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Synthetic applications of the amine-base treatment in the ozonolysis of substituted-allyl silyl ethers or -allyl esters via a novel ene–diol type rearrangement

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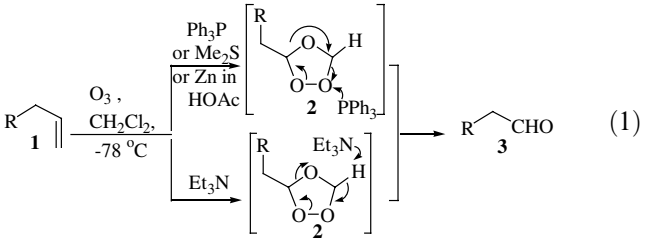
Abstract—The ozonolysis of substituted-allyl silyl ethers or -allyl esters followed by treatment with bases gave the corresponding α-silyloxy ketones or α-acyloxy ketones in good yields. The reaction is proposed to proceed via a novel ene–diol rearrangement of the corresponding α-silyloxy aldehydes or α-acyloxy aldehydes intermediates.

We have reported that ozonides **2** derived from terminal alkenes **1** when treated with Et_3N gave the corresponding aldehydes **3** in good yield (Eq. 1).[1] The reaction of ozonide with Et_3N has been demonstrated to follow the E1cb mechanism. The yields of the aldehydes **3** obtained from the reaction of the ozonides with Et_3N are comparable to those with the reducing agent, such as Ph_3P, Me_2S or Zn in acetic acid. As far as the reaction rate, easy of removal of the by-product, and the price and odor of the reagent are concerned, the base treatment is a better choice to workup the ozonolytic reaction. This methodology has been commonly utilized in our laboratory for the synthetic designs.[2]



(1)

Recently, our interests are in studying the Tishchenko reaction and Oppenauer reaction of aldehydes promoted by diisobutylaluminium hydride (Dibal-H).[3] When the aldehydes were prepared from the corresponding terminal alkenes, we usually adopted our standard protocol with the ozonolysis followed by treatment with base. Thus, the allyl silyl ether **4** was subjected to ozonolysis in CH_2Cl_2 at −78 °C followed by the treatment with Et_3N. Surprisingly, we obtained the α-silyloxy ketone **4e** in 72% yield instead of the α-silyloxy aldehyde **4b**.[4] Presumably, the reaction of ozonide **4a** with Et_3N does not stop at the α-silyloxy aldehyde **4b**, which should be the precursor of the α-silyloxy ketone **4e**. The α-proton acidity of the α-silyloxy aldehyde **4b** is enhanced by the neighboring phenyl group so that it is deprotonated by Et_3N to give the enolate **4c**, which subsequently undergoes 1,4-silyl group migration to give the triethylammonium α-silyloxy enolate **4d**.[5] The intermediate **4d** undergoes intramolecular proton transfer to give α-silyloxy ketone **4e** and Et_3N, which is reused in the next reaction cycle (Scheme 1). By theoretical calculation, compound **4e** is more stable than compound **4b** by 3.2 kcal/mol.[6] Interestingly, if the ozonide derived from allyl silyl ether **4** was treated with Ph_3P, the α-silyloxy aldehyde **4b** was obtained in 78% yield. The fact that no rearranged product was obtained is due to the low basicity of the Ph_3P. In other words, the phenyl-substituted ozonide **4a** gave different products **4b** and **4e** in high yields when it was treated with Ph_3P and Et_3N, respectively.

The ketose–aldose isomerization is prevailing in the glycolysis catalyzed by enzyme.[7] The conversion involves acid/base catalysis, and is thought to proceed via an

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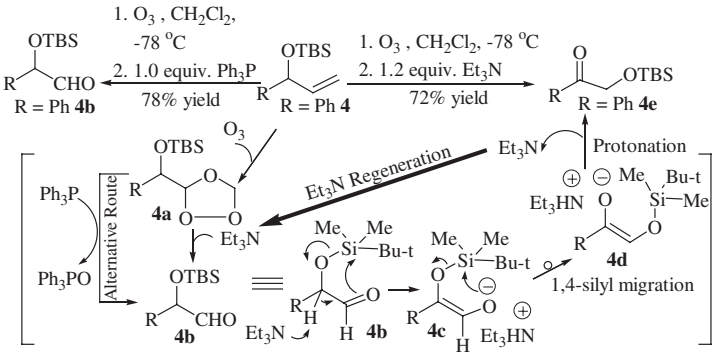


