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1,3-O- TO C-ALKYL MIGRATION OF 1-ALKENYL ALKYL ACETALS CATALYZED BY BORON TRIFLUORIDE. A NOVEL CROSS ALDOL TYPE REACTION

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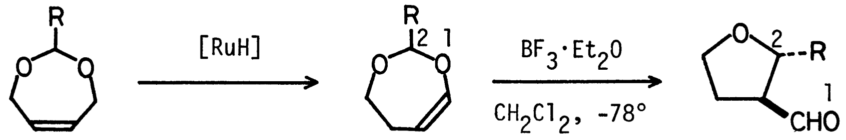
1,3-O- to C-alkyl migration of acyclic 1-alkenyl alkyl acetals catalyzed by $BF_3 \cdot Et_2O$ gives selectively α-alkyl-β-alkoxyaldehydes.

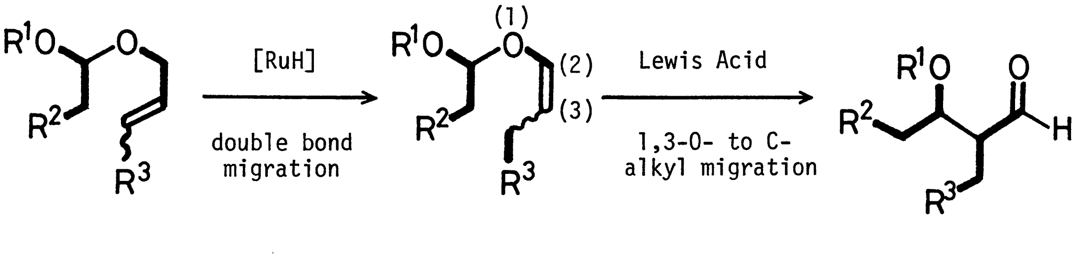
Particular interest has recently been denoted to the selective cross aldol reaction and intensive studies in this area have developed several useful methods.1) In the previous paper, we presented a selective synthesis of *trans*-2-alkyl-3-formyltetrahydrofurans from 2-alkyl-4,5-dihydro-1,3-dioxepines via a Lewis acid catalyzed intramolecular aldol type reaction, that is, 1,3-O- to C-alkyl migration where cleavage of carbon-oxygen bond exclusively occured between C(2) and O(1) to generate an intermediary vinyloxy borate and a carbocation stabilized by the neighboring oxygen atom (eq. 1).2)



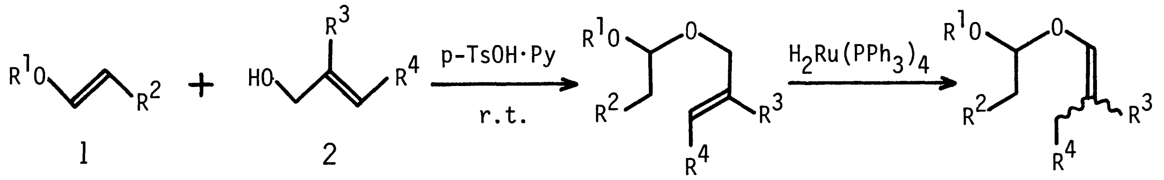
(1)

In this paper, we report a novel and effective process for the synthesis of α-alkyl-β-alkoxyaldehydes via a $BF_3 \cdot Et_2O$ catalyzed 1,3-alkyl migration of acyclic alkenyl alkyl acetals. Ruthenium hydride catalyzed double bond migration of alkyl allyl acetals and subsequent 1,3-O- to C-alkyl migration catalyzed by $BF_3 \cdot Et_2O$ to α-alkyl-β-alkoxyaldehydes are outlined in the following scheme.

[Scheme]



Alkyl allyl acetals (3a-3h) were easily prepared from 1-alkenyl alkyl ethers (1)[3] with the corresponding allylic alcohols (2) under acidic conditions. Double bond migration of 3 to 1-alkenyl alkyl acetals (4) proceeded quantitatively in the presence of $H_2Ru(PPh_3)_4$ catalyst. Experimentally, to a mixture of ethyl vinyl ether (1.08 g, 15 mmol) and allyl alcohol (0.58 g, 10 mmol) were added the catalytic amounts of pyridinium *p*-toluenesulfonate[4] (10 μmol). The reaction mixture was stirred for 5 h at ambient temperature, and the reprecipitation of the catalyst indicated the completion of the reaction. Then excess K_2CO_3 was added, and the reaction mixture was stirred for several minutes. Filtration followed by the removal of excess ethyl vinyl ether by evaporation afforded acetaldehyde allyl ethyl acetal (3b) as colorless liquid. Subsequently, 3b was heated at 150°C for 2 h in the presence of catalytic amounts of $H_2Ru(PPh_3)_4$ (1/100-1/235 equiv) in a sealed tube. Bulb to bulb distillation of the resulting reaction mixture gave analytically pure acetaldehyde ethyl 1-propenyl acetal (4b) in a 84% yield (1.09 g) based on the starting allyl alcohol. In the similar manner, 1-alkenyl alkyl acetals of acetaldehyde, propanal, and butanal (4a, 4c-4h) were prepared from the corresponding allylic alcohols and alkenyl alkyl ethers in excellent yields, respectively (eq. 2). In all cases, 1-alkenyl alkyl acetals (4) were obtained as the mixture of (*Z*)- and (*E*)-stereoisomers, of which ratio was determined by means of ^{1}H-NMR and GLC. Results of double bond migration of 3 to 4 are summarized in Table 1.



