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Practical regioselective synthetic method for (*E*)-enol ether

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Abstract

A new practical and highly regioselective synthetic method for (*E*)-enol ether is reported. (*E*)-enol ethers (*E*:*Z* = 93:7–99:1) were prepared from the corresponding enol acetates (*E*:*Z*≅3:1) in two steps by bromination and anti-elimination of α-bromodialkylacetal via metal halogen exchange.

Keywords: (*E*)-enol ether; α-bromodialkylacetal; anti-elimination.

Enol ethers have been considerable synthetic intermediates in various organic reactions such as the [2+2]-cycloaddition[1] and Claisen rearrangement[2] because the regioselective isomer of di-, or trisubstituted enol ether can provide a new diastereogenic center. Generally, (*Z*)-enol ether could be easily obtained via *syn*-addition of alkoxide to alkyne,[3a] partial *syn*-hydrogenation of alkoxyalkynes[3b] or direct alkylidenation using 1,1-dibromoalkane and ester,[3c] but the preparation of regioselective (*E*)-enol ether has been quite a challenge. Several synthetic methods for (*E*)-enol ether have been introduced but they did not provide good regioselectivity or they were relatively less practical.[4] Recently, the conversion of α-bromobicyclic ketal to methylene pyran moiety was employed in the total synthesis of natural product.[5] Also Utimoto et al. reported a stereospecific conversion of *erythro* α-iodosilylalkylacetal to (*E*)-enol ether via elimination.[6] We have developed a new synthetic method for (*E*)-enol ether by the combination of these two synthetic strategies. Here, the practical and highly regioselective synthetic method of (*E*)-enol ether via *anti*-elimination of α-bromodialkylacetals (**2**) as a key step was reported.

The synthetic strategy was shown in Scheme 1. The α-bromodialkylacetals (**2**) were prepared from the corresponding enol acetates (**1**, ca. *E*:*Z*≅3:1) by the modified method of Bedoukian.[7a] Compound **1** was easily prepared by the treatment of acetic anhydride and potassium acetate with corresponding aldehydes in quantitative yield.[3a,7] Bromination of **1** with a carbon tetrachloride solution of bromine at 0°C followed by the double substitution of halide and acetate by alcohol gave **2**[8] in high yield (Table 1). The addition of *n*-BuLi (1.2 equiv.) to a tetrahydrofuran solution of **2** at –78°C gave highly regioselective (*E*)-enol ethers **3**[8] (*E*:*Z* = 93:7–99:1) (Table 1).

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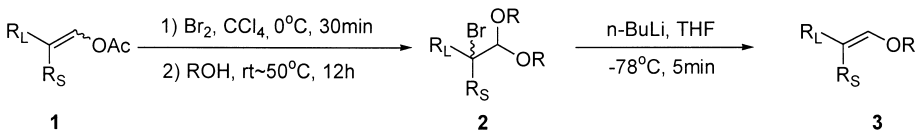


Scheme 1.

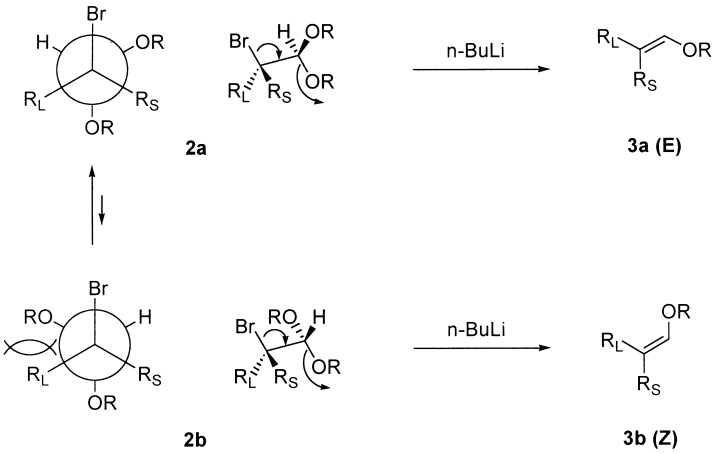
Table 1
Preparation of (*E*)-enol ether from enol acetate (**1**)

