Research Article

$TiCl_4/Et_3SiH$-Mediated Regioselective Reductive Opening of Benzylidene Acetals

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ABSTRACT

The reductive ring opening of benzylidene acetals of 1,2- and 1,3-diol in the presence of titanium tetrachloride/triethyl silane has been described. All the substrates studied are unsymmetrical and found that the opening occurs from sp^2-carbon side over sp^3-carbon.

Keywords: Benzylidene acetal; Titanium tetrachloride; Triethylsilane.

1. INTRODUCTION

Benzylidene acetal is a commonly used protecting group for the immediate protection of 1,2 and 1,3-diol derivatives.[1] In particular, it plays a major role in carbohydrate chemistry.[2] The advantage of this group is either it can be deprotected to get back the diol or it can be reductively opened to get the monobenzyl ether having one free-hydroxyl group. The later approach results the selective protection of one hydroxyl group of the diol functionality, which is very significant for organic synthesis.[3] Previously, various reductive ring opening reactions of 1,3-benzylidene acetal have been studied in which a secondary benzyl ether having free primary hydroxyl group, is the usually obtained product.[4] In addition, the reductive opening of 1,2-benzylidene acetal was also explored, which may give the mixture of products.[5] However, the opening of benzylidene acetal of unsymmetrical 1,2-diols is less explored.[6] During one of our ongoing projects, we required to have an a method for the regioselective opening of benzylidene acetal of a unsymmetrical 1,2-diol. Towards this, we found titanium tetrachloride/triethylsilane[7] as an efficient reagent system and the results of our study are described in this paper (Table 1).

2. RESULTS AND DISCUSSION

Firstly, benzylidene acetal of the 1,2-diol **1a**, derived from cinnamyl alcohol using a literature procedure[8] was subjected to reductive opening using $TiCl_4$ and Et_3SiH in dichloromethane at -78 ^oC for 20 min., which provided (1*S*,2*S*)-2-(benzyloxy)-3-(*tert*-butyl-dimethylsilyloxy)-1-phenylpropan-1-ol (**2a**) in 92% yield without any traces of the other isomer (entry 1). This example clearly demonstrates the regioselectivity of benzylidene acetal opening is from sp2-carbon side over sp3-carbon to give the the product **2a** having free benzylic hydroxyl group. After this success, the reductive opening of another unsymmetrical 1,2-benzylidene acetal **1b**[9] containing one side an alkyl group and the other side α,β–unsaturated ester under TiCl4/Et3SiH reaction conditions. To our delight this reaction is also provided exclusively single isomer **2b** in 96% yield, in which the reductive opening occurred from α,β–unsaturated ester (sp2-carbon) side (entry 2). Similarly, the 1,2-benzylidene acetal **1c**[10] having TBDPS-protecting group was also gave the reductive opening product **2c** in 94% yield as a single isomer (entry 3). It is noteworthy to mention that the TBDPS protecting group is stable under the present reaction conditions. Finally, we have tested the reductive opening of a 1,3-benzylidene acetal **1d**[11], derived from tri-O-acetyl-D-glucal, using TiCl4/Et3SiH reagent system. In this case, the reductive opening was observed from primary alcohol side to give the product **2d** in 95% yield (entry 4), which demonstrates that steric factor played a role over electronic factor (sp^2/sp^3 carbon).

The plausible mechanism of acetal opening

The reaction pathway may be explained through the mechanism shown in Figure 1. In first step, the reversible formation of a linear silane-titanium adduct **A** which undergoes following nucleophilic attack by the acetal of the substrate to yield an *O*-silylated cationic intermediate **B** along with a titanium hydride anion. The titanium hydride ion then transfers a hydride to the carbon center of the O-

silylated cation to yield the reduction product **C** and regenerated free titanium. The compound gives the required product **D** upon acid hydrolysis.