Scheme 1.

ene–diol intermediate. However, examples of the rearrangement of the α-hydroxy aldehyde to α-hydroxy ketone in nonenzymatic system rarely appear in the literature. To the best of our knowledge, there is no report for the interconversion of alkene **4** to ketone **4e** via aldehyde **4b** intermediate (Scheme 1; Table 1, entry 1). It represents a convenient and useful method for the one-carbon homologation of aldehyde **A** to ketone **D** (Fig. 1). In this letter, we would like to disclose the scope of the functional group transformation from compound **B** to product **D**. The scope of the migratory groups (i.e., Σ groups in Fig. 1) will also be discussed.

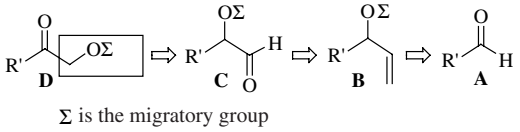
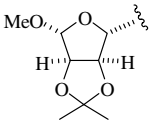
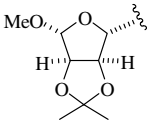


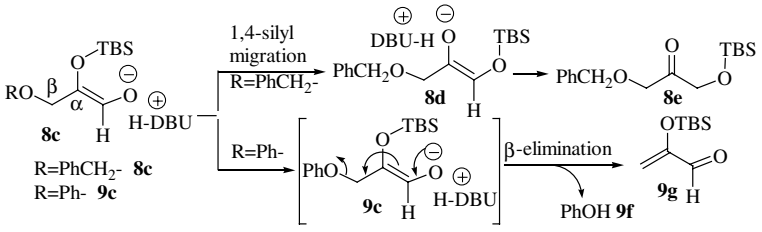
Figure 1. One carbon homologation of the aldehyde to make the α-alkoxy ketones.

When ozonide **5a**, derived from alkyl-substituted allyl silyl ether **5**, was treated with Et_3N, α-silyloxy aldehyde **5b** was obtained in good yield instead of its further rear-

Table 1. The ozonolysis of allyl silyl ether or allyl ester in CH_2Cl_2 followed by the treatment with base to give the corresponding ketone derivatives

Entry	R	Σ	Starting material	Product	Condition	Time (h)	Yield (%)[f]
1	Ph–	*t*-BuMe_2Si–	**4**	**4e**	A[a]	8	72
2	Ph$(CH_2)_3$–	*t*-BuMe_2Si–	**5**	**5e**	B[b]	14	71
3	Cyclohexyl	*t*-BuMe_2Si–	**6**	**6e**	B[b]	12	81
4	*t*-Bu–	*t*-BuMe_2Si–	**7**	**7e**	B[b]	60[e]	60
5	PhCH_2OCH_2–	*t*-BuMe_2Si–	**8**	**8e**	B[b]	5	84
6	PhOCH_2–	*t*-BuMe_2Si–	**9**	**9e**	B[b]	5	0[g]
7		*t*-BuMe_2Si–	**10**	**10e**	C[c]	7	56
8	Phenyl	Ac–	**11**	**11e**	D[d]	8	82
9	Ph$(CH_2)_3$–	Ac–	**12**	**12e**	B[b]	12	70
10	Cyclohexyl	Ac–	**13**	**13e**	B[b]	8	70
11	*t*-Butyl	Ac–	**14**	**14e**	B[b]	12	75
12		Ac–	**15**	**15e**	C[c]	7	61
13	Phenyl	Me_3CCO–	**16**	**16e**	A[a]	10	81
14	Cyclohexyl	Me_3CCO–	**17**	**17e**	B[b]	12	73
15	*t*-Butyl	Me_3CCO–	**18**	**18e**	B[b]	16	71
16	Phenyl	PhCO–	**19**	**19e**	A[a]	6	74
17	Cyclohexyl	PhCO–	**20**	**20e**	B[b]	8	67
18	Phenyl	H	**21**	**21e**	D[d]	7	55
19	Cyclohexyl	H	**22**	**22e**	C[c]	8	46

