxide in the presence of stannic chloride gave a mixture of cis and trans isomers of 4,4-dimethyl-2-phenyl-5-(p-substituted phenyl)-1,3-dioxolanes. Tishchenko et al[2] reported that the reaction of methyl thiocyanate in dichloromethane with epichlorohydrin in the presence of boron trifluoride afforded 5-chloromethyl-2-methylthio-2-oxazoline in 62 % yield. This paper deals with the reaction of 2-bromocyclohexanone fused with an aromatic or heteroaromatic ring (1-4) with dl-epibromohydrin, dl-3-bromo-1,2-propanediol, or glycerol in the presence of stannic chloride or p-toluenesulfonic acid, and discusses the stereochemistry of the products.

dl-5-Bromo-3-methoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]furan-4-one 1[5] (3.2 mM) in 1,2-dichloroethane (4 ml) was ketalized with dl-epibromohydrin (6.4 mM) in the presence of stannic chloride (0.32 mM) at 26-28°C for 2 h and gave a mixture of stereoisomeric 2,2-spiro-4-bromomethyl-1,3-dioxolanes 5 (5'-bromo-4-bromomethyl-6',7'-dihydro-3'-methoxycarbonyl-spiro[1,3-dioxolane-2,4'-(5'H)-benzo-[b]furans]), which was fractionated by column chromatography into two crystalline compounds, 5a and 5b, in 16 and 18 % yields, respectively (Scheme 1). On the other hand, azeotropic distillation of 1 (1.5 mM) in petroleum ether (20 ml) with

Scheme 1



1 5-a,b (5-a,b,c,d) 10-a,b,c, or d

Table 1 Preparation and Modification of Dioxolanes

Starting material	Reagent (Conditions)	Dioxolane	Yield (%) a	b	c	d	Total yield (%)
1[5]	Epibromohydrin/$SnCl_4$ (in $(CH_2Cl)_2$, rt/2 h)	5[9]	16	18	–	–	34
1	Bromopropanediol/TsOH (in petr.ether, reflux/17 h)	5	5	10	6	11	32
2[6]	Epibromohydrin/$SnCl_4$ (in CH_2Cl_2, rt/2.5 h)	6	46	47	–	–	93
2	Bromopropanediol/TsOH (in benzene, reflux/5.5 h)	6	20	27	18	28	93
3[7]	Epibromohydrin/$SnCl_4$ (in $(CH_2Cl)_2$, rt/2 h)	7	41	45	–	–	86
4[8]	Epibromohydrin/$SnCl_4$ (in $(CH_2Cl)_2$, rt/24 h)	8	27	29	–	–	56
4	Bromopropanediol/TsOH (in benzene, reflux/2 d)	8	20	28	24	27	99
2[6]	Glycerol/TsOH (in benzene, reflux/7 d)	9[10]	15	18	15	20	68
9c[10]	TsCl/Py (rt/3.5 h)	11c[12]	–	–	85	–	85
6a,b	i-PrNH_2 (reflux/4 d)	12a,b[13]	43	44	–	–	87
11c[12]	" (reflux/5 d)	12c[12]	–	–	89	–	89
7a,b	" (reflux/6 d)	13a,b[14]	42	45	–	–	87
8	" (reflux/5 d)	14[15]	18	25	21	24	88
12a,c[13]	BsCl/Et_3N (rt/24 h)	15a,c[16]	45	–	41	–	86
14a,b,c	" (rt/5 h)	16a,b,c[17]	26	36	31	–	93

