Stereoselective Preparation of 3-Alkanoylprop-2-en-1-ol Derivatives

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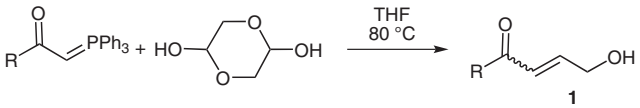
Received 10 November 2008

Abstract:: 3-Alkanoylprop-2-en-1-ol derivatives were prepared stereoselectively by ring-opening reaction of β,γ-epoxyketone with amines.

Key words: epoxide, amine, enone, rearrangement, alcohol

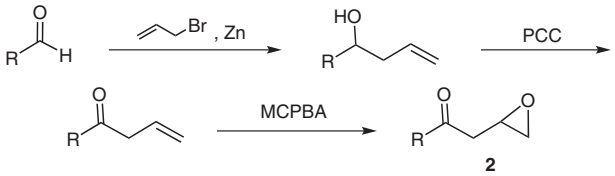
The high reactivity of 3-alkanoylprop-2-en-1-ol derivatives **1** as a Michael acceptor was explained by an assistance of oxygen atom at γ-position.[1] Various transformations starting from **1** such as furan[1a] or β,γ-dihydroxy ketone formation[1b] have been already reported. A preparation of the substrate had been performed by Wittig reaction between benzoylmethylenetriphenyphosphorane and glycoaldehyde dimer (Scheme 1).[2] Although the reaction was proceeded efficiently in the reported literature, the availability of Wittig reagent, however, will cause a limitation for this method, so we had tried to develop the more general scheme for the preparation of 3-alkanoylprop-2-en-1-ol.[3]



Scheme 1 Preparation of 3-alkanoylprop-2-en-1-ol (**1**) by Wittig reaction

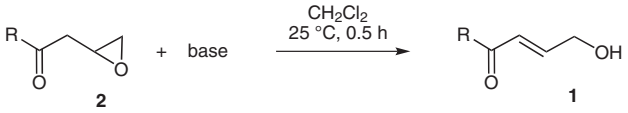
We planned to prepare the series of 3-alkanoylprop-2-en-1-ol **1** stereoselectively by a ring opening of β,γ-epoxy ketone with base. As shown in Scheme 2, a homoallylic alcohol, which was prepared by a reaction of aldehyde, allyl bromide, and zinc,[4] was converted into β,γ-unsaturated ketone by PCC. Treatment of the unsaturated ketone with MCPBA gave the corresponding β,γ-epoxy ketone **2**. All steps proceeded in good yields. For example, starting from benzaldehyde (R = Ph), the corresponding epoxide **2a** was obtained in 53% overall yield. Starting from **2**, a ring opening of β,γ-epoxy ketone with a base was examined.[5]

As shown in Table 1, 2-(oxiran-2-yl)-1-phenylethanone (**2a**, R = Ph) was treated with various amines (entries 1–5). Among them, triethylamine and *N*,*N*-dimethylpyridin-4-amine (DMAP) gave the satisfactory results. In both cases, the corresponding *E*-isomer was obtained exclusively. Treatment of **2a** with pyridine, imidazole, or Hünig's base (*i*-Pr_2NEt) was suffered from low conversion. A use of catalytic amount of DMAP with a stoichiometric amount of pyridine or K_2CO_3 did not give a satisfactory result (entries 6 and 7). Other epoxides, **2b** and **2c**, were also converted into the corresponding *E*-enones **1b**,**c** efficiently (entries 9–12) with triethylamine or DMAP.



