Study on $FeCl_3$ Induced Rearrangement Reaction of Bicyclic Acetal Compound

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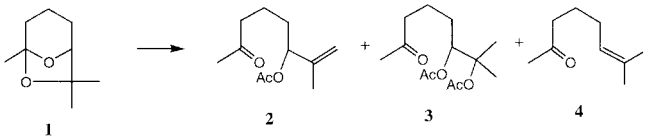
Lewis acid induced C-O bond cleavage has been well documented because it is not only important but also variable depending on the structure of starting materials.[1] In our laboratory, we explored Lewis acid systems for the specific transformation of bicyclic acetal **1** to other important structures in unique one-flask reactions.[2] Recently, we reported an interesting transformation reaction of acetal **1** to monoacetate **2**, diacetate **3** and enone **4** as 37%, 16% and 16% yield, respectively by using AcCl-NaI (Scheme 1).[3] We proposed the transformation mechanism (Scheme 2) and selectively obtained the monoacetate **2** in 85% yield as a single product by using $MgBr_2$-Ac_2O-NaOAc system.[4] We now wish to report the production of the diacetate **3** selectively.

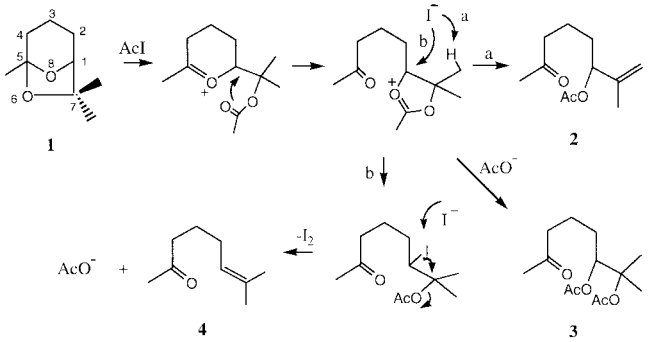
Ether cleavage and acylation with ferric chloride/acetic anhydride have been reported.[5] On the other hand, ferric chloride on silica gel has been used in dehydration of alcohols,[6] cleavage of acetals[7] and in coupling of phenol ethers.[8] Also, ferric chloride in acetic acid has been used in acetylation of alcohols, ethers and acetals.[9]

We have extended the use of $FeCl_3$ as a Lewis acid to the one pot conversion of bicyclic acetal to the corresponding

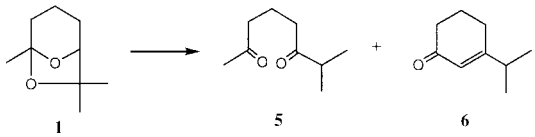


	1	2	3	4
AcCl-NaI		37%	16%	16%
$MgBr_2$-Ac_2O		5%	20%	0
$MgBr_2$-Ac_2O-NaOAc		85%	0	0

