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# 1,3-O- TO -C-ALKYL MIGRATION OF 1-ALKENYL ALKYL ACETALS AND KETALS CATALYZED BY BORON TRIFLUORIDE. SELECTIVE CROSS- AND REGIOSELECTIVE ALDOL TYPE REACTIONS

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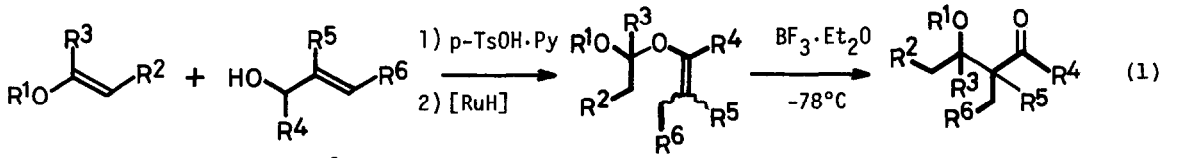
Summary: *1,3-Alkyl migration of 1-alkenyl alkyl acetals and ketals is effectively catalyzed by trifluoroborane etherate to give cross aldol type products selectively. Remarkable regioselectivity is observed in the synthesis of α-alkyl-β-alkoxyketones.*

Although the cross aldol reaction is one of the useful methods for the C-C bond formation, the selectivity of this reaction seriously depends on the reactivity of the original carbonyl compounds and is often depressed by several concomitant paths under the equilibrium conditions.[1] Even in the improved procedure using the metal enolate or its equivalent, it is difficult to employ the labile enolate of aldehyde as nucleophile,[2] and hence there have been few generalized methods for the selective cross aldol reaction. Recently, we have shown a novel method for the synthesis of protected aldol via a double bond migration and subsequent 1,3-alkyl migration catalyzed by ruthenium hydride complexes and $BF_3 \cdot Et_2O$.[3] We describe herein (1) application of the 1,3-alkyl migration to various types of the cross aldol reaction, and (2) the highly regioselective synthesis of protected ketols.




1 2 3 4 (1)

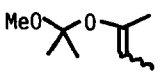
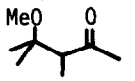
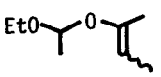
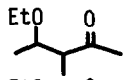
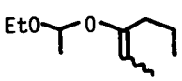
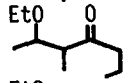
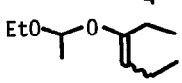
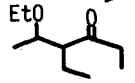
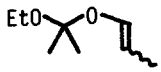
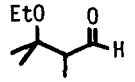
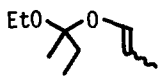
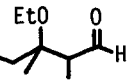
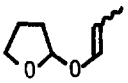
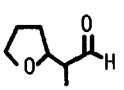
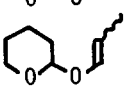
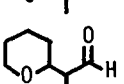
Classification of the cross aldol reaction according to the combination of the nucleophile with the electrophile and its correlation with Lewis acid-catalyzed 1,3-O- to -C-alkyl migration of 1-alkenyl alkyl acetals and ketals (eq. 1) are shown in Table 1.

Table 1. Types of Cross Aldol Reaction Correlated with 1,3-Alkyl Migration of 3

| Type | Cross Aldol Reaction | | 1,3-Alkyl Migration | |
|---|---|---|---|---|
| | $E^+$ | $Nu^-$ | $R^3$ | $R^4$ |
| I | ketone | ketone | alkyl | alkyl |
| II | aldehyde | ketone | H | alkyl |
| III | ketone | aldehyde | alkyl | H |
| IV | aldehyde | aldehyde | H | H |

Since the Lewis acid-catalyzed 1,3-O- to -C-alkyl migration of 1-alkenyl alkyl acetals or ketals is regarded as the coupling reaction of enolate anion with carboxonium ion, complete repression of the fatal sub-reaction observed in the aldol reaction, such as enolate exchange or polycondensation, is expected in