Scheme 2 Preparation of 2-(oxiran-2-yl)-1-alkylethanone **2**

Table 1 Reaction of β,γ-Epoxy Ketone with Various Bases[a]



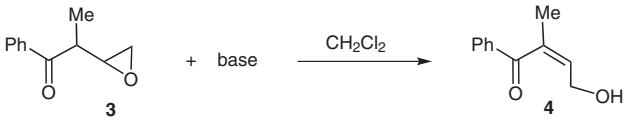
Entry	R	Base	Recovered **2** (%)	Yield of **1** (%)	*E*/*Z*[b]
1	Ph	Et_3N (1.0)	**2a** 0	**1a** 93	95:5
2	Ph	pyridine (1.0)	**2a** 90	**1a** 0	–
3	Ph	*i*-Pr_2NEt (1.0)	**2a** 55	**1a** 42	97:3
4	Ph	imidazole (1.0)	**2a** 53	**1a** 14	95:5
5	Ph	DMAP (1.0)	**2a** 0	**1a** 82	98:2
6	Ph	DMAP (0.2), pyridine (1.0)	**2a** 43	**1a** 36	98:2
7	Ph	DMAP (0.2), K_2CO_3 (1.0)	**2a** 37	**1a** 37	98:2
8	Ph	Et_3N (0.2), pyridine (1.0)	**2a** 3	**1a** 94	96:4
9	4-$F_3CC_6H_4$	Et_3N (1.0)	**2b** 0	**1b** 82	93:7
10	4-$F_3CC_6H_4$	DMAP (1.0)	**2b** 0	**1b** 82	98:2
11	$PhCH_2CH_2$	Et_3N (1.0)	**2c** 0	**1c** 98	*E* only[6]
12	$PhCH_2CH_2$	DMAP (1.0)	**2c** 0	**1c** 51	94:6

[a] Compound **2** (0.5 mmol) was treated with base in CH_2Cl_2 (1.0 mL) for 0.5 h at 25 °C.
[b] The ratio of diastereomers were determined with ^1H NMR analysis.

SYNLETT 2009, No. 5, pp 0724–0726
Advanced online publication: 24.02.2009
DOI: 10.1055/s-0028-1087930; Art ID: U11908ST

The ring-opening reaction of 2-(oxiran-2-yl)-1-phenylpropan-1-one (**3**) was also examined as shown in Table 2. The substrate will give trisubstituted alkene. In this case, treatment with triethylamine or DMAP at 25 °C did not afford the ring-opening product. Under increased reaction temperature, the product was obtained in only 5% yield. The configuration of the product was determined to be *Z*.[7] A use of DBU as a base at 25 °C gave the corresponding product in 97% yield with the perfect *Z*-diastereoselectivity.

Table 2 Reaction of 2-(Oxiran-2-yl)-1-phenylpropan-1-one (**3**) with Amines[a]

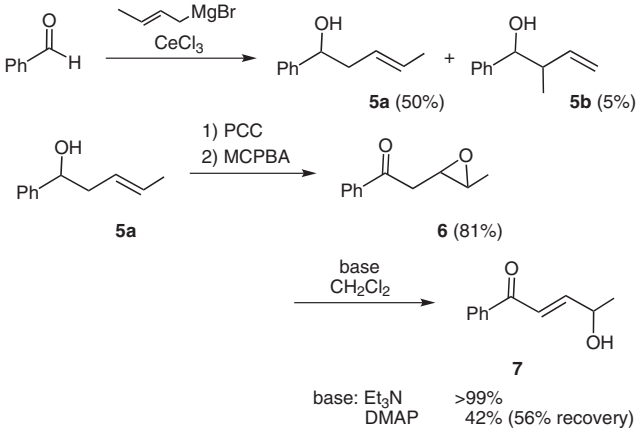


Entry	Temp (°C)	Time (h)	Base	Yield of **4** (%)	*E*/*Z*[b]
1	25	0.5	Et_3N (1.0)	0	–
2	50	3	Et_3N (1.0)	5	*Z* only
3	25	0.5	DMAP (1.0)	0	–
4	50	3	DMAP (1.0)	5	*Z* only
5	25	0.5	DBU (1.0)	97	*Z* only
6	50	0.5	DBU (1.0)	94	*Z* only