dl-3-bromo-1,2-propanediol (15 mM) in the presence of p-toluenesulfonic acid (0.05 mM) for 17 h gave 5a (5 %) and 5b (10 %) together with two other crystalline compounds, 5c (6 %) and 5d (11 %)[9] (Table 1). These four compounds were found to be stereoisomers of the possible configurations of the bromine atom at position 5', the unsymmetrical 1,3-dioxolane ring, and the bromomethyl group at position 4, according to elemental analysis data and ir, nmr, and mass spectra[9]. An isomerization of the compounds 5a in dichloromethane (reflux 24 h) in the presence of anhydrous p-toluenesulfonic acid (0.033 M equiv.) gave the isomer 5d (37 %) with recovery of 5a (59 %) by neutralization with triethylamine, while another isomerization of 5b afforded 5c (25 %) with recovery of 5b (71 %) under the same conditions. The structures of 5a and 5b were conclusively determined by X-ray analysis using the corresponding phthalimide derivatives, 10a and 10b[11], as depicted in Scheme 2[4]. In 10a, the bonds of C(5')-Br and C(2)-O(3) are trans and the phthalimidomethyl group at position 4 has an endo configuration (endo means a configuration near the furan plane), while in 10b, those of C(5')-Br and C(2)-O(3) are also trans and the phthalimidomethyl group at position 4 has an exo configuration. Accordingly, the structures of two other phthalimidomethyl compounds, 10c and 10d[11], are considered to be cis-endo and cis-exo configurations, respectively (Scheme 2).

Scheme 2

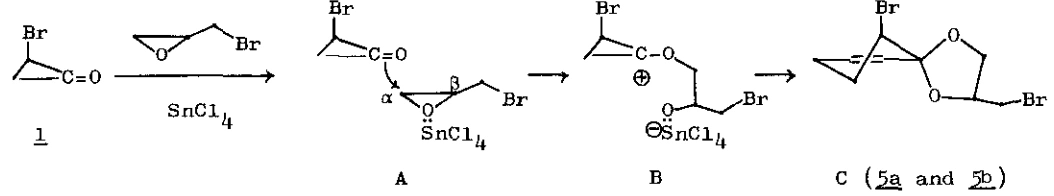
10a: trans-endo   10b: trans-exo

10c: cis-endo   10d: cis-exo

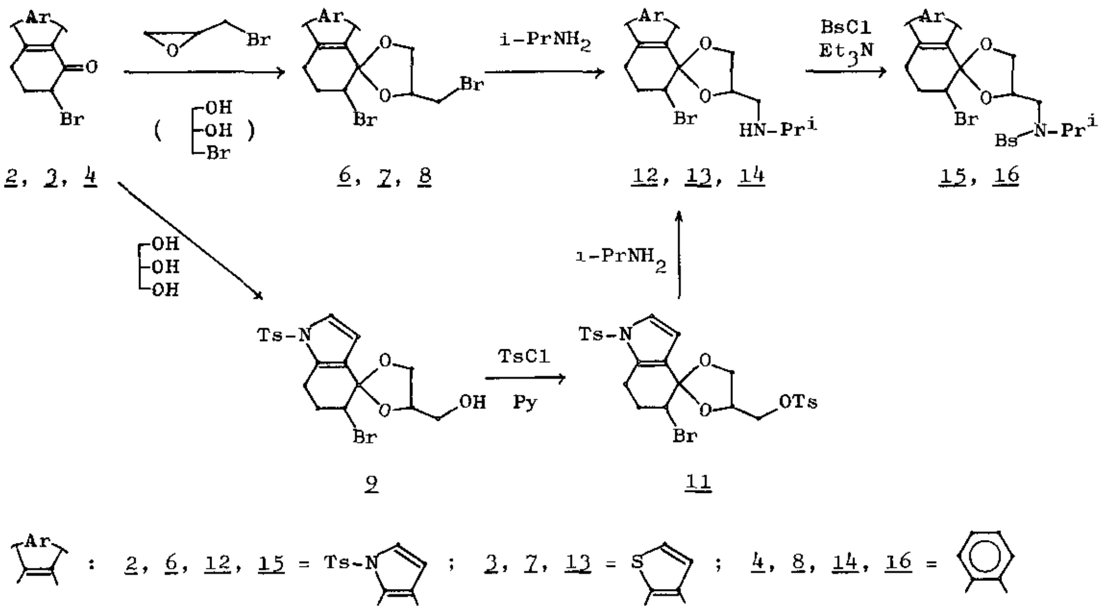
It is known that the epoxide ring of epichlorohydrin is opened at the α-carbon by the attack of a nucleophile in the presence of boron trifluoride[2] or of an acid with or without a base[3]. Activation of dl-epibromohydrin with stannic chloride would result in a δ+ charge distribution mainly at the epoxide's α-carbon. The carbonyl oxygen of 1 could approach the α-carbon charged with δ+ in the least hindered direction (Phase A, Scheme 3). In the following Phase B, the attraction between the carbenium ion (C $\oplus$) and the complex-anion (O:$SnCl_4$$\ominus$) would afford those final products, trans-dioxolanes 5a and 5b (Phase C). On the other hand, in the ketalization of the furanone 1 with dl-3-bromo-1,2-propanediol, four possible stereoisomers of 1,3-dioxolanes (5a, 5b, 5c, and 5d) were isolated by column chromatography. This result seems reasonable since the ketalization could run first with a predominant attack by the primary alcoholic hydroxy group to the carbonyl carbon followed by cyclization with water elimination.