(2)

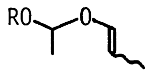
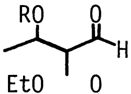
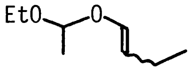
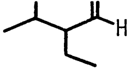
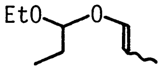
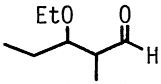
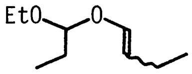
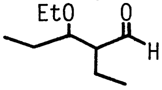
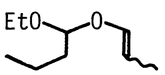
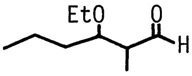
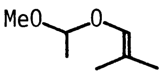
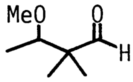
Table 1. Double Bond Migration of Alkyl Allylic Acetals (3) to 1-Alkenyl Alkyl Acetals (4)

	R^1	R^2	R^3	R^4	Reaction Conditions [3]/[RuH]	 Temp(°C)	 Time(h)	4 Yield(%)[a]	 Z/E
a	Me	H	H	H	100	120	2	84	64/36
b	Et	H	H	H	100	150	2	84	67/33
c	^{i}Bu	H	H	H	130	150	2	90	77/23
d	Et	H	H	Me	125	160	2	88	56/44
e	Et	Me	H	H	235	170	24	94	67/33
f	Et	Me	H	Me	200	160	3	87	67/33
g	Et	Et	H	H	200	160	28	83	52/48
h	Me	H	Me	H	200	160	48	67	——

a) Isolated yields based on the starting allylic alcohols.

Since 1-alkenyl alkyl acetals (4) have both acetal and enol ether moieties in the molecule, the directed C-O bond cleavage of 4 between C(2) and O(1) may permit the selective cross aldol type reaction without any side reaction (scheme). Thus, $BF_3 \cdot Et_2O$ catalyzed 1,3-O- to C-alkyl migration was carried out in the following procedure: To a cooled (-78°C) and stirred solution of 4b (1.09 g, 8.4 mmol) in dry dichloromethane (25 ml) was added dropwise $BF_3 \cdot Et_2O$ (4 mmol) over a period of 5 min under an atmosphere of dry nitrogen. The reaction mixture was stirred for an additional 20 min at -78°C and quenched with aqueous K_2CO_3. Extraction with diethyl ether followed by removal of the solvent under reduced pressure gave analytically pure 2-methyl-3-ethoxybutanal (5b) as colorless liquid in a 96% yield (1.05 g, 81% overall yield from allyl alcohol). 5b: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ 1.02-1.24(9H, m), 2.5(1H, m), 3.3-3.9(3H, m), 9.55 and 9.62(total 1H, each d, J=2.2 and 1.2 Hz), IR (in CCl_4; cm^{-1}) 1718(νC=O). α-Alkyl-β-alkoxyaldehydes (5a, 5c-5h) were similarly obtained in excellent yields from the corresponding 1-alkenyl alkyl acetals (4a, 4c-4h), respectively.[5)] Results of the 1,3-O- to C-alkyl migration of 4 to 5 are listed in Table 2. The diastereomeric ratio in 5 was determined by meanes of ^{1}H-NMR and GLC by comparison with authentic material (threo) derived from tiglic acid via hydroboration.

Table 2. 1,3-O- to C-Alkyl Migration of 4 to α-Alkyl-β-alkoxyaldehydes (5)

4			Reaction Conditions[a)]		5		
		(Z/E)	$BF_3 \cdot Et_2O$/4	Time(min)		Isolated Yield(%)	threo/erythro
		a; R=Me (64/36) b; R=Et (67/33) c; R=i-Bu (77/23)	0.5 0.5 0.5	20 20 20		a; 97(81)[b)] b; 96(81) c; 88(79)	54/46 56/44 55/45
d		(56/44)	0.1	30		79(70)	54/46
e		(67/33)	0.5	20		79(74)	46/54
f		(67/33)	0.5	25		77(67)	45/55
g		(52/48)	0.5	10		95(78)	45/55
h		——	0.5	60		94(63)	——

a) All reactions were carried out under dry nitrogen pressure at -78°C.
b) Overall yields from the starting allylic alcohols.

