retention times, a mixture of **4**, **3a**, and the tentatively identified **3b**, in relative ratio 1:2:1. The residue after evaporation of the dried extract (73 mg) was combined with a similar mixture (11 mg) resulting from a smaller scale NaOH treatment, dissolved in 19:1 chloroform/acetone, and subjected to chromatography on silica gel (2.5 g, Bio-Sil A, Bio-Rad Laboratories, Richmond, CA). Elution with 9:1 chloroform acetone gave first **3a** (22 mg) as a pure solid and then 4 (14 mg) as the major constituent of a mixture. Characteristics of **3a**: mp 143–144 °C; high resolution (HR) EIMS, calcd for $C_{14}H_{21}ClO_4$ m/z 288.1128, found 288.1122.

Conversion of 3a to 4. To a solution of **3a** (19.9 mg, 0.07 mmol) in methanol (2 mL) was added 1 N aqueous NaOH (20.5 mL). The mixture was heated 7 h under N_2 at 97–98 °C, then cooled, and worked up as above, yielding **4** (17.4 mg, 91%), >96% pure by GC/MS. The material was further purified by recrystallization from acetone–ether. Characteristics of **4**: mp 134–135 °C; HREIMS, calcd for $C_{14}H_{20}O_4$, m/z 252.1362, found 252.1362.

Acknowledgment. We thank Mr. John M. Roman for the exact mass determinations. We are also grateful to one reviewer for valuable comment on the mechanism.

Registry No. **1a**, 101199-68-2; **1b**, 101199-69-3; **2**, 2198-92-7; **3a**, 104532-66-3; **3b**, 104597-40-2; **4**, 104532-67-4.

Synthesis of Tetrahydrofurans from Active Methylene Compounds via Radical Cyclization

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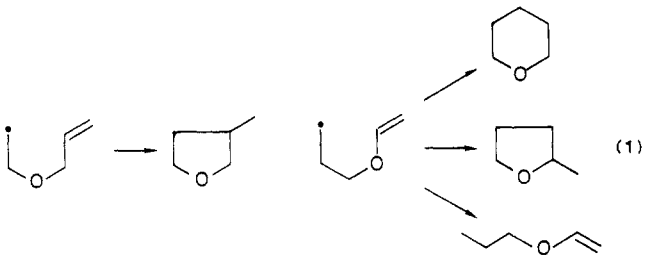
Radical Cyclization has been now variously applied as a useful method to the preparations of heterocyclic and carbocyclic compounds.[1] In view of efficient regioselectivity and rate of intramolecular radical addition, the reaction to give five-membered heterocyclic structures via analogues of 5-hexenyl radicals, which contain an allylic heteroatom such as oxygen or nitrogen in the chain, is often employed[2,3] (eq 1). Our continuous investigations on



(1)

synthetic application of the radical process have been hitherto developed along this cyclization system.[4] On the other hand, intramolecular radical addition onto a vinyl ether group has not been studied enough to utilize in organic synthesis, although this type of reaction is expected to alter some properties of radical cyclization.[5] Very recently, two works based on such cyclization process have been reported by Kuwajima[6] and Pattenden,[7] in which trimethylsiloxy-substituted carbocyclic compounds and alkoxy-substituted cyclic acetals have been prepared, respectively. We report herein a new synthetic route to tetrahydrofurans from active methylene compounds via

Scheme I

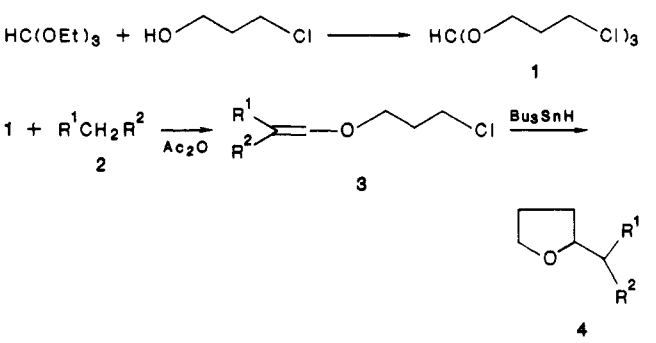


Table I. Synthesis of Vinyl Ethers 3 and Tetrahydrofurans 4

			3		4[a]	
	R^1	R^2	reacn time, h	yield, %	reacn time,[b] h	yield, %
a	CN	CO_2Et	5	59	4.5	74
b	COMe	CO_2Me	3	45	5	75
c	COMe	COPh	1	60[c]	6	54
d	CO_2Et	CO_2Et	7	43	6	81