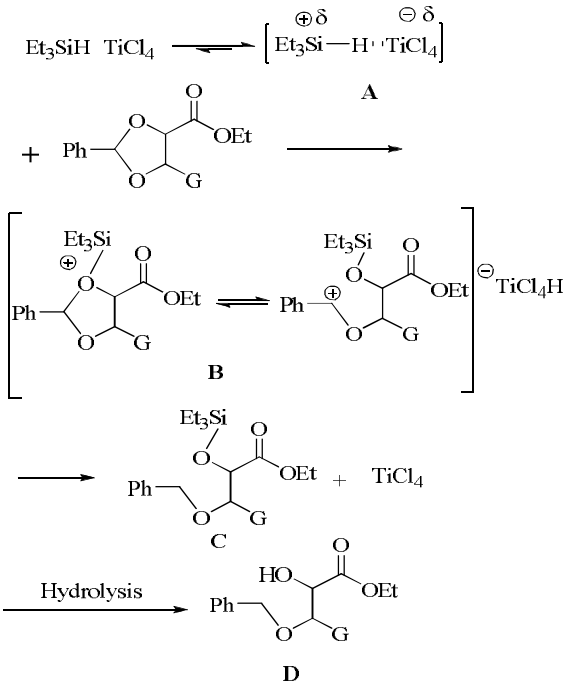
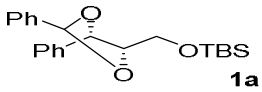
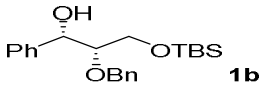
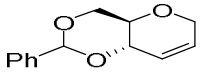
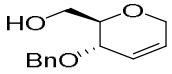
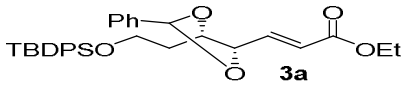
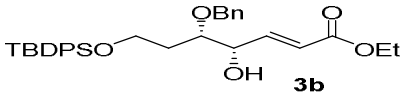
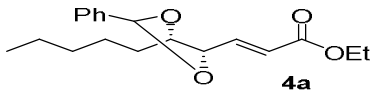
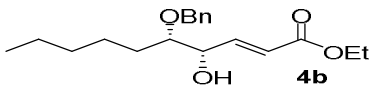


Fig. 1: Proposed Mechanism

Table 1: Reductive Opening of Benzylidene acetal[a]

Entry	Substrate (**a**)	Time (min)	Product (**b**)	Yield (%)[b]
1	 **1a**	20	 **1b**	92
2	 **2a**	25	 **2b**	95
3	 **3a**	15	 **3b**	94
4	 **4a**	20	 **4b**	96

[a]All the reactions were carried out using 4 equiv. of Et_3SiH and 1.5 equiv of $TiCl_4$ in CH_2Cl_2
[b]Isolated yields.

3. Experimental section

General procedure To a solution of acetal (Entry 3, 0.96 mmol) and Et_3SiH (0.61 ml, 3.84 mmol) in CH_2Cl_2 (10 ml) was added $TiCl_4$ (1M solution in CH_2Cl_2; 1.4 ml, 1.4mmol) at -78 ^oC and the resulting yellow solution was stirred at this temperature for 20 min. The mixture was diluted with 50 ml of EtOAc and added 10 ml of H_2O. The organic layer was extracted and aqous layer was washed with 10 ml of ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silicagel coloumn chromatography to afford the compound.

Spectral data for the new compounds

***tert*-Butyl(((4S,5S)-2,5-diphenyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (1a)**

Data on diastereoisomeric mixture $[\alpha]^{30}_D$ = +20.2 (*c* 2.0, $CHCl_3$); IR (KBr): ν_{max} 2929, 2858, 1459, 1405, 1360, 1254, 1217, 1140, 1092, 1025, 1001, 835, 775, 754 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$): *δ* 7.11-7.70 (10H, stack), 6.11,6.03 (s, 1H), 5.10,5.03 (d, *J* = 6.79, 1H), 4.16-3.60 (3H, stack), 0.87,0.83 (s, 9H), 0.04,0.02 (s, 6H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 139.5, 138.6, 138.0, 137.5, 129.2, 129.1, 128.4, 128.2, 128.2, 128.0, 127.7, 126.7, 126.5, 126.0, 104.2, 104.0, 84.7, 83.7, 80.6, 79.6, 62.6, 62.4, 25.8, 25.7, 18.2, -5.3, -5.4; HRMS (ESI): (*m/z*) calcd for $C_{22}H_{30}O_3SiNa$ 393.1856 $[M+Na]^+$; found, 393.1852.

