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STEREOCONTROL IN RADICAL CYCLIZATION: STEREOSELECTIVE SYNTHESIS OF 2,4-CIS AND 2,4-TRANS TETRAHYDROFURAN DERIVATIVES VIA MONO- OR DICHLOROMETHYL RADICAL.

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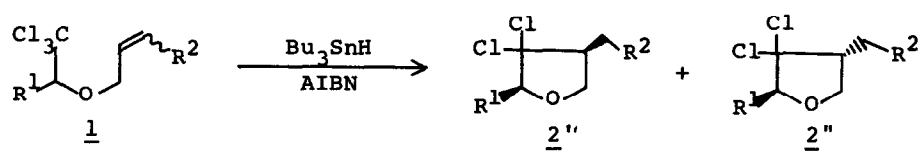
Abstract; A novel stereocontrol method for the preparation of 2,4-disubstituted tetrahydrofurans was presented. 2,4-Cis-disubstituted-3,3-dichlorotetrahydrofurans 2 were provided predominantly by the radical cyclization of allyl-2,2,2-trichloroethylethers 1 with tributyltin hydride. The effect of geometry of chlorine atom and olefin on products stereochemistry was also discussed.

Trichloromethyl group is a synthetically interesting functional group in carbon-carbon bond formation or functional group transformation. Especially in the carbene or carbenoid chemistry versatile applications to organic synthesis have been reported.[1] And the reaction of polyhaloalkyl radical is the traditional one in the radical chemistry.[2] Besides, some radical cyclizations of compounds containing trichloromethyl group catalysed by transition metal complexes or salts were reported,[3] however, the stereocontrol relied on the bulkiness of chlorine atom of trichloromethyl group has been hitherto unknown. In the preceding paper we described highly stereo selective pyrrolidine synthesis via dichloromethyl radical using radical cyclization.[4] It is noteworthy that trichloromethyl group can selectively generate dichloromethyl radical with tributyltin radical, and the chlorine atoms can effectively control the stereoselectivity and remaining chlorine atoms in the cyclization product are easily removable. We report in this communication the stereoselective synthesis of tetrahydrofuran derivatives using radical cyclization via dichloromethyl radical and effect of halomethyl group on stereoselectivity.



1 2" 2"

Thus, allyl-2,2,2-trichloroethylether 1 afforded 2,4-disubstituted-3,3-dichlorotetrahydrofurans 2 in excellent yields by the treatment with an equimolar of tributyltin hydride (Eq. 1, Table 1).[5] From ^{1}H and ^{13}C nmr, it was concluded that in any case (1a-1g) cis diastereomers were obtained predominantly although the cyclization products were the mixture of two diastereomers 2' and 2".[6] This high stereoselective ring construction method also shows high regioselectivity (only five membered product was obtained) and chemoselectivity (no protection of carbonyl group was needed).

Table 1. Radical cyclization of allyl-2,2,2-trichloroethylethers 1.

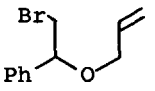
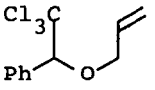
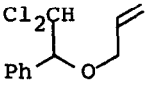
Substrate 1	R^1	R^2	Yield(%)[a]	Diastereomer ratio[b] cis : trans	
a	Ph	Ph (E-olefin)	79	92	8
b	p-Cl-C_6H_4	H	82	91	9
c	$C_5H_{11}CH(C_2H_5)$	H	80	90	10
d	C_3H_7	H	72	86	14
e	CH_3COCH_2	H	74	87	13
f	Ph	CH_3 (E-olefin)	86	90	10
g	Ph	CH_3 (Z-olefin)	83	75	25

a) Isolated yields. b) Estimated by ^{1}H and ^{13}C nmr.

In the analogous radical cyclization of allyl-2-polyhaloethylethers (1h-1j), cis-selectivity was observed in the radical cyclization of trichloromethyl derivatives 1i, in contrast to trans-selectivity for monobromo derivative 1h (Table 2). This fact indicates that outcome of these cyclizations does not reflect the probable thermodynamic stabilities of the products. The importance of the chlorine atoms attached to the radical site in this cyclization was demonstrated by the reverse stereoselectivity by replacing of one chlorine atom with hydrogen (1j; cis : trans = 5 : 95). These results suggest the posibility of the selective synthesis of desired diastereomer by choice of the number of chlorine atom attached to the radical site.[7] The ratio of 2a to 2b depended on the olefin geometry. Namely the stereoselectivity dropped down slightly in the cyclization of 1g whose olefin had Z-geometry.[8]

Varying cis and trans selectivity mentioned above suggests that in the cyclization mechanism transition states illustrated in Figure 1 emphasize the importance of the steric repulsion of substituent R^1 with chlorine atom. The stereochemistry of the acyclic di- or monochloromethyl radical can be rationalized by favoring a chair-like conformation. Cis-selectivity may be explained by the repulsion between R^1 and two chlorine atoms [R' = Cl, (B)] as dscribed in the previous paper.[4] On the other hand, in the