Entry	R_L	R_S	R	Yields[a](%) **2**	Yields[a](%) **3**	E : Z (**3**)[b]
1	*n*-C_4H_9	H	CH_3	94	98	96:4
2	*n*-C_8H_{17}	H	CH_3	94	76	97:3
3	Ph	H	CH_3	96	99	97:3
4	Ph	H	ethyl	92	83	98:2
5	Ph	H	*i*-Pr	63[c]	86	99:1
6	Ph	H	CH_2=$CHCH_2$	86[c]	85	96:4
7	*p*-$CH_3OC_6H_4$	H	CH_3	94	82	98:2
8	*p*-$CH_3C_6H_4$	H	CH_3	92	82	95:5
9	Ph	CH_3	CH_3	95	63	93:7
10	cyclohexyl	CH_3	CH_3	93	0	-

[a] Isolated yields. [b]The *E*/*Z* ratios were measured by ^{1}H NMR. [c]The substitution by alcohol was done at 50°C.

We suspect that the high selectivity was due to the relative conformational stability of **2** in the stage of *anti*-elimination via a metal–halide exchange. The molecular conformational energy minimization[9] studies showed that **2a** (entry 3: 0.690 kcal/mol) with the *gauche* conformation between R_L (large group) and H have lower energy than **2b** (entry 3: 1.457 kcal/mol) with the *gauche* conformation between R_L and alkoxy (Scheme 2). Severe steric repulsion between the alkoxy and R_L groups makes **2b** a less favorable conformation (Scheme 2). Generally, the more bulky alkoxy group gave higher selectivity (entries 3–5). Surprisingly, trisubstituted enol ether gave quite high selectivity (entry 9). But the cyclohexyl substrate (entry 10) did not give enol ether product because *tert*-aliphatic bromide (**2**) would not permit metal–halogen exchange, even by *t*-BuLi at –78°C. In the case of allylic enol ether (entry 6), the high selectivity could make it possible to apply this method to the Claisen rearrangement. In conclusion, a new practical and highly regioselective synthetic method for (*E*)-enol ether by the elimination of α-bromodialkylacetal which can be easily prepared from corresponding aldehydes is reported. This synthetic method could be connected with other useful reactions that require regioselective pure (*E*)-enol ether such as the Claisen rearrangement or asymmetric dihydroxylation for chiral α-hydroxy aldehyde. The applications of this method are currently being investigated.

General procedure for preparing (*E*)-enol ether **3**: To a carbon tetrachloride solution of enol acetate (10 mmol) was added a 0.5 M bromine in carbon tetrachloride in an ice-bath until the reaction solution was slightly brown. The reaction was stirred for 0.5 h and then the excess bromine was removed in vacuo. The residue was diluted with carbon tetrachloride and excess corresponding alcohol (5 equiv.) was added. The reaction solution was stirred for 12 h. To the



Scheme 2.

reaction solution was added sat. aq. $NaHCO_3$ and carbon tetrachloride solvent was removed in vacuo. The water layer was extracted with EtOAc (50 mL×3) and the combined EtOAc solution was washed with H_2O (30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by column chromatography (*n*-hexane:EtOAc = 30:1) to give **2**. To a tetrahydrofuran solution (5 mL) of **2** was added *n*-BuLi (1.6 M solution in hexane, 1.2 equiv.) at –78°C. The reaction was stirred for 5 min at –78°C and excess *n*-BuLi was quenched by methyl alcohol. The tetrahydrofuran solvent was removed in vacuo and the residue was diluted with EtOAc (50 mL) and washed with H_2O (10 mL×2), and brine (10 mL) and dried over anhydrous $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by column chromatography (*n*-hexane:EtOAc = 60:1) to give (*E*)-enol ether **3**.

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8. All compounds gave satisfactory spectroscopic data consistent with the proposed structure.
9. The calculations were done using the program SYBYL 6.5 from Tripos Software Inc. Saint Louis, MI, USA.