[a] Condition A: (a) O_3, CH_2Cl_2, −78 °C; (b) 1.2 equiv Et_3N, −78 °C to rt.
[b] Condition B: (a) O_3, CH_2Cl_2, −78 °C; (b) 1.2 equiv DBU, −78 °C to rt.
[c] Condition C: (a) O_3, CH_2Cl_2, −78 °C; (b) 0.8 equiv Ph_3P; (c) 0.5 equiv DBU, −78 °C to rt.
[d] Condition D: (a) O_3, CH_2Cl_2, −78 °C; (b) 0.8 equiv Ph_3P; (c) 0.5 equiv Et_3N, −78 °C to rt.
[e] Under refluxing condition.
[f] The isolated yields. All compounds were characterized by exact mass spectroscopy, IR, NMR (^1H and ^{13}C).
[g] Phenol was isolated in almost quantitative yield.



Scheme 2.

ranged product **5e**. Presumably, the α-proton acidity of the alkyl-substituted aldehyde **5b** is not strong enough to be removed by Et_3N. Therefore, a stronger base such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) is required, and α-silyloxy ketone **5e** was obtained in 71% yield (entry 2). The results of entries 1 and 2 imply that the tendency of the α-deprotonation for the α-silyloxy aldehyde is α-substituent-dependent. Et_3N is good for α-aryl substituent and DBU is good for α-alkyl substituent. Once deprotonation occurs, the subsequent 1,4-silyl migration should be a facile process because no more α-silyloxy aldehyde **5b** was observed from the reaction. Increasing the steric hindrance of the α-substituent of α-silyloxy aldehydes also gave the rearranged products in high yields (entries 3 and 4). However, for the *tert*-butyl substituted aldehyde **7b**, it needed to heat the reaction mixture in CH_2Cl_2 under refluxing for 60 h to give the *tert*-butyldimethylsilyloxy ketone **7e** in good yield (entry 4).

Both the β-elimination and 1,4-silyl migration should be the possible processes for the α-alkoxymethyl-substituted α-silyloxy aldehyde intermediates **8c** and **9c**, generated from the deprotonation of aldehydes **8b** and **9b**, respectively (Scheme 2). We found that only 1,4-silyl migration occurred for the α-benzyloxymethyl-substituted aldehyde **8c** to give α-silyloxy ketone **8e** in 84% yield (entry 5). For the reaction of α-phenoxymethyl-substituted aldehyde **9c**, however, we isolated the phenol (**9f**) resulted from the β-elimination (entry 6). The results of entries 5 and 6 indicate that any moiety with leaving aptitude better than phenoxide can not be applied to the 1,4-silyl migration purpose as shown in Scheme 2.

The high yield of the aldehyde derived from terminal alkene is crucial to the success of the present study. In some cases, if the yield of the aldehyde from the ozonide by base treatment (i.e. Conditions A and B in Table 1) was not satisfactory, Ph_3P usually was an alternative reagent (i.e. conditions C and D) for this purpose. The ozonolysis of α-(tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl) allyl silyl ether **10** followed by sequential treatment with Ph_3P and DBU gave the rearranged product **10e** in 56% yield. Even though in the presence of DBU, the retention of the C-4 configuration of the ribose ring of compound **10e** was observed (entry 7).[8] The success of this reaction may open a new entry for the chain elongation of the carbohydrates.

As for the aptitude of the migratory group in the ene–diol rearrangement, we found that the acetyl (entries 8–12), trimethylacetyl (entries 13–15) and benzoyl (entries 16 and 17) groups were comparable with *tert*-butyldimethylsilyl group (entries 1–5). When the migratory group was hydrogen, the rearranged products **21e** and **22e** were formed only in modest yields (entries 18 and 19).

