Notes

Facile Conversion of Active Amide to Ester by Acidic Al_2O_3 and Resin in Alcohol Solution : Synthesis of 5-Substituted-2(5*H*)-Furanones

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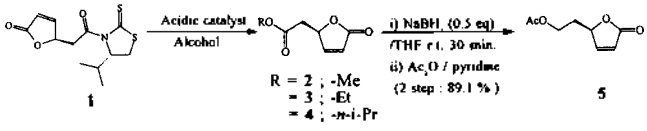
Optically active 5-substituted-2(5*H*)-furanone (**2**, **3** and **4**) should be remarkably useful as chiral synthons for the synthesis of a large number of natural products.[1] Due to the increasing interests in the high versatility of butenolide, there have been many reports on the preparation of optically active α,β-unsaturated-γ-lactones.[2] In connection with our synthetic approach to optically pure 5-acetoxyethyl-2(5*H*)-furanone **5** by use of asymmetric chiral induction methods, we envisioned that it would be possible to prepare the optically pure 5-alkoxycarbonylmethyl-2(5*H*)-furanone derivatives (**2**, **3** and **4**) as intermediates for the preparation of **5** from **1**.

The reported synthesis of methyl- or ethyl ester **2** and **3** involved chromatographic resolution experiment[3] and other methods.[4] The methyl ester **2** was reported as a mildly cytotoxic compound isolated from marine sponges.[5] The methyl ester **2** has been prepared through high temperature thermolysis followed by oxidation reaction,[6] enzymatic method,[7] or biochemical methods.[8] In this paper, we would like to describe an efficient method for the synthesis of **2**, **3** and **4** utilizing acidic catalytic hydrolysis of active amide **1** in alcohol solution (Scheme 1).

The optically active compound **1** was synthesized by asymmetric methods between the chiral tin(II)enolate[9] and 5-hydroxy-2(5*H*)-furanone[10] [86% yield, $[\alpha]_D$ 222.5 (*c* 0.59, $CHCl_3$), >99% ee].[11] Greenleea[12] have shown that Amberlyst 15 ion exchange resin could undergo the conversion of carboxamide to ester under mild conditions. With the encouraging results of Greenlee, we sought that the use of acidic resin or aluminium oxide (Al_2O_3) would result in similar catalytic behaviors.

We initiated our experiments with catalytic amount of *p*-toluenesulfonic acid (entry 1) for testing the effectiveness of acidc hydrolysis. As a consequence, *p*-toluenesulfonic acid have proven to be effective for esterification of active amide **1** at 60 °C in alcoholic solution (78% yield of **2a**, 65% yield of **3a**, 78% yield of **4a**) as shown in Table 1.

In acidic aluminium oxide (entry 2 and 5), it showed low effectiveness for conversion in catalytic amounts, however when used in 50% wt amount of **1**, the conversion (by TLC) was almost proceeded though there were some difference in reaction time. In case of acidic resin, it also showed similar efficacy (entry 3, 6 and 8) with *p*-TsOH when used in 50% wt amount of **1**. Therefore, both acidic aluminium oxide and resin effectively underwent the conversion of active amide **1** to ester in high yield under mild condition.



Scheme 1.

The (*R*)-absolute configration of the asymmetric center in **2a**, which follows from **1**, has been confirmed by comparison with reported analytical data.[5] In this method, we obtained **2a** very effectively under mild conditions and the recovered **6** (4(*S*)-IPTT) was also useful reagent for the preparation of optically active **1**. Compound **2a** was reduced by $NaBH_4$ (0.5 eq) in THF solution, followed by acylation with acetic anhydride in pyridine to afford **5**[13] [89.1% overall yield, $[[\alpha]_D$ −48.6 (*c* 2.2, $CHCl_3$)] as shown in Scheme 1.

In conclusion, we have demonstrated that *p*-TsOH, acidic aluminium oxide and resin can be effectively applied to the synthesis of esters (**2**, **3** and **4**) from **1** under mild conditions.