[a] Obtained from **3**. [b] The reaction was followed by taking the IR spectrum (1810 cm^{-1}, Sn–H). [c] With a trace of impurities.

radical addition onto vinyl ether moiety, which presents a straightforward example of radical cyclization when vinylic oxygen is contained in a chain.

The preparation of the tetrahydrofurans **4** was attained via three steps shown in the Scheme I. Tris(3-chloropropyl) orthoformate (**1**) was obtained readily from triethyl orthoformate and 1-chloropropan-3-ol by a transesterification. The vinyl ethers **3**, containing two electron-withdrawing groups such as CN, COR, and CO_2R at the β-position of vinyl ether moiety, were prepared from active methylene compounds **2** and **1** by the similar procedures to those reported for the syntheses of ethyl vinyl ethers.[8] The radical cyclization of **3**, conducted with 1.1 equiv of tri-*n*-butyltin hydride (Bu_3SnH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) in dry benzene, gave the tetrahydrofurans **4** having a mul-

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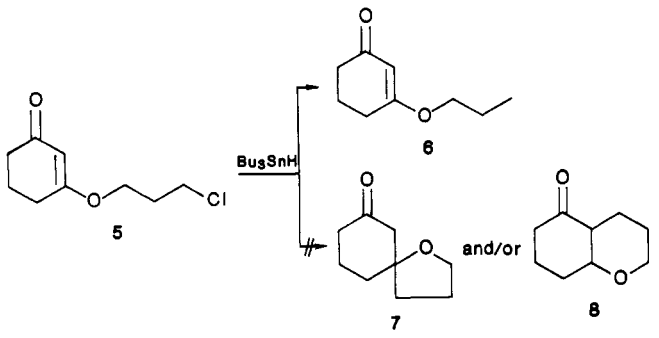
Scheme II



tifunctional substituent in moderate yields (Table I). The decreased yield of **4c** was caused by the difficulty in removing an organotin byproduct (Bu_3SnCl) from the reaction products.

The efficient cyclization of **3** may be attributed to the effects, coupled with radical stabilizing and steric one, of the electron-withdrawing groups.[9] The successful results are also correlated with the feature of radical process performed under neutral conditions, i.e., the functional groups listed in the Table I are inert toward the radical species involved. Thus, synthesis of the tetrahydrofurans with a multifunctional substituent was achieved by utilizing the radical process designed to force and exo-cyclic mode of cyclization, in which active methylene compounds were shown to be a useful starting material. Further, the cyclization via radical intermediates bearing a vinylic oxygen in the chain enables the selective introduction of a substituent into C-2 position of tetrahydrofuran ring different from that containing an allylic oxygen, which afford the C-3-substituted tetrahydrofurans as a result of cyclization.[3,4]

In addition, the method mentioned above was also applied to the preparation of the cyclic compounds bearing a cyclohexanone moiety, but it was unsuccessful (Scheme II). When the vinyl ether **5**, obtained from 1,3-cyclohexanedione with orthoformate **1**,[10] was treated with Bu_3SnH, the reduction product **6** was predominantly obtained contrary to our expectation to get spirocyclic **7** and/or bicyclic **8** compounds.[11]

Experimental Section

IR spectra were measured on a JASCO A-3 grating infrared spectrophotometer and ^1H NMR spectra on a JEOL-FX90Q spectrometer with $CDCl_3$ solution and with Me_4Si as internal standard. The silica gel used for column chromatography was Wakogel C-200 (100–200 mesh). Benzene was distilled over sodium metal before use, and other reagents were used as supplied from commercial sources. All the reactions employing tri-*n*-butyltin hydride were carried out under nitrogen.