Similar results were obtained with the ketalization and modification of 5-bromo-1-p-toluenesulfonyl-4,5,6,7-tetrahydroindol-4-one 2[6], 5-bromo-4,5,6,7-tetrahydrobenzo[b]thiophen-4-one 3[7], and 2-bromo-1,2,3,4-tetrahydronaphthalen-1-one 4[8] with dl-epibromohydrin, dl-3-bromo-1,2-propanediol, or glycerol and gave the corresponding 2,2-spiro-4-(substituted methyl)-1,3-dioxolanes 6-9 (Scheme 4 and Table 1).

Scheme 3



Scheme 4



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REFERENCES AND NOTES

1. V. N. Yandovskii and T. I. Temnikova, J. Org. Chem., (U.S.S.R.), 1968, 4, 1695.

2. I. G. Tishchenko, O. N. Bubel, and O. A. Grinkevich, U.S.S.R. Inventor's Certificate, 70.7196 (1980).

3. E. L. Eliel, "Steric Effects in Organic Chemistry" edited by M. S. Newman, John Wiley & Sons Inc., New York, N.Y., pp. 106-108 (1956).

4. M. Sakai, H. Nakai, and M. Shiro, Cryst. Struct. Comm., in press.

5. The furanone 1 was prepared from 4-oxo-4,5,6,7-tetrahydrobenzo[b]furan-3-carboxylic acid (H. Stetter and R. Lauterbach, Ann. Chem., 1962, 655, 20) by methylation (CH_2N_2, 96 % yield) followed by bromination ($PyHBr_3$, 45 %), mp 80-81°C (decomposition). ir ν_{max}^{KBr} cm^{-1}: 1705, 1688. ^{1}H-nmr ($CDCl_3$) δ (Hz): 2.52 (2H, ddd, J=8, 4.5, 4), 2.91 (dt, J=17.5, 8), 3.89 (s), 4.59 (1H, t, J=4), 7.99 (s).

6. The bromoindolone 2 (colorless crystals, mp 150-152°C) was prepared from 4,5,6,7-tetrahydroindol-4-one according to the method of W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, J. Org. Chem., 1971, 36, 1232.

7. D. T. Drewry and R. M. Scrowton, J. Chem. Soc., (C), 1969, 2750.

8. K. G. Rutherford and C. L. Stevens, J. Am. Chem. Soc., 1955, 77, 3278.

9.

Cpd	mp (°C)	ir ν_{max}^{KBr} cm^{-1}	^{1}H-nmr ($CDCl_3$) δ (Hz) -COOMe	C(4)-H	C(2')-H	ms m/z (M^+)
5a	123-4	1735	3.79(s)	4.54(dddd, J=6.5, 6.5, 6.5, 6.5)	7.86(s)	412, 410, 408
5b	112-3	1705	3.84(s)	4.82-5.20 (m)	7.96(s)	412, 410, 408
5c	93-4.5	1729	3.78(s)	4.85(dddd, J=7, 7, 7, 7)	7.84(s)	412, 410, 408
5d	102-3.5	1729	3.78(s)	4.87-5.23 (m)	7.83(s)	412, 410, 408

10.

		ir	^{1}H-nmr ($CDCl_3$) δ (Hz)	
Cpd	mp (°C)	ν_{max} cm^{-1}	p-Me	C(3')-H
9c	—	3580 ($CHCl_3$)	2.41 (s)	6.31 (1H, d, J=3.5)
9d	139-40	3530 (KBr)	2.42 (s)	6.31 (1H, d, J=3)