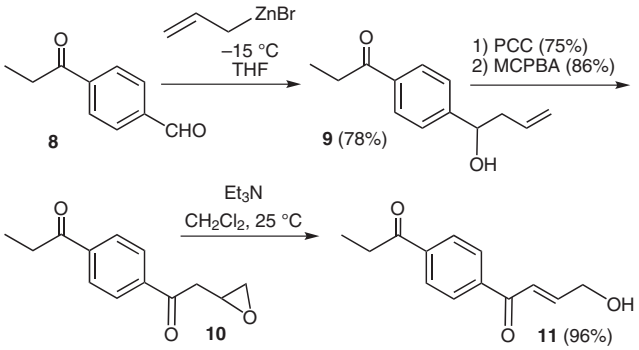
[a] Compound **3** (0.5 mmol) was treated with base in CH_2Cl_2 (1.0 mL) for 0.5 h at 25 or 50 °C.
[b] The ratio of diastereomers was determined with ^1H NMR analysis.

Derivatives of 2-(3-methyloxiran-2-yl)-1-alkylethanone **6** can be prepared starting from aldehyde and crotylmagnesium bromide as shown in Scheme 3. In this transformation, α-selective nucleophilic addition of crotylmagnesium was necessary. We chose cerium(III) chloride mediated reaction developed by Imamoto.[8] The exclusively formed α-adduct **5a** was converted into β,γ-epoxy ketone **6** in good yield. Treatment of **6** with triethylamine gave (*E*)-4-hydroxy-1-phenylpent-2-en-1-one (**7**) quantitatively (Scheme 3).

As mentioned above, the β,γ-epoxy ketone was prepared from aldehyde via three steps. Because the first step, allylation of aldehyde, is able to be performed in the presence of ketone, the transformations to the γ-hydroxyenones were applied to the ketoaldehyde such as ethyl 4-formylphenyl ketone (**8**) (Scheme 4). Reaction of the ketoaldehyde **8** with allylzinc bromide at –15 °C gave homoallylic alcohol **9** in 78% yield. Treatment of **9** with PCC and MCPBA sequentially afforded the epoxy diketone **10** in 86% yield. The compound **10** was converted into γ-hydroxyenones containing keto group **11** in 96% yield.

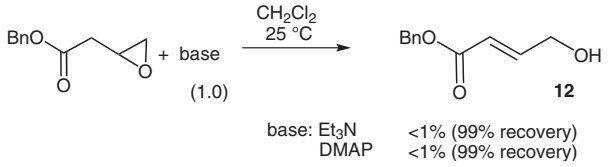


Scheme 3 Preparation of 2-(3-methyloxiran-2-yl)-1-phenylethanone (**6**) and its transformation into (*E*)-4-hydroxy-1-phenylpent-2-en-1-one (**7**)



Scheme 4 Preparation of (*E*)-4-hydroxy-1-(4-propionylphenyl)but-2-en-1-one (**11**)

Preparation of 3-hydroxy-α,β-unsaturated ester was also studied (Scheme 5). Benzyl 2-(oxiran-2-yl)acetate, which was prepared from benzyl 3-betenoate and MCPBA, was treated with amines. While treatment with triethylamine and DMAP in dichloromethane resulted in a complete recovery of starting material, **12** was obtained in the presence of DBU in 91% yield.



Scheme 5 Preparation of (*E*)-benzyl 4-hydroxybut-2-enoate

The stereoselective formation of 3-alkanoylprop-2-en-1-ol via ring-opening of the β,γ-epoxy carbonyl compounds can be achieved efficiently by the amine having the appropriate basicity. As the substrates **2**, **3**, and **6** are easily obtained via a three-step transformation from the aldehyde as shown in Scheme 2, we can solve the problem concerning the availability of the title compound.