Tris(3-chloropropyl) Orthoformate (1). A mixture of ethyl orthoformate (5.35 g, 36 mmol) and 1-chloropropan-3-ol (11.3 g, 120 mm01) was heated to 120 °C under atmospheric pressure for 4–5 h by distilling ethyl alcohol formed. Then the bath temperature was raised to 170 °C, and distillation was continued for 2 h. After that, fractional distillation of the residual oil under reduced pressure gave the ortho ester **1** (7.57 g, 71%) [145 °C (2 mmHg)]: IR (neat) 2970, 2900, 1110 cm^{-1}; ^1H NMR δ 2.02 (m, 6 H), 3.65 (m, 12 H), 5.80 (s, 1 H). Anal. Calcd for $C_{10}H_{19}Cl_3O_3$: C, 40.91; H, 6.52; Cl, 36.22. Found: C, 40.65; H, 6.49; Cl, 36.47.

Synthesis of Vinyl Ethers 3. General Procedure. A solution of active methylene compound **2** (6.5 mmol) and **1** (8.5 mmol) in acetic anhydride (2 mL) was stirred at 140–150 °C for the time shown in the Table I. The resulting solution was concentrated by distillation under reduced pressure from 100 to 5 mmHg at 160–170 °C. The residual black viscous oil was subjected to silica gel column chromatography using benzene and purified, further, by Kugelrohr distillation to give **3a–d** (Table I).

3a (R^1 = CN, R^2 = CO_2Et): bp 170 °C (0.04 mmHg) (Kugelrohr); IR (neat) 2240 ($\nu_{C\equiv N}$), 1720, 1620, 1300, 1275, 1110 cm^{-1}; ^1H NMR δ 1.30 (t, 3 H, J = 8.0 Hz), 2.25 (m, 2 H), 3.70 (t, 2 H, J = 6.5 Hz), 4.15–4.60 (m, 4 H), 8.02 (s, 1 H). Anal. Calcd for $C_9H_{12}ClNO_3$: C, 49.67; H, 5.56; N, 6.43; Cl, 16.29. Found: C, 49.50; H, 5.30; N, 6.67; Cl, 16.51.

3b (R^1 = COMe, R^2 = CO_2Me): bp 160 °C (0.05 mmHg) (Kugelrohr); IR (neat) 1715, 1670, 1630, 1110 cm^{-1}; ^1H NMR δ 2.00–2.40 (m, 2 H), 2.34, 2.38 (ss, 3 H)8 3.50–3.80 (m, 5 H), 4.20–4.50 (m, 2 H), 7.62, 7.65 (ss, 1 H). Anal. Calcd for $C_9H_{13}ClO_4$: C, 48.99; H, 5.94; Cl, 16.07. Found: C, 48.98; H, 5.95; Cl, 16.63.

3c (R^1 = COMe, R^2 = COPh): bp 200 °C (0.05 mmHg) (Kugelrohr); IR (neat) 1740, 1680, 1630, 1290, 1165 cm^{-1}; ^1H NMR δ 1.80–2.04 (m, 2 H), 2.22 (s, 3 H), 3.30 (t, 2 H, J = 6.0 Hz), 4.15 (t, 2 H, J = 7.0 Hz), 7.50 (m, 3 H), 7.70 (s, 1 H), 7.80 (m, 2 H). Anal. Calcd for $C_{14}H_{16}ClO_3$: C, 62.81; H, 6.02; Cl, 13.24. Found: C, 63.30; H, 6.09; Cl, 13.85.

3d (R^1, R^2 = CO_2Et): bp 180 °C (0.05 mmHg); IR (neat) 1740, 1630, 1290, 1190, 1160, 1110 cm^{-1}; ^1H NMR δ 1.25, 1.27 (tt, 6 H, J = 7.0 Hz), 1.90–2.30 (m, 2 H), 3.50–3.75 (m, 2 H), 4.00–4.40 (m, 6 H), 7.60 (s, 1 H). Anal. Calcd for $C_{11}H_{17}ClO_5$: C, 49.91; H, 6.47. Found: C, 49.63; H, 6.45.

