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SELECTIVE CLEAVAGE OF UNSYMMETRICAL 2,2-SPIRO-1,3-DIOXOLANES III[1]

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

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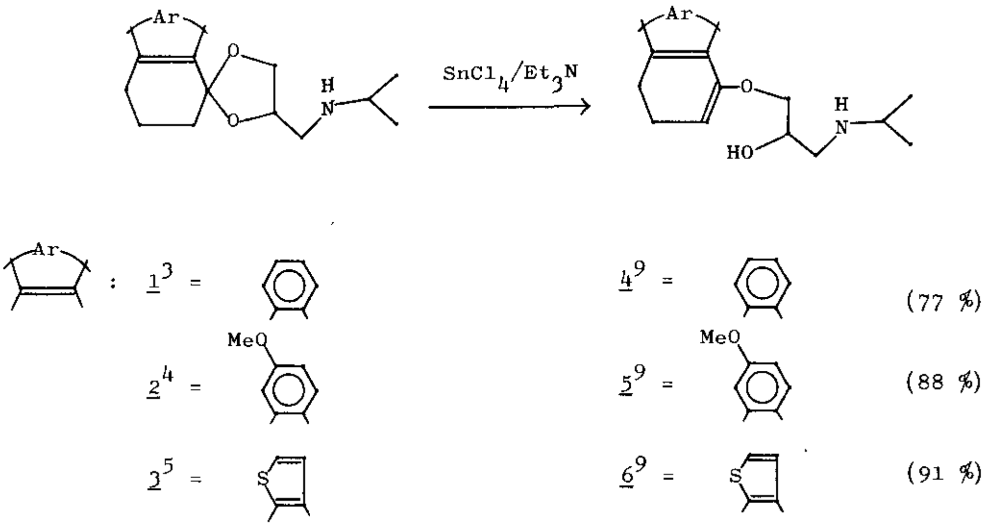
Abstract The dioxolanes (1-3 and 7-11) were treated with stannic chloride and tertiary amine (triethylamine or tri-n-octylamine) and gave aromatic ethers 12-14, enol-ethers 4-6, and a bromo-enol-ether 15, respectively.

In part II of this series[1], 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.

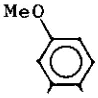
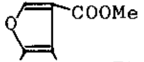
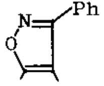
Stannic chloride (1.2 mM) in 1,2-dichloroethane (1.5 ml) was added with stirring dropwise to 1,2-dichloroethane (1.0 ml) solution of the dioxolane 1-3 (1.0 mM) and triethylamine (4 mM) at -17~-20°C for 10 min. The reaction mixture was kept at -17°C for 1 h, made alkaline with 5N sodium hydroxide, and 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.

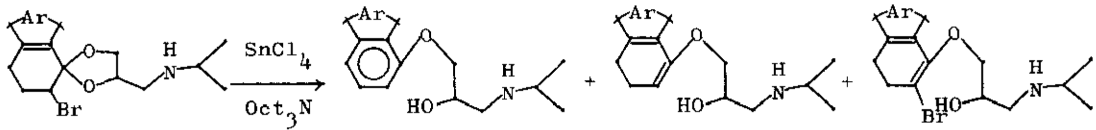
Scheme 1



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.

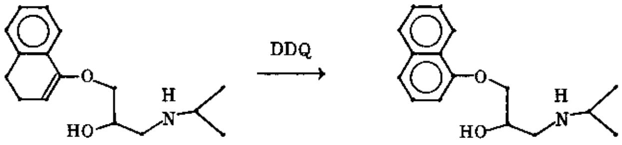
Table 1 Reaction of Dioxolanes 7-11 with Stannic Chloride and Tri-n-Octylamine

Dioxol-ane		Yield (%) of ether[9]			Recovery (%) of dioxolane
		Aromatic	Enol	Bromo-enol	
$\underline{7}^1$		—	47 (4)	—	27
$\underline{8}^6$		—	15 (5)	24 (15)	—
$\underline{9}^1$		35 (12)	19 (6)	—	—
$\underline{10}^7$		64 (13)	—	—	23
$\underline{11}^8$		31 (14)	—	—	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 (propranolol^{2}, known as a β-adrenergic blocking agent) (Scheme 2).

Scheme 2



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16 (59 %)

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.

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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/SnCl$_4$, 88 %) followed by amination (i-PrNH$_2$, 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}	^1H-nmr ($CDCl_3$) δ (Hz)		ms m/z (M^+)
			CH_2-CH-CH_2 -O OH N<	-C=C-H -O CH_2-	
4	68-9	3310, 1646	3.72-4.31 (m)	4.96 (dd, J=4.5, 4.5)	261
5	84-5	3280, 1646	3.70-4.18 (m)	4.92 (dd, J=4.5, 4.5)	291
6	75-6	3315, 1637	3.74-4.13 (m)	4.70 (dd, J=4.5, 4.5)	267
12	86.5-7	3290	4.00-4.34 (m)	—	265
13	115.5-6.5	3280, 1743	3.93-4.46 (m)	—	307
14	110-1	3320	3.75-4.13 (m)	—	326
15	76-7	3280, 1642	3.73-4.24 (m)	—	369 371

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