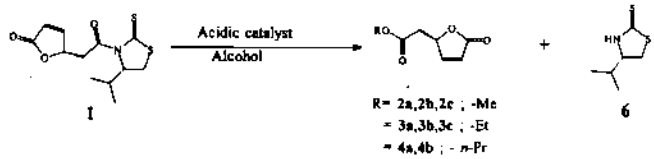
Further use of the optically active butenolide **5** for the synthesis of new nucleoside derivatives are currently under investigation.

Experimental

All melting points were determined on a Thomas Hoover Capillary melting point apparatus and are incorrected. Proton magnetic resonance (NMR) were recorded on either a Varial Gemini XL-200 or Bruker AM 300 spectrometer. Shift were reported in d units relative to internal tetramethylsilane (TMS) as a standard. ^{13}C NMR spectra were recorded at 100 Hz on the same instruments. Mass spectra were obtained using a Jeol JMS-DX 303 GC/MS and Shimadzu GCMS-QP 5000 Mass spectrometer. All relative intensity were reported only 15% over. Infrared (IR) spectra were recorded in reciprocal centimeter (cm^{-1}) units. Products were purified by column chromatography using Merck silica gel 60 (230-400 mesh ASTM).

Typical procedure for the synthesis of 2a, 3a and 4a. Mixure of **1** (0.10 g, 0.35 mmol) and 0.05 g of *p*-toluenesulfonic acid in 5 mL of alcohol (**2a**: methonal; **3a**: ethanol; **4a**: isopropanol) solution was stirred at 60 °C (reaction time-methanol: 36 hrs; ethanol: 42 hrs; propanol:

Table 1. Reaction results for the conversion of **1** to esters in acidic conditions



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Entry	Product	Alcohol	Catalyst[a]	Temp (°C)	Time (h)	Yield (%)	$[\alpha]_D$ (c in $CHCl_3$)
1	**2a**	MeOH	*p*-TsOH	60	36	78	+56.3 (0.24)
2	**2b**	"	Al_2O_3	"	43	73	+58.2 (0.94)
3	**2c**	"	Resin	"	38	73	+55.8 (1.00)
4	**3a**	EtOH	*p*-TsOH	"	42	65	+70.8 (0.12)
5	**3b**	"	Al_2O_3	"	60	53	+71.0 (0.12)
6	**3c**	"	Resin	"	48	77	+69.0 (0.72)
7	**4a**	*n*-PrOH	*p*-TsOH	"	56	78	+73.8 (1.50)
8	**4b**	"	Resin	"	58	78	+75.0 (0.72)

[a] Used amount of catalyst: 50% wt of **1**. i) Al_2O_3: activated, acidic, Brockmann I, standard grade, 150 mesh. ii) Resin: Amberlyst 15 ion-exchange resin, strongly acidic.