Table 2. 1,3-O- to C-Alkyl Migration of 3 to 4

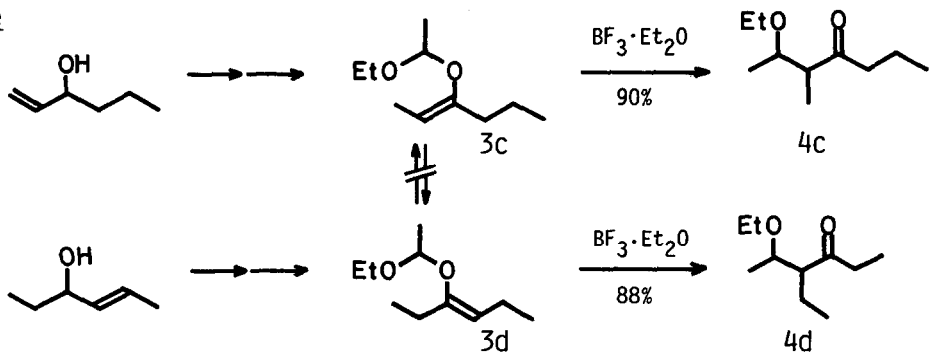
| Type | | 3 (Z/E)[a] | Time (min)[b] | 4 | | Yield (%)[c] |
|---|---|---|---|---|---|---|
| I | a |  (53/47) | 5 |  | (——)[d] | 89(60) |
| II | b |  (50/50) | 5 |  | (46/54) | 87(70) |
| | c |  (55/45) | 5 |  | (45/55) | 90(64) |
| | d |  (60/40) | 5 |  | (40/60) | 88(53) |
| III | e |  (70/30) | 2 |  | (——) | 74(56) |
| | f |  (62/38) | 5 |  | (44/56) | 83(66) |
| V | g |  (63/77) | 15 |  | (30/70) | 87(74) |
| | h |  (68/32) | 15 |  | (30/70) | 70(63) |

*a)* Determined by means of $^1$H-NMR and GLC. *b)* All reactions were conducted in dry dichloromethane in the presence of 1/2 equiv of trifluoroborane etherate at -78°C. *c)* Isolated yields. Yields shown in parentheses are overall yields based on the starting allylic alcohols. *d)* Diastereomeric ratio determined by means of proton NMR, carbon-13 NMR, and GLC.

the present method. Actually, α-alkyl-β-alkoxy carbonyl compounds (4a-4h) ranking with the products of type I-III reactions[4] were obtained in excellent yields from the corresponding 1-alkenyl alkyl ethers (1) and allylic alcohols (2) by way of 3.[5] The results of 1,3-alkyl migration of 3 to 4[6] are summarized in Table 2.

The 1,3-alkyl migration has an advantage of being available to the cyclic alkenyl ethers as electrophile of cross aldol type reaction (type V) and can be applied to the preparation of β-tetrahydrofuranyl and β-tetrahydropyranyl carbonyl compounds which are the useful precursors for the synthesis of ionophore antibiotics. Another advantage of present reaction is its high regioselectivity. When α- and α'-carbons of ketone are unsymmetrically substituted, regioselective aldol reaction can be generally achieved via the enolate anion formed under conditions of either kinetic or thermodynamic control.[7] However, in the case of both α- and α'-carbons being equally substituted, attempts for the regioselective aldol reaction will be confronted with a difficulty that the enolate of such ketones will be afforded as a mixture of the regioisomers under usual conditions employed in the aldol reaction. On the contrary, in the double bond migration proceeding via the addition-elimination mechanism of metal hydride, possibility of the interconversion between regioisomeric enol ether is disregarded. Therefore, the present process makes it possible to generate regioisomeric enol ethers (3c and 3d) and, as a result, to produce regioisomeric ketols (4c and 4d) individually as shown in the following scheme.

Scheme




Typical experimental procedure is as follows: To a mixture of ethyl vinyl ether (1b) and 3-buten-2-ol (2b) (molar ratio=1.2/1) was added the catalytic amounts of pyridinium p-toluene sulfonate. The reaction mixture was stirred for 6h at room temperature. Addition of excess $K_2CO_3$ and filtration followed by removal of 1b by evaporation afforded acetaldehyde ethyl but-1-en-3-yl acetal. Subsequently, this was heated at 150°C for 24h in the presence of 1/200 equiv of $H_2Ru(PPh_3)_4$ in a sealed tube. Bulb to bulb distillation of resulting reaction mixture gave acetaldehyde ethyl but-2-en-2-yl acetal (3b) in a 80% yield based on 2b. To a cooled (-78°C) solution of 3b in dry dichloromethane was added dropwise $BF_3 \cdot Et_2O$ (1/2 equiv). The reaction mixture was stirred for 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 4-ethoxy-3-methyl-2-pentanone (4b) in a 70% overall yield from the starting alcohol (2b).