In summary, the ozonolysis of substituted-allyl silyl ethers or -allyl esters followed by treatment with bases or Ph_3P afforded the corresponding α-silyloxy aldehydes or α-acyloxy aldehydes intermediates, which could be converted to the corresponding α-silyloxy ketones or α-acyloxy ketones in good yields by base (Et_3N or DBU) in the same flask. The reaction via a novel ene–diol rearrangement is proposed. In addition, the trialkylsilyl, acetyl, trimethylacetyl, and benzoyl are suitable groups for the 1,4-migration in the present synthesis. Efforts to exploit this methodology in organic synthesis are currently underway in our laboratory.

Acknowledgements

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References and notes

1. (a) Hon, Y. S.; Lin, S. W.; Chen, Y. J. *Synth. Commun.* **1993**, *23*, 1543–1553; (b) Hon, Y. S.; Lin, S. W.; Lu, L.; Chen, Y. J. *Tetrahedron* **1995**, *51*, 5019–5034.
2. (a) Hon, Y. S.; Lu, L. *Tetrahedron Lett.* **1993**, *34*, 5309–5312; (b) Hon, Y. S.; Yan, J. L. *Tetrahedron Lett.* **1993**, *34*, 6591–6594; (c) Hon, Y. S.; Yan, J. L. *Tetrahedron Lett.* **1994**, *35*, 1743–1746; (d) Hon, Y. S.; Lu, L. *Tetrahedron* **1995**, *51*, 7937–7942; (e) Hon, Y. S.; Yan, J. L. *Tetrahedron* **1997**, *53*, 5217–5232; (f) Hon, Y. S.; Yan, J. L. *Tetrahedron* **1998**, *54*, 8525–8542; (g) Hon, Y. S.; Lu, L.; Chang, R. C.; Lin, S. W.; Sun, P. P.; Lee, C. F. *Tetrahedron* **2000**, *56*, 9269–9279; (h) Hon, Y. S.; Wu, K. C. *Tetrahedron* **2003**, *59*, 493–498.
3. Hon, Y. S.; Chang, C. P.; Wong, Y. C. *Tetrahedron Lett.* **2004**, *45*, 3313–3315.
4. The typical procedure of this study is described as follows. A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar was charged with terminal alkene **4** (1 mmol) in CH_2Cl_2 (5 mL). The flask was cooled to −78 °C and ozone was bubbled through the solution. When the solution turned blue, ozone addition was stopped. Nitrogen was passed through the solution until the blue color was discharged. To the resulted

ozonide solution, Et_3N (1.2 mmol) was added at −78 °C and the reaction temperature was slowly warmed to room temperature. The reaction mixture was concentrated, chromatographed on silica gel column to give the corresponding ketone **4a** in 72% yield. Its characteristic peak in ^1H NMR is a singlet at δ 4.92 ppm due to the α-methylene group.

5. Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453–8463.
6. The geometry optimization and total electronic energy in the ground state were calculated by PM3 method. All semiempirical calculations were performed by HyperChem 6.03 on Win2000 Professional at Intel PIII 800 computer. The total energy of **4e** and **4b** are −3902.720 and −3899.544 kcal/mol, respectively.
7. Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 5th ed.; Freeman, W. H. and Company, Chapter 20.
8. The spectral data for compounds **10e**. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.27 (s, 3H), 1.40 (s, 3H), 3.35 (s, 3H), 4.40 (1/2 ABq, J = 18.0 Hz, 2H, –CH_2OTBS), 4.45 (1/2 ABq, J = 18.0 Hz, –CH_2OTBS), 4.56 (d, J = 5.8 Hz, 1H), 4.72 (d, J = 4.2 Hz, 1H), 5.04 (s, 1H), 5.10 (dd, J = 5.8 and 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.7 (q), −5.5 (q), 18.4 (s), 24.6 (q), 25.78 (q), 25.79 (q), 54.9 (q), 68.6 (t), 80.4 (d), 84.1 (d), 84.3 (d), 107.2 (d), 113.0 (s), 204.2 (s); $[\alpha]_D^{33}$ +63.1 (*c* 0.08, $CHCl_3$); IR 1742 cm^{-1}; MS *m*/*z* (relative intensity): 347 (M^++1, 2), 331 (11), 315 (9), 257 (20), 115 (36), 73 (100), 59 (26); HRMS Calcd. For $C_{16}H_{30}O_6Si$ 346.1812. Found 346.1810.