

SELECTIVE CLEAVAGE OF UNSYMMETRICAL 2,2-SPIRO-1,3-DIOXOLANES III¹
 CLEAVAGE OF 4-ISOPROPYLAMINOMETHYL-1,3-DIOXOLANES LINKED WITH
 BENZENE, THIOPHENE, FURAN, OR ISOXAZOLE ON THE C(2)-SPIRO ATOM

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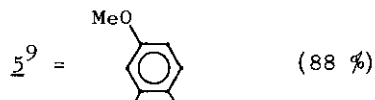
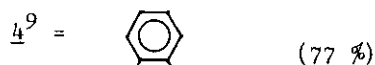
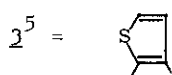
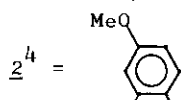
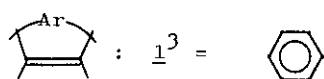
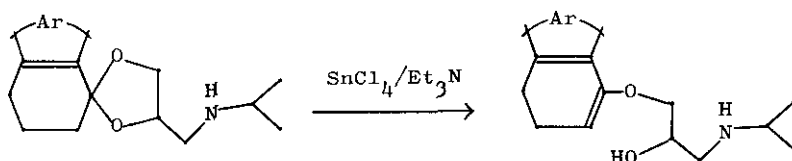
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Abstract The dioxolanes (1-3 and 7-11) were treated with stannic chloride and tertiary amine (triethylamine or tri-n-octylamine) and gave aromatic ethers 12-14, enol-ethers 4-6, and a bromo-enol-ether 15, respectively.

In part II of this series¹, preparation of 4-(2-hydroxy-3-isopropylaminopropoxy)-1-p-toluenesulfonylindole (tosyl-pindolol) from 5'-bromo-6',7'-dihydro-4-isopropylaminomethyl-1'-p-toluenesulfonyl-spiro[1,3-dioxolane-2,4'-(5H)-indole] by selective ring opening of the dioxolane ring and dehydrobromination with stannic chloride and tri-n-octylamine was reported. This report relates to similar reaction of the dioxolanes linked with benzene, thiophene, furan, or isoxazole.

Stannic chloride (1.2 mM) in 1,2-dichloroethane (1.5 ml) was added with stirring dropwise to 1,2-dichloroethane (1.0 ml) solution of the dioxolane 1-3 (1.0 mM) and triethylamine (4 mM) at -17~-20°C for 10 min. The reaction mixture was kept at -17°C for 1 h, made alkaline with 5N sodium hydroxide, and extracted with ethyl acetate. The extract was washed with water, dried with anhydrous sodium sulfate, and concentrated under reduced pressure giving a crystalline residue. Recrystallization afforded pure compounds 4-6 in 77, 88, and 91 % yields, respectively (Scheme 1). The structures of the products were determined to be enol-ethers having a secondary alcohol group from ir and nmr spectra.

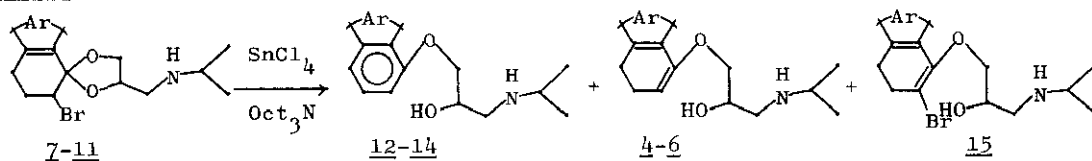
Scheme 1



Similar ring-opening was observed for the bromodioxolanes 7-11 with stannic chloride (3.5 M equiv.) and tri-n-octylamine (5 M equiv.) as shown in Table 1.

Table 1 Reaction of Dioxolanes 7-11 with Stannic Chloride and Tri-n-Octylamine

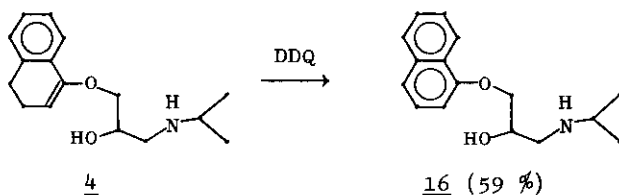
Dioxolane		Yield (%) of ether ⁹			Recovery (%) of dioxolane
		Aromatic	Enol	Bromo-enol	
<u>7</u> ¹		—	47 (<u>4</u>)	—	27
<u>8</u> ⁶		—	15 (<u>5</u>)	24 (<u>15</u>)	—
<u>9</u> ¹		35 (<u>12</u>)	19 (<u>6</u>)	—	—
<u>10</u> ⁷		64 (<u>13</u>)	—	—	23
<u>11</u> ⁸		31 (<u>14</u>)	—	—	43



Although the tetralin-dioxolane 7 gave the enol ether 4 (47 %) with recovery of the starting material 7 (27 %), 6-methoxytetralin-dioxolane 8 afforded the enol ether 5 (15 %) and a bromo-enol ether 15 (24 %). Dehydrogenation of the

enol ether 4 with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) gave the corresponding aromatic ether 16 (propranolol², known as a β -adrenergic blocking agent) (Scheme 2).