(1*S*,2*S*)-2-(Benzyloxy)-3-(*tert*-butyldimethyl silyloxy)-1-phenylpropan-1-ol (1b)

$[\alpha]^{30}_D$ = +53.6 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max}3422, 2954, 2931, 2857, 1466, 1254, 1123, 1072, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.45-7.25 (m, 10H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.42 (AB q, *J* = 11.3 Hz, 2H), 3.78 (dt, *J* = 8.3, 4.5 Hz, 1H), 3.60 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.40 (dd, *J* = 10.5, 4.5 Hz, 1H), 2.86 (d, *J* = 3.7 Hz, 1H), 0.89 (S, 9H), 0.03(S, 3H), 0.02(S, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 138.5, 137.8, 128.3, 128.3, 128.0, 127.8, 127.6, 127.5, 81.3, 75.8, 70.6, 63.1, 25.8, -5.4, -5.5.

(4a*R*,8a*S*)-2-Phenyl-4,4a,6,8a-tetrahydropyrano [3,2-*d*][1,3]dioxine (2a)

$[\alpha]^{30}_D$ = +27.9 (*c* 2.0, $CHCl_3$); IR (KBr): ν_{max} 2933,2846, 1454, 1384, 1309, 1131, 989, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.61-7.25 (m, 5H), 5.94 (d, J = 9.82, 1H), 5.71 (d, j = 10.5, 1H), 5.56 (s, 1H), 4.39-4.11 (m, 4H), 3.74 (t, *J* = 9.8 Hz, 1H), 3.58-3.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 137.4, 128.9, 128.1, 127.3, 126.1, 126.0, 101.7, 75.1, 70.1, 69.3, 66.2; HRMS (ESI): (*m/z*) calcd for $C_{13}H_{14}O_3SiK$ 257.0784 $[M+K]^+$; found, 257.0782.

((2*R*,3*S*)-3-(Benzyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methanol (2b)

$[\alpha]^{30}_D$ = +78.8 (*c* 2.0, $CHCl_3$); IR (KBr): ν_{max} 3422, 3033, 2928, 2870, 1647, 1452, 1094, 1019, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.43-7.22 (m, 5H), 6.02-5.70 (m, 2H), 4.74-4.47 (m, 2H), 4.20-4.11 (m, 2H), 4.06-3.97 (m, 1H), 3.92-3.81 (m, 1H), 3.75-3.62 (m, 1H), 3.53-344 (m, 1H), 2.35 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 137.9, 128.3, 127.9, 127.8, 127.4, 125.5, 76.8, 71.0, 70.4, 65.4, 62.7; HRMS (ESI): (*m/z*) calcd for $C_{13}H_{16}O_3Na$ 243.0991 $[M+Na]^+$; found, 243.0989.

(*E*)-Ethyl 3-((4*S*,5*S*)-5-(2-(*tert*-butyldiphenylsilyloxy)ethyl)- 2-phenyl-1,3-dioxolan-4-yl)acrylate (3a)

Data on diastereoisomeric mixture $[\alpha]^{25}_D$ = -5.0 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 2931, 2858, 1459, 1405, 1360, 1254, 1217, 1140, 1092, 1025, 1001, 835, 775, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.73-7.60 (4H, stack), 7.52-7.29 (11H, stack), 7.03-6.92 (1H, stack), 6.22-6.10 (1H, stack), 5.98, 5.91 (s, 1H), 4.48-4.39 (1H, stack), 4.29-4.02 (q, *J* = 7.5 Hz, 2H), 3.83-3.68 (m, 3H), 2.89 (d, *J* = 8.6 Hz, 1H), 1.96-1.72 (m, 2H), 1.30 (3H, stack), 3.91-3.81 (2H, stack), 2.02-1.80 (2H, stack), 1.36-1.22(3H, stack), 1.05, 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 165.8, 165.8, 143.7, 142.9, 137.7, 137.2, 135.5, 133.4, 129.6, 129.3, 129.2, 128.3, 127.6, 126.5, 126.5, 123.1, 122.6, 103.5, 81.2, 80.0, 79.6, 78.0, 60.5, 60.4, 60.3, 35.0, 34.9, 26.8, 19.1, 14.2; HRMS (ESI): (*m/z*) calcd for $C_{32}H_{38}O_5SiNa$ 553.2380 $[M+Na]^+$; found, 553.2379.