Scheme 1



Scheme 2

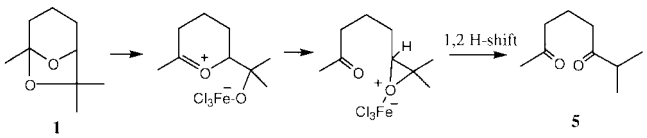


	1	5	6
$FeCl_3$-AcOH		54%	7%
$FeCl_3$-AcOH-NaI		68%	0

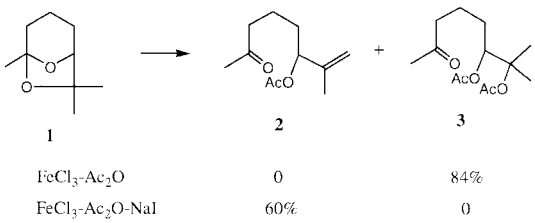
Scheme 3

diketone by rearrangement reactions. Sharma[9] used $FeCl_3$ in AcOH for the acetylation of acetal and we adopted this method for the acetylation of bicyclic acetal. The acetal **1** was refluxed overnight with $FeCl_3$ (0.3 equiv)-AcOH (3 equiv) in CH_2Cl_2 to produce the mixture of 1,5-diketone **5** (54%) and cyclohexenone **6** (7%) as shown in Scheme 3. The mechanism for the 1,5-diketone **5** should be similar to $AlCl_3$ case.[10] The C (5)-O (6) bond cleavage followed by 1,2-hydride shift *via* an epoxide intermediate produced the diketone **5**, and further reaction proceeded to afford the cyclohexenone **6** as aldol product (Scheme 4). The addition of NaI (1 equiv) in the reaction produced only the diketone in 68% yield. The reaction mechanism of NaI in the reaction was not exactly known, but it prohibited the aldol condensation as shown in TMSCl-NaI system.[2j]

The substitution of AcOH to acetic anhydride in the reaction produced the expected diacetate **3** (Scheme 5). Thus, the acetal **1** was refluxed overnight with $FeCl_3$ (0.3 equiv)-Ac_2O (3 equiv) in CH_2Cl_2 and yielded the diacetate **3** in 84% yield



Scheme 4



	1	2	3
$FeCl_3$-Ac_2O		0	84%
$FeCl_3$-Ac_2O-NaI		60%	0

Scheme 5

as a single product. Addition of NaI (1 equiv) in the reaction produced only the monoacetate **2** in 60% yield. From the results, we can propose the role of NaI in the reaction as a diminishing the nucleophilicity of acetate anion, but increasing the basicity.

In conclusion, the diacetate **3** was selectively obtained from the acetal **1** by using $FeCl_3$ with Ac_2O in CH_2Cl_2, while, the monoacetate **2** was also obtained selectively by the addition of NaI in the reaction. But, the best way to make the monoacetate will be the use of $MgBr_2$-Ac_2O-NaOAc system.

Experimental Section

All chemicals used were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded at Varian Gemini-400 MHz FT-NMR for ^1H and 100 MHz for ^{13}C, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Infrared spectra were recorded on a Shimadzu IR-435 spectrometer. GC-MS analyses were performed using a HP-5890/JMS-AM 150, JEOL. Flash chromatography was carried out using silica gel Merck 60 (230-400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F254 (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with *p*-anisaldehyde.

Procedure by using $FeCl_3$-AcOH. To a solution of $FeCl_3$ (50 mg, 0.19 mmol) and AcOH (0.11 mL, 1.92 mmol) in methylene chloride (10 mL) under nitrogen atmosphere was added bicyclic acetal **1** (0.10 g, 0.64 mmol) and refluxed for 15 hr. The reaction was quenched by the addition of 10% aqueous sodium hydroxide solution (10 mL). The organic product was extracted with diethyl ether, washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 2 : 1) to give the 1,5-diketone **5** (54 mg, 54%, R_f 0.38) and the cyclohexenone **6** (7 mg, 7%, R_f 0.69).[2f]

Procedure by using $FeCl_3$-AcOH-NaI. To a solution of $FeCl_3$ (50 mg, 0.19 mmol), NaI (100 mg, 0.64 mmol) and AcOH (0.11 mL, 1.92 mmol) in methylene chloride (10 mL) under nitrogen atmosphere was added bicyclic acetal **1** (0.10 g, 0.64 mmol) and refluxed for 15 hr. The reaction was quenched by the addition of 10% aqueous sodium hydroxide solution (10 mL). The organic product was extracted with diethyl ether, washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 2 : 1) to give 7-methyloctane-2,6-dione (**5**) (68 mg, 68%, R_f 0.38).]: ^1H NMR ($CDCl_3$): δ 2.58 (1H, m, H-7), 2.49 (2H, t, J = 7 Hz, $COCH_2$), 2.46 (2H, t, J = 7 Hz, $COCH_2$), 2.13 (3H, s, CH_3CO), 1.83 (2H, quintet, J = 7 Hz, CH_2) 1.09 (6H, d, J = 7 Hz, 2 x CH_3); ^{13}C NMR ($CDCl_3$): δ 214.2 (s), 208.4 (s), 42.6 (t), 40.8 (d), 39.0 (t), 29.8 (q), 18.2 (q, 2 x Me), 17.8 (t); IR (neat): 2963, 1709 (br, C=O), 1465, 1410, 1379, 1174, 1089 cm^{-1}. Ms m/z 156 (M^+), 141, 123, 113, 85(base), 71, 55; HRMS calcd for $C_9H_{16}O_2$ (M^-) 156.1150, found 156.1148.