Other Lewis acids, such as $AlCl_3$, $SnCl_4$, $TiCl_4$, $ZnCl_2$, and $NiCl_2$, also promoted 1,3-O- to C-alkyl migration of 1-alkenyl alkyl acetals (4) to give satisfactory results. However, $BF_3 \cdot Et_2O$ was the most suitable one for this reaction because of homogeneity in CH_2Cl_2 to bring considerable reduction in the reaction time.

The simplicity in procedure of this reaction, in spite of relatively long process, achieved the excellent overall yields. Moreover, the mild reaction conditions in the final stage of the reaction sequence facilitated the isolation of 5 without the formation of α,β-unsaturated aldehydes by the unfavorable elimination of alcohol from 5.

In conclusion, it has been shown that the $BF_3 \cdot Et_2O$ catalyzed 1,3-O- to C-alkyl migration of 1-alkenyl alkyl acetals can selectively give cross aldol products of aldehydes and thus can be synthetically useful operation.

Mechanistic investigation and the extention of the present reaction to the diastereoselective one are now in progress.

References

1. S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc., 102, 3248 (1980); K. Narasaka, J. Syn. Org. Chem. Jpn., 37, 307 (i979) and references are cited therein.
2. H. Suzuki, H. Yashima, T. Hirose, M. Takahashi, Y. Moro-oka, and T. Ikawa, Tetrahedron Lett., 21, 4927 (1980).
3. Substituted 1-alkenyl alkyl ethers (1; $R^2 \neq H$) were derived from the corresponding alkyl allylic ethers via a double bond migration catalyzed by $H_2Ru(PPh_3)_4$.
4. An equilibrium mixture of acetaldehyde allyl ethyl acetal, acetaldehyde diallyl acetal, and acetaldehyde diethyl acetal was produced when *p*-toluenesulfonic acid or benzenesulfonic acid was used as catalyst instead of pyridinium *p*-toluenesulfonate.
5. 5a: ^{1}H-NMR($CDCl_3$-TMS; ppm) δ1.05-1.23(6H, m), 2.50(1H, m), 3.36(3H, s), 3.52-3.92(1H, m), 9.56 and 9.58(total 1H, each d, J=2.2 and 1.0Hz). IR(CCl_4; cm^{-1}) 1728($^{\nu}$C=O).

   5c: ^{1}H-NMR($CDCl_3$-TMS; ppm) δ0.85(6H, d, J=7Hz), 1.05-1.25(6H, m), 1.85(1H, m), 2.52(1H, m), 3.3-3.5(2H, m), 3.52-3.92(1H, m), 9.68 and 9.70(total 1H, each d, J=2.2 and 1.2Hz). IR(CCl_4; cm^{-1}) 1728($^{\nu}$C=O).

   5d: ^{1}H-NMR($CDCl_3$-TMS; ppm) δ0.92(3H, t, J=7Hz), 1.08-1.28(6H, m), 1.5-1.9(2H, m), 2.3(1H, m), 3.35-3.92(3H, m), 9.50 and 9.56(total 1H, each d, J=3.8 and 2.5Hz). IR(CCl_4; cm^{-1}) 1728($^{\nu}$C=O).

   5e: ^{1}H-NMR($CDCl_3$-TMS; ppm) δ0.93(3H, t, J=7Hz), 1.04-1.22(6H, m), 1.44-1.80(2H, m), 2.55(1H, m), 3.35-3.70(3H, m), 9.56 and 9.58(total 1H, each d, J=2.0 and 1.0Hz). IR(CCl_4; cm^{-1}) 1728($^{\nu}$C=O).

   5f: ^{1}H-NMR($CDCl_3$-TMS; ppm) δ0.93(6H, t, J=7Hz), 1.18(3H, t, J=7Hz), 1.45-1.90 (4H, m), 2.4(1H, m), 3.4-3.7(3H, m), 9.55 and 9.62(total 1H, each d, J=3.0 and 2.2Hz). IR(CCl_4; cm^{-1}) 1725($^{\nu}$C=O).

   5g: ^{1}H-NMR($CDCl_3$-TMS; ppm) δ0.93(3H, t, J=7Hz), 1.04-1.26(6H, m), 1.3-1.8(4H, m), 2.55(1H, m), 3.35-3.75(3H, m), 9.65 and 9.68(total 1H, each d, J=2.0 and 1.0Hz). IR(CCl_4; cm^{-1}) 1728($^{\nu}$C=O).

   5h: ^{1}H-NMR(CCl_4-TMS; ppm) δ0.94(3H,s), 1.00(3H, s), 1.03(3H, d, J=6.5Hz), 3.26 (3H, s), 3.35(1H, q, J=6.5Hz), 9.43(1H, s). IR(CCl_4; cm^{-1}) 1724($^{\nu}$C=O).

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