56 hrs). The solvent was evaporated and crude products was purified by column chromatography using EOAc-hexane (1 : 2) as an eluent to yield **2a** (50 mg, 78%), **3a** (38.7 mg, 65%) and **4a** (50 mg, 78%) as an oil. Spectral data of **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, J=5.6, 1.5 Hz, H-4), 6.16 (dd, J=5.9, 1.9 Hz, H-3), 5.41 (tt, J_{ax+bx}=16 Hz, J_{1t}=3.11 Hz, H-5), 3.75 (s, -OMe), 2.61-2.93 (8-linemult, J_{ab} =16.6 Hz, H-6, H-6'); ^{13}C NMR (75.5 MHz, $CDCl_3$) 172.3 (C-2 or C-7), 169.4 (C-7 or C-2), 155.4 (C-4), 122.2 (C-3), 78.9 (C-5), 52.3 (-OMe), 37.6 (C-6); IR (neat) 1748, 1678, 1153 cm^{-1}; MS m/z (fragment, %) 157 (M^++1, 55), 156 (M^+, 18), 125 (M^+, -OMe), 96 (M^+, -H, -CO_2Me), 83 (M^+, -CH_2CO_2Me, 100); $[\alpha]_D$ +56.3 (c 0.24 in $CHCl_3$); Anal. Calcd for $C_7H_{12}O_4$: C, 58.85; H, 5.16; Found. C, 58.86; H, 5.19. Spectral data of **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J=5.8, 1.5 Hz, H-4), 6.15 (dd, J=5.7, 2.0 Hz, H-3), 5.39 (tt, J_{ax+bx}=14.1 Hz, J_{1t}=3.0 Hz, H-5), 4.09 (q, -CH_2-), 2.55-2.89 (8-linemult, J_{ab}=39.4 Hz, H-6, H-6'), 1.22 (t, -CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 172.3 (C-2 or C-7), 168.9 (C-7 or C-2), 155.4 (C-4), 122.1 (C-3), 78.9 (C-5), 61.3 (C-6), 37.8 (-CH_2-), 21.0 (-CH_3); IR (neat) 1744, 1151, 1017 cm^{-1}; MS m/z (fragment, %) 171 (M^++1, 35), 170 (M^+), 143 (M^+, -CH_2CH_3), 125 (M^+, -OEt), 96 (M^+, -CO_2Et), 83 (M^+, -CH_2CO_2Me, 100); $[\alpha]_D$ +70.8 (c 0.12 in $CHCl_3$); Anal. Calcd for $C_8H_{10}O_4$: C, 56.45; H, 5.93; Found. C, 56.45; H, 5.94. Spectral data of **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J=4.2, 1.5 Hz, H-4), 6.15 (dd, J=3.7, 1.9 Hz, H-3), 5.40 (tt, J_{ax+bx}=16 Hz, J_{1t}=3.6 Hz, H-5), 4.05 (t, -OCH_2-), 2.58-2.89 (8-linemult, J_{ab}=40.5 Hz, H-6, H-6'), 1.65 (m, -CH_2-), 0.95 (t, -CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 172.3 (C-2 or C-7), 168.9 (C-7 or C-2), 155.8 (C-4), 122.1 (C-3), 79.1 (C-3), 66.9 (C-6), 41.9 (-OCH_2-), 21.8 (-CH_3), 10.3 (-CH_3); IR (neat) 1745, 1694, 1150 cm^{-1}; MS m/z (fragment, %) 185 (M^+), 83 (M^+, -CH_2CO_2-n-Pr, 100); $[\alpha]_D$ +73.8 (c 1.50 in $CHCl_3$); Anal. Calcd for $C_9H_{12}O_4$: C, 58.67; H, 6.57; Found. C, 58.69; H, 6.59.

Typical procedure for the synthesis of 2b and 3b. Mixure of **1** (0.13 g, 0.46 mmol) and 0.06 g of aluminium oxide (activated acidic, Brockmann I, standard grade, 150 mesh) in 8 mL of alcohol (**2b**: methonal; **3b**: ethanol) solution was stirred at 60 °C (reaction time-methanol: 43 hrs; ethanol: 60 hrs). Aluminium oxide was removed by filtration through the celite pad and washed with alcohol (8 mL). The alcohol was evaporated and crude products was purified by column chromatography using EOAc-hexane (1 : 2) as an eluent to yield **2b** (52.4 mg, 73%) and **3b** (41.4 mg, 53%) as an oil. Spectral data was refered in previous experimental.

Typical procedure for the synthesis of **2c**, **3c** and **4b**. Mixure of **1** (0.26 g, 0.92 mmol) and 0.12 g of resin (Amberlyst 15 ion-exchange resin, strongly acidic) in 10 mL of alcohol (**2c**: methonal; **3c**: ethanol; **4b**: *n*-propanol) solution was stirred at 60 °C (reaction time-methanol: 38 hrs; ethanol: 48 hrs; propanol: 58 hrs). resin was removed by filtration through the celite pad and washed with alcohol (10 mL). The alcohol was evaporated and crude products was purified by column chromatography using EOAc-hexane (1 : 2) as an eluent to yield **2c** (105 mg, 73%), **3c** (120 mg, 77%) and **4b** (132 mg, 78%) as an oil. Spectral data was refered in previous experimental.