(4*S*,5*S*,*E*)-Ethyl 5-(benzyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4-hydroxyhept-2-enoate (3b)

$[\alpha]^{25}_D$ = -9.4 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3449, 2925, 2856, 1715, 1649, 1387, 1272, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.71-7.60 (m, 4H), 7.47-7.19 (m, 11H), 7.02 (dd, *J* = 15.8, 4.5 Hz, 1H), 6.16 (dd, *J* = 15.8, 1.5 Hz, 1H), 4.54 (AB q, *J* = 11.3 Hz, 2H), 4.36-4.27 (m, 1H), 4.22 (q, *J* = 7.5 Hz, 2H), 3.83-3.68 (m, 3H), 2.89 (d, *J* = 8.6 Hz, 1H), 1.96-1.72 (m, 2H), 1.30 (t, *J* = 7.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 166.3, 147.3, 137.8, 135.5, 133.2, 133.2, 129.7, 128.4, 127.8, 127.7, 121.8, 78.7, 72.8, 72.4, 60.3, 60.2, 33.7, 26.8, 19.0, 14.2; HRMS (ESI): (*m/z*) calcd for $C_{32}H_{40}O_5SiNa$, 555.2537 $[M+Na]^+$; found, 555.2570.

(*E*)-Ethyl 3-((4*S*,5*S*)-5-pentyl-2-phenyl-1,3-dioxolan-4-yl)acrylate (4a)

Data on diastereoisomeric mixture $[\alpha]^{30}_D$ = -10.2 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 2925, 2855, 1724, 1662, 1461, 1371, 1299, 1270, 1174, 1094, 1066 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.75-7.45 (2H, stack), 7.44-7.34 (3H, stack), 6.96, 6.93 (d, *J* = 5.9 Hz, 1H), 6.22-6.12 (1H, stack), 6.02, 5.94 (s, 1H), 4.39-4.30 (1H, stack), 4.27-4.17 (2H, stack), 3.93-3.84 (1H, stack), 1.82-1.21 (1H, stack), 0.96-0.84 (3H, stack); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 165.9, 165.9, 143.9, 143.2, 129.4, 129.2, 128.3, 126.6, 126.4, 122.9, 122.4, 103.7, 103.4, 82.5, 81.4, 81.0, 80.2, 60.6, 32.3, 31.9, 31.6, 25.6, 25.5, 22.4, 14.1, 13.9; HRMS (ESI): (*m/z*) calcd for $C_{19}H_{26}O_4Na$ 341.1723 $[M+H]^+$; found, 341.1723.

(4*S*,5*S*,*E*)-Ethyl 5-(benzyloxy)-4-hydroxydec-2-enoate (4b)

$[\alpha]^{30}_D$ = +2.6 (*c* 2.0, $CHCl_3$); IR (KBr): ν_{max} 3462, 2928, 2859, 1717, 1658, 1457, 1306, 1270, 1174, 1093, 1043, 983, 871, 983, 739, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.39-7.20 (m, 5H) 6.91 (d, *J* = 15.4, 4.3 Hz, 1H),

6.10 (dd, *J* = 15.4, 1.5 Hz, 1H), 4.54 (AB q, *J* = 11.5 Hz, 2H), 4.25-4.12 (m, 3H), 3.35 (q, *J* = 5.6 Hz, 1H), 2.56 (s, 1H), 1.67-1.48 (m, 2H), 1.45-1.19 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 165.7, 142.5, 137.9, 128.3, 127.9, 127.7, 122.4, 79.2, 72.8, 72.7, 60.5, 31.6, 30.4, 25.1, 22.4, 14.1, 13.9; HRMS (ESI): (*m/z*) calcd for $C_{19}H_{28}O_4Na$ 343.1879 $[M+H]^+$; found, 343.1876.

4. CONCLUSION

In conclusion, we have demonstrated the regioselective opening of benzylidene acetal of unsymmetrical 1,2-diol using $TiCl_4$/Et3SiH reagent system to obtain the exclusively single product. This study disclosed that the reductive opening occurs from sp2-carbon side over sp3-carbon.

5. ACKNOWLEDGEMENTS

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