Radical Cyclization of Vinyl Ethers 3. General Procedure. Tri-*n*-butyltin hydride (1.9 mmol) was added dropwise over 30 min to a solution of **3** (1.7 mmol) and azobisisobutyronitrile (0.1 mmol) in benzene (50 mL). After being stirred under reflux for the time shown in the Table I, the solution was concentrated via a rotary evaporator. The residue was subjected to column chromatography (SiO_2, $CHCl_3$) to give the tetrahydrofurans **4a–d** (Table I).

4a (R^1 = CN, R^2 = CO_2Et): IR (neat) 2250 ($\nu_{C\equiv N}$), 2950, 1740, 1260, 1190, 1070 cm^{-1}; ^1H NMR δ 1.30 (t, 3 H, J = 8.0 Hz), 1.50–2.10 (m, 4 H), 3.60–4.05 (m, 3 H), 4.10–4.60 (m, 3 H). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.01; H, 7.15; N, 7.64. Found: C, 59.30; H, 7.12; N, 7.68.

4b (R^1 = COMe, R^2 = CO_2Me): IR (neat) 1730, 1280, 1075 cm^{-1}, ^1H NMR δ 1.80–2.30 (m, 4 H), 2.25 (s, 3 H), 3.30–3.85 (m, 6 H), 4.30 (t, 1 H, J = 6.0 Hz). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.14; H, 7.61.

4c (R^1 = COMe, R^2 = COPh): IR (neat) 1720, 1680, 1250 cm^{-1}; ^1H NMR δ 1.90–2.25 (m, 4 H), 2.18 (s, 3 H), 3.60–3.85 (m, 3 H), 4.45 (q, 1 H, J = 7.0 Hz), 7.50 (m, 3 H), 7.90 (m, 2 H). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.33; H, 6.93. Found: C, 72.38; H, 6.67.

4d (R^1, R^2 = CO_2Et): IR (neat) 1740, 1150 cm^{-1}; ^1H NMR δ 1.28 (t, 6 H, J = 8.0 Hz), 1.60–2.20 (m, 4 H), 3.45 (d, 1 H, J = 10 Hz), 3.60–4.00 (m, 2 H), 4.00–4.50 (m, 5 H). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.02; H, 7.92.

1-(3-Chloropropoxy)cyclohexen-3-one (5). A solution of 1,3-cyclohexanedione (0.63 g, 5.62 mmol), **1** (2.50 g, 8.53 mmol), and *p*-toluenesulfonic acid (0.9 mmol) in benzene (3 mL) was stirred at room temperature for 2 days and then concentrated by distillation under reduced pressure [120 °C (20 mmHg)]. The residue was subjected to column chromatography (SiO_2, $CHCl_3$) and purified by Kugelrohr distillation to give **5** (0.44 g, 41%): bp 145 °C (1 mmHg) (Kugelrohr); IR ($CHCl_3$ solution) 1650, 1610, 1220, 1185 cm^{-1}; ^1H NMR δ 1.80–2.50 (m, 8 H), 3.70 (t, 2 H, J = 7.5 Hz), 4.00 (t, 2 H, J = 6.5 Hz), 5.40 (s, 1 H).

1-Propoxycyclohexen-3-one (6). The reaction was carried out in the same manner as described above for the preparation of **4**. **5** (0.35 g, 1.85 mmol) was converted into **6** (0.26 g, 95 %): IR ($CHCl_3$ solution) 2950, 1640, 1605, 1190 cm^{-1}; ^1H NMR δ 0.95 (t, 3 H, J = 8.0 Hz), 1.40–2.40 (m, 8 H), 3.80 (t, 2 H, J = 7.5 Hz), 5.30 (s, 1 H). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.11.

Registry No. 1, 38565-66-1; **2a**, 105-56-6; **2b**, 105-45-3; **2c**, 93-91-4; **2d**, 105-53-3; **3a**, 104808-09-5; **3b**, 104808-10-8; **3c**, 104808-11-9; **3d**, 104808-12-0; **4a**, 104808-13-1; **4b**, 104808-14-2; **4c**, 104808-15-3; **4d**, 70398-41-3; **5**, 104808-16-4; **6**, 104808-17-5; $HC(OEt)_3$, 122-51-0; $HO(CH_2)_3Cl$, 627-30-5; 1,3-cyclohexanedione, 504-02-9.

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