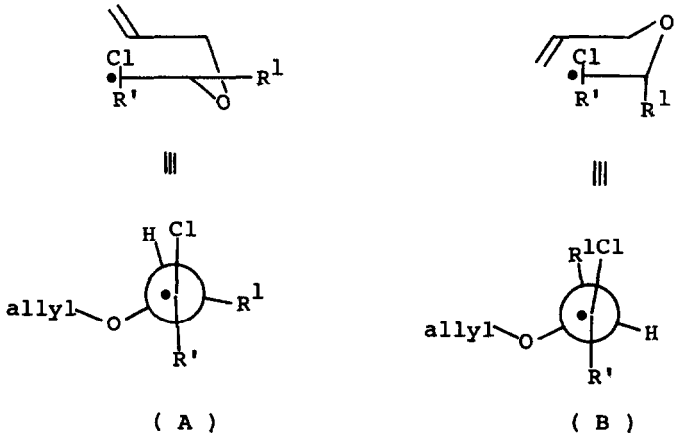
Table 2. The effect of the number of halogen atom on the diastereoselectivity.

	Substrate 1	Reaction condition	Yield (%)[a]	Diastereomer ratio[b] cis : trans	
h		80°C / 2 h	83	34	66
i		70°C / 4 h	92	90	10
j		70°C / 3 h	78[c]	5	95

a) Isolated yields of combined diastereomers. b) Estimated by ^{1}H ^{13}C nmr.
c) This yield is given for the completely dehalogenated product by the treatment with two equivalent of tributyltin hydride.[9]

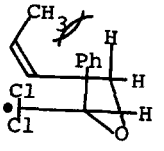
cyclization of monochloromethyl radical reverse stereoselectivity may be explained by the pseudo staggered conformation illustrated in (A). Namely substituent R^1 may be considered to demand less hindered equatrial position, thus leading to the 2,4-trans form [R' = H, (A)].

The present method of enforcing stereocontrol by introduction of large but easily removable chlorine atoms at the radical site provides an attractive entry to highly stereoselective preparation of 2,4-disubstituted tetrahydrofuran derivatives.



Reference

1. W.Kirmse, "Carbene Chemistry", Academic Press New York, 1971.
2. a) C.Walling, F.S.Huyser, "Organic Reactions", Vol. 13, John Wiley and Sons, New York, 1963. b) B.Giese, Angew. Chem., Int Ed. Engl., 22, 753, 1983.
3. a) H.Nagashima, H.Wakamatsu, K.Itoh, Y.Tomo, J.Tsuji. Tetrahedron Lett., 24, 2395, 1983. b) H.Nagashima, H.Wakamatsu, K.Itoh. J. Chem. Soc., Chem. Commun., 652, 1984.
4. Y.Watanabe, Y.Ueno, C.Tanaka, M.Okawara, T.Endo. Tetrahedron Lett., 28, 3953, 1987.
5. Typical experimental procedure is as follows. To a solution of allyl-1-phenyl-2,2,2-trichloroethylether 1i (1.00 g, 3.77 mmol) and catalytic amount of AIBN (3 mol%) in dry benzene (50 ml) was added dropwise a solution of tributyltin hydride (1.10 g, 3.77 mmol) in benzene (20 ml) over a period of 1 h at 70°C. After stirring for 3 h the solvent was removed in vacuo. The residure was diluted with ether and treated with aquous pottasium fluoride. After white solid was filtered, 2i was isolated 0.80 g (92%) by silica gel column chromatography (eluted by a mixed solvent of hexane and ether (95 : 5)).
6. The assignment of relative conformation at 2,4-position in the cyclization product of N-analogue follows from NOE study to be cis-diastereomer (ref. 4).
7. 2,2-Dichloro-1-phenylethanol was prepared as follows. To the solution of 2,2,2-trichloro-1-phenylethanol (4.00 g, 17.74 mmol) and AIBN (3 mol%) in dry benzene (50 ml) was added dropwise a solution of tributyltin hydride (5.16 g, 17.73 mmol) in dry benzene (50 ml) over a period of half an hour at 70°C. The reaction mixture was then stirred for 3 h. Distillation, (121-122°C / 6-7 mmHg), afforded 3.39 g of colorless liquid.
8. The important observation had been reported by Wilcox et al. In their study the stereoselectivity was improved in the cyclization of Z-olefines due to its steric repulsion. C.S.Wilcox, L.M.Thomasco. J. Org. Chem., 50, 546, 1985. Our dropped stereoselectivity may be explained by the slight steric repulsion between methyl and phenyl groups.



9. Four diastereomers were observed in the mixture of cyclization products i.e.,3-chloro-4-methyl-2-phenyltetrahydrofurans. In order to estimate the ratio of diastereomers (2,4-cis and 2,4-trans) chlorine atom at 3-position was removed by the reduction with tributyltin hydride to give 4-methyl-2-phenyltetrahydrofuran.

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