Though methyl and ethyl 1-alkenyl ethers were adopted here as starting materials for convenience' sake, the present method is generally applicable to alkyl or aryl 1-alkenyl ethers to afford variously protected aldols and ketols. For the synthesis of parent α-alkyl-β-hydroxyaldehydes, 1-alkenyl benzyl ethers would be the most suitable precursors. Further application of the present method to a diastereoselective synthesis of α-alkyl-β-alkoxyaldehydes will be reported in due course.

References and Notes


1) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, 16, 1 (1968).

2) K. Narasaka, *J. Syn. Org. Chem. Jpn.*, 37, 307 (1979) and references cited therein.

3) M. Takahashi, H. Suzuki, Y. Moro-oka, and T. Ikawa, *Chem. Lett.*, 1981, 1435.

4) Type IV reaction was reported in the preceding paper (ref. 3).

5) Reaction conditions and yields of double bond migration to 3 are as follows.
3a: $H_2Ru(PPh_3)_4$ (1/150 equiv), 140°C, 32h, 67%. 3b: $H_2Ru(PPh_3)_4$ (1/200 equiv), 150°C, 24h, 80%. 3c: $HRuCl(PPh_3)_3$(toluene) (1/150 equiv), 150°C, 4h, 71%. 3d: $HRuCl(PPh_3)_3$(toluene) (1/100 equiv), 150°C, 48h, 60%. 3e: $H_2Ru(PPh_3)_4$ (1/200 equiv), 160°C, 2h, 75%.
3f: $H_2Ru(PPh_3)_4$ (1/200 equiv), 150°C, 4h, 80%. 3g: $H_2Ru(PPh_3)_4$ (1/200 equiv), 160°C, 2h, 85%.
3h: $H_2Ru(PPh_3)_4$ (1/200 equiv), 150°C, 2h, 90%.

6) 4a: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ1.05(3H, d, J=7 Hz), 1.16(3H, s), 1.19(3H, s), 2.22(3H, s), 2.86 (1H, q, J=7 Hz), 3.23(3H, s). IR ($CCl_4$; $cm^{-1}$) 1718($\nu$C=O).
4b: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ0.95-1.12(9H, m), 2.16(3H, s), 2.7(1H, m), 3.25-3.75(3H, m). IR ($CCl_4$; $cm^{-1}$) 1718($\nu$C=O).
4c: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ0.76-1.18(12H, m), 1.54(2H, tq, J=7 and 7 Hz), 2.30-2.76(3H, m), 3.1-3.8(3H, m). IR ($CCl_4$; $cm^{-1}$) 1718($\nu$C=O).
4d: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ0.76-1.22(12H, m), 1.4-1.8(2H, m), 2.2-2.8(3H, m), 3.1-3.7(3H, m). IR ($CCl_4$; $cm^{-1}$) 1718($\nu$C=O).
4e: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ1.03(3H, d, J=7 Hz), 1.06(3H, t, J=7 Hz), 1.26(3H, s), 2.48 (1H, dq, J=2.2 and 7 Hz), 3.44(2H, q, J=7 Hz), 9.59(1H, d, J=2.2 Hz). IR ($CCl_4$; $cm^{-1}$) 1725 ($\nu$C=O).
4f: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ0.8-1.2(12H, m), 1.4-1.8(2H, m), 2.2-2.7(1H, m), 3.41(2H, q, J=7 Hz), 9.72 and 9.83(total 1H, each d, J=2.2 and 1.6 Hz). IR ($CCl_4$; $cm^{-1}$) 1723($\nu$C=O)
4g: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ1.04 and 1.15(total 3H, each d, J=7 and 7 Hz), 1.5-2.1(4H, m), 2.44-2.78(1H, m), 3.65-4.25(3H, m), 9.64-9.68(1H, m). IR ($CCl_4$; $cm^{-1}$) 1728($\nu$C=O).
4h: $^1$H-NMR ($CDCl_3$-TMS; ppm) δ1.04 and 1.10(total 3H, each d, J=7 and 7 Hz), 1.3-1.9(6H, m), 2.3-2.6(1H, m), 3.3-4.1(3H, m), 9.60-9.64(1H, m). IR ($CCl_4$; $cm^{-1}$) 1728($\nu$C=O).

7) J. d'Angelo, *Tetrahedron*, 32, 2979 (1976).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