Scheme 2



On the other hand, the benzo[b]thiophene-dioxolane 9 gave the aromatic ether 12 (35 %) together with the corresponding enol ether 6 (19 %). Benzo[b]furan-dioxolane 10 or 1,2-benzisoxazole-dioxolane 11 yielded the respective aromatic ether 13 (64 %) or 14 (31 %) with higher recovery percentage of the starting material, 23 % or 43 %. It can be said that the dioxolane 9-11 linked with a five-membered heteroaromatic ring gave the corresponding aromatic ether 12-14 as the main product, while those with benzene 7-8 afforded enol ether 4-5 and bromo-enol ether 15 without yielding any aromatic ether.

Acknowledgement The author thanks Drs. K. Igarashi, M. Fujimoto, and K. Shibata of Shionogi Research Laboratories for their helpful suggestions.

REFERENCES AND NOTES

1. Part I and Part II: M. Sakai, this journal, in press.
2. I. C. I., U.S. Patent 3,337,628 (1967).
3. The tetralin-dioxolane 1 was prepared from tetralone by ketalization (3-bromo-1,2-propanediol/TsOH, 60 %) followed by amination with isopropylamine (69 %) ¹. Pale yellow oil.
4. The 6-methoxytetralin-dioxolane 2 was prepared from 6-methoxytetralone by ketalization (epibromohydrin/SnCl₄, 88 %) followed by amination (i-PrNH₂, 96 %). Colorless oil.
5. The benzo[b]thiophene-dioxolane 3 was similarly prepared from 4,5,6,7-tetrahydrobenzo[b]thiophen-4-one as in 4 in 86 and 95 % yields, respectively. Colorless oil.
6. The 2-bromo-6-methoxytetralin-dioxolane 8 was prepared from 2-bromo-6-methoxy-1-tetralone [T. R. Kasturi and T. Arunachalam, Can. J. Chem., 1968, 46, 3625],

by ketalization (3-bromo-1,2-propanediol/TsOH, 75 %) followed by amination (with isopropylamine, 96 %). Pale yellow oil.

7. The benzo[b]furan-dioxolane 10 was prepared from 5'-bromo-4-bromomethyl-6',7'-dihydro-3'-methoxycarbonyl-spiro[1,3-dioxolane-2,4'-(5'H)-benzo[b]furan]¹ with isopropylamine. Yield of colorless crystalline product: 71 %.
8. The isoxazole dioxolane 11 was prepared from 5-bromo-3-phenyl-4,5,6,7-tetrahydro-1,2-benzisoxazol-4-one (I. Adachi, Y. Hiramatsu, M. Yamamoto, and T. Yamamori: Abstract Papers of the 101st Annual Meeting of the Pharmaceutical Society of Japan, p. 421, in Kumamoto, 1981) by ketalization (3-bromo-1,2-propanediol/TsOH in benzene, 98 %) followed by aminolysis with isopropylamine (67 %). Colorless oil.

9.

Compd.	mp (°C)	IR ν_{max} KBr cm^{-1}	¹ H-nmr (CDCl ₃) δ (Hz)		ms m/z (M ⁺)
			$\begin{array}{c} \text{CH}_2 \\ \\ -\text{O} \end{array}$ - $\begin{array}{c} \text{CH} \\ \\ \text{OH} \end{array}$ - $\begin{array}{c} \text{CH}_2 \\ \\ \text{N} < \end{array}$	$\begin{array}{c} -\text{C}=\text{C}-\text{H} \\ \quad \\ -\text{O} \quad \text{CH}_2- \end{array}$	
<u>4</u>	68-9	3310, 1646	3.72-4.31 (m)	4.96 (dd, J=4.5, 4.5)	261
<u>5</u>	84-5	3280, 1646	3.70-4.18 (m)	4.92 (dd, J=4.5, 4.5)	291
<u>6</u>	75-6	3315, 1637	3.74-4.13 (m)	4.70 (dd, J=4.5, 4.5)	267
<u>12</u>	86.5-7	3290	4.00-4.34 (m)	—	265
<u>13</u>	115.5-6.5	3280, 1743	3.93-4.46 (m)	—	307
<u>14</u>	110-1	3320	3.75-4.13 (m)	—	326
<u>15</u>	76-7	3280, 1642	3.73-4.24 (m)	—	369 371

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