Procedure by using $FeCl_3$-Ac_2O. To a solution of $FeCl_3$ (30 mg, 0.01 mmol) and Ac_2O (0.10 mL, 0.96 mmol) in methylene chloride (10 mL) under nitrogen atmosphere was added bicyclic acetal **1** (0.05 g, 0.32 mmol) and refluxed for 15 hr. The reaction was quenched by the addition of 10% aqueous sodium hydroxide solution (10 mL). The organic product was extracted with diethyl ether, washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 2 : 1) to give 6,7-diacetoxy-7-methyl-2-octanone (**3**) (42 mg, 84%, R_f 0.32): ^1H NMR ($CDCl_3$): δ 5.15 (1H, m, H-6), 2.43 (2H, m, $COCH_2$), 2.12 (3H, s, CH_3CO), 2.08 (3H, s, $OCOCH_3$), 1.94 (3H, s, $OCOCH_3$), 1.7-1.5 (4H, m, CH_2CH_2), 1.43 (3H, s, CH_3), 1.40 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$): δ 208.4 (s), 170.5 (s), 170.0 (s), 82.4 (s), 76.2 (d), 42.7 (t), 29.8 (q), 28.1 (t), 22.2 (q), 22.1 (t), 22.0 (q), 20.8 (q), 19.7 (q); IR (neat): 1690 (br, C=O), 1351, 1220, 1130, 1010 cm^{-1}; Ms m/z 157 (M^--2CH_2CO-OH), 141, 115, 97, 71, 59, 43 (base); HRMS calcd for $C_9H_{17}O_2$ (M^+-2CH_2CO-OH) 157.1229, found 157.1201.

Procedure by using $FeCl_3$-Ac_2O-NaI. To a solution of $FeCl_3$ (30 mg, 0.01 mmol), NaI (50 mg, 0.32 mmol) and Ac_2O (0.10 mL, 0.96 mmol) in methylene chloride (10 mL) under nitrogen atmosphere was added bicyclic acetal **1** (0.05 g, 0.32 mmol) and refluxed for 15 hr. The reaction was quenched by the addition of 10% aqueous sodium hydroxide solution (10 mL). The organic product was extracted with diethyl ether, washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 2 : 1) to give 6-acetoxy-7-methyl-7-octen-2-one (**2**) (30 mg, 60%, R_f 0.32): ^1H NMR ($CDCl_3$): δ 5.14 (1H, t, J = 5.5 Hz, H-6), 4.93 (1H, br s, C=CH), 4.87 (1H, br s, C=CH), 2.43 (2H, t, J = 7 Hz, $COCH_2$), 2.12 (3H, s, CH_3CO), 2.04 (3H, s, $OCOCH_3$), 1.70 (3H, br s, CH_3C=C), 1.7-1.5 (4H, m, CH_2CH_2); ^{13}C NMR ($CDCl_3$): δ 208.3 (s, C=O), 170.2 (s, ester C=O), 142.8 (s, $\underline{C}$=CH_2), 112.8 (t, $\underline{C}H_2$=C), 76.8 (d, $\underline{C}$HOAc), 43.0 (t, CO$\underline{C}H_2$), 31.9 (t, $\underline{C}H_2$CHOAc), 29.8 (q, $\underline{C}H_3CO$), 21.1 (q, $\underline{C}H_3COO$), 19.4 (t, $CH_2\underline{C}H_2CH_2$), 18.0 (q, $\underline{C}H_3C$=C); IR (neat): 1695 (br, C=O), 1351, 1225, 1012 cm^{-1}; Ms m/z 156 (M^--CH_2CO), 138, 95, 81, 71, 58, 43 (base); HRMS calcd for $C_9H_{16}O_2$ (M^--CH_2CO) 156.1150, found 156.1151.

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