Preparation of 5-acetoxyethyl-2(5*H*)-furanones (5). Compound **2a** (2.4 g, 15.4 mmol) was dissolved in 10 mL of anhydrous THF. $NaBH_4$ (0.29 g, 7.7 mmol) was added to the mixture at room temperature and stirred for 30 minutes. To the mixture 5% aqueous HCl solution was added at 0 °C and extracted with EtOAc (10 mL × 3). The organic layer was seperated and dried by anhydrous Na_2SO_4, and then concentrated. The crude residue was dissolved in 10 mL of pyridine. Aceticanhydride (1.9 mL, 20.0 mmol) was added to the mixture at 0 °C and stirred at room temperature for 3 hrs. The mixture was poured into the ice-water (20 mL) and extracted with EtOAc (10 mL). The organic layer was seperated and dried by anhydrous $MgSO_4$, and then concentrated to afford **5** (0.26 g, 89.1%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (dd, J=5.8, 1.5 Hz, 1H), 6.12 (dd, J=5.7, 2.1 Hz, 1H), 5.28-5.24 (m, 1H), 3.91-3.69 (m, 2H), 2.25 (s, 3H), 2.13-2.00 (m, 1H), 1.91-1.85 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 173.5 (C-2), 167.4 (CH_3CO-), 158.0 (C-4), 120.8 (C-3), 81.6 (C-5), 58.5 (-CH_2), 36.1 (-CH_2-), 21.8 (-CH_3) ppm; IR (neat) 1759, 1693, 1610, 1110, 1069, 1050, 819 cm^{-1}; MS m/z (fragment, %) 171 (M^++1, 10), 170 (M^+, 45), 127 (M^+, -$COCH_3$), 111 (M^+, -$OCOCH_3$),

83 (M^+, $-CH_2CH_2-OCOCH_3$, 100); $[\alpha]_D$ -48.6 (*c* 2.2, $CHCl_3$); Anal. Calcd for $C_8H_{10}O_4$: C, 56.47 H, 5.92; Found. C, 56.48; H, 5.94.

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Ordering Behavior in A-Site Modified $Pb_{1-x}Bi_x(Mg_{(1+x)/3}Nb_{(2-x)/3})O_3$ and $Pb_{1-x}La_x(Mg_{(1+x)/3}Ta_{(2-x)/3})O_3$ Ceramics

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Complex perovskite compounds, $A(B'B'')O_3$, exhibit a different ordering behavior depending on the charge and size differences of B-site cations.[1-3] Among them, the order-disorder phenomena in lead-based $Pb(B'B'')O_3$ ceramics have been extensively investigated because the dielectric properties of the ceramics are closely related to the degree of the ordering of B-site cations. The degree of ordering can be controlled in some ceramics such as $Pb(Sc_{1/2}Ta_{1/2})O_3$ and $Pb(Sc_{1/2}Nb_{1/2})O_3$ by thermal annealing.[2,4,5] Generally, the presence of the ordering in $A(B'B'')O_3$ perovskites has been expected by considering the electrostatic and mechanical forces, generated by the differences in ionic valence and in ionic radii of the B' and B'' ions. In addition, the degree of ordering in $Pb(Mg_{1/3}Nb_{2/3})O_3$ (PMN), firstly observed by Krause *et al.*, can be only enhanced by incorporation La^{3+} into Pb^{2+} sites in PMN lattices.[6-8]

In this study, we have investigated the charge and size effects of donor dopants on the degree of ordering in perovskite type $Pb_{1-x}Bi_x(Mg_{(1+x)/3}Nb_{(2-x)/3})O_3$ (PBiMN) and $Pb_{1-x}La_x(Mg_{(1+x)/3}Ta_{(2-x)/3})O_3$ (PLaMT) ceramics.

Experimental

To fabricate the polycrystalline samples of perovskite phases with minimal pyrochlore impurities, the columbite precursor method was used.[9] The appropriate amounts of MgO and Nb_2O_5 or Ta_2O_5 powder were mixed by ball-milling in ethanol for 12 h. After drying, the mixture was calcined at 1000 °C for 4 h. The columbite precursors ($MgNb_2O_6$ and $MgTa_2O_6$) were then mixed with the required amounts of PbO, Bi_2O_3, La_2O_3 and MgO powder, and calcined in a covered alumina crucible at 800 °C for 2 h at a heating rate of 200 °C/h.

The calcined powders were mixed with 2 wt.% poly (vinyl alcohol) added as a binder and cold-pressed into cylindrical pellets. Following binder burnout at 600 °C, the pel-