11.

		ir	^{1}H-nmr ($CDCl_3$) δ (Hz)		ms
Cpd	mp (°C)	ν_{max}^{KBr} cm^{-1}	-COOMe	C(4)-H	m/z (M^+)
10a	133.5-4.5	1712, 1732 (sh)	3.73 (s)	4.51-4.92 (m)	477, 475
10b	139-140	1711 (br)	3.72 (s)	4.73-5.08 (m)	477, 475
10c	184-5	1714, 1742	3.79 (s)	4.60-5.04 (m)	477, 475
10d	154-5	1709, 1734 (sh)	3.73 (s)	4.90-5.23 (m)	477, 475

12.

	ir	^{1}H-nmr ($CDCl_3$) δ (Hz)		
Cpd	$\nu_{max}^{CHCl_3}$cm^{-1}	p-Me	C(4)-H	C(3')-H
11c	1179, 1374	2.41 (s), 2.44 (s)	4.43-4.73 (m)	6.22 (d, J=3)
11d	1180, 1376	2.42 (s), 2.45 (s)	4.46-4.79 (m)	6.23 (d, J=3)

13.

	^{1}H-nmr ($CDCl_3$) δ (Hz)			
Cpd	-CHMe$_2$	p-Me	1H of C(5)-H$_2$	C(3')-H
12a	1.07 (d, J=6.5)	2.43 (s)	3.93 (dd, J=7.5, 7.5)	6.31 (d, J=3)
12b	1.06 (d, J=6.5)	2.42 (s)	3.92 (dd, J=7.5, 7.5)	6.35 (d, J=3.5)
12c	1.07 (d, J=6.5)	2.43 (s)	3.91 (dd, J=7.5, 7.5)	6.32 (d, J=3)
12d	1.06 (d, J=6.5)	2.42 (s)	3.91 (dd, J=8, 8)	6.35 (d, J=3.5)

14.

	^{1}H-nmr ($CDCl_3$) δ (Hz)			
Cpd	-CHMe$_2$	1H of C(5)-H$_2$	C(3')-H	C(2')-H
13a	1.06 (d, J=6.5)	4.01 (dd, J=7.5, 7.5)	7.04 (d, J=5.5)	7.17 (d, J=5.5)
13b	1.07 (d, J=6.5)	4.00 (dd, J=7.5, 7.5)	7.11 (d, J=5.5)	7.22 (d, J=5.5)

15. 14d: ^{1}H-nmr ($CDCl_3$) δ (Hz): 1.07 (d, J=6), 3.90 (1H, dd, J=7.5, 7.5), 4.30 (1H, dd, J=7.5, 7.5).

16.

Cpd	^{1}H-nmr (CDCl$_3$) δ (Hz) -CH$\underline{\text{Me}}_2$	 p-$\underline{\text{Me}}$	 -C$\underline{\text{H}}_2$-N<
15a	1.01(d, J=7), 1.12(d, J=7)	2.41(s)	3.24(dd, J=6, 15), 3.47(dd, J=5, 15)
15c	0.98(d, J=7), 1.14(d, J=7)	2.41(s)	3.26(dd, J=6, 15), 3.49(dd, J=5, 15)

17.

Cpd	mp (°C)	^{1}H-nmr (CDCl$_3$) δ (Hz) -CH$\underline{\text{Me}}_2$	 -C$\underline{\text{H}}_2$-N<
16a	168.5-9	1.02(d, J=6.5),1.14(d, J=6.5)	3.30(dd, J=6, 15),3.51(dd,J=4.5, 15)
16b	128-9	1.00(d, J=6.5),1.06(d, J=6.5)	3.23(dd, J=5.5, 15),3.46(dd,J=5, 15)
16c	151-2	1.03(d, J=7),1.17(d, J=7)	3.30(dd, J=6, 15), 3.54(dd,J=5.5, 15)
16d	—	1.02(d, J=6.5),1.14(d, J=6.5)	3.37(dd, J=6, 15),3.60(dd,J=5.5, 15)

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