2-(Oxiran-2-yl)-1-phenylethanone (2a)
To a dispersion of zinc dust (70 mmol) in THF (20 mL), allyl bromide (5.0 mmol) was added at 25 °C. After exothermic reaction started, a mixture of allyl bromide (55 mmol) and benzaldehyde (50 mmol) in THF (50 mL) was added dropwise. The whole was stirred vigorously for 10 h at 25 °C. After addition of 1 M HCl, the mixture was extracted with EtOAc–hexane (1:1). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was dissolved into CH_2Cl_2 (70 mL). Then, PCC (65 mmol) was added to the solution in several portions at 0 °C. After an addition of PCC, the mixture was stirred vigorously at 25 °C for 6 h. The mixture was diluted with CH_2Cl_2 (100 mL) and passed through a short silica gel column. The residue was washed with EtOAc (50 mL). The EtOAc solution was also passed through the silica gel column. The combined organic solution was dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved into CH_2Cl_2 (50 mL). Then, MCPBA (55 mmol) was added to the solution in several portions at 0 °C. After addition of MCPBA, the whole was stirred for 10 h at 25 °C. Saturated aq solution of $Na_2S_2O_3$ (50 mL) was added to the mixture. The whole was stirred for 0.5 h, and extracted with EtOAc several times. The combined organic phases were washed with sat. aq solution of $NaHCO_3$ (3×), dried over Na_2SO_4, and concentrated in vacuo. Purification by a short silica gel column chromatography (hexane–EtOAc, 3:1) gave epoxy ketone **2a** in 53% overall yield.

(*E*)-4-Hydroxy-1-phenylbut-2-en-1-one (1a)
To a solution of epoxide **2a** (10 mmol) in CH_2Cl_2 (15 mL), Et_3N (11 mmol) was added dropwise at 25 °C. The mixture was stirred for 30 min, and diluted with EtOAc (30 mL) and poured into 1 M HCl aq (30 mL). The aqueous phase was extracted with EtOAc. The combined organic phases was dried over Na_2SO_4, and concentrated in vacuo. Purification by a short silica gel column chromatography (hexane–EtOAc, 3:1) gave **1a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.90 (m, 2 H), 7.57–7.42 (m, 3 H), 7.23 (dt, *J* = 15.2, 1.6 Hz, 1 H), 7.13 (dt, *J* = 15.2, 3.6 Hz, 1 H), 4.48 (br s, 2 H), 2.05 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 147.2, 137.8, 133.1, 128.8, 128.7, 123.9, 62.7 ppm.

(*Z*)-4-Hydroxy-2-methyl-1-phenylbut-2-en-1-one (4)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00–7.90 (m, 2 H), 7.57–7.42 (m, 1 H), 7.42–7.25 (m, 2 H), 6.34 (qt, *J* = 6.2, 1.2 Hz, 1 H), 4.42 (dq, *J* = 6.2, 0.8 Hz. 2 H), 2.35 (br s, 1 H), 1.92 (dt, *J* = 1.2, 0.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 143.7, 137.6, 136.1, 131.6, 129.1, 128.0, 59.9, 12.9 ppm.

(*E*)-4-Hydroxy-1-(4-propionylphenyl)but-2-en-1-one (11)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (s, 4 H), 7.22 (ddt, *J* = 20.0, 3.5, 1.2 Hz, 1 H), 7.14 (ddt, *J* = 20.0, 3.0, 1.2 Hz, 1 H), 4.52–4.45 (m, 2 H), 3,03 (q, *J* = 6.3 Hz, 2 H), 2.60–2.30 (m, 1 H), 1.2 (t, *J* = 6.3, Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.4, 189.9, 148.5, 141.0, 140.0, 128.9, 128.3, 123.7, 62.6, 32.6, 8.5 ppm.

(*E*)-Benzyl 4-Hydroxybut-2-enoate (12)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5 H), 7.09 (dt, *J* = 16.0, 4.0 Hz, 1 H), 6.16 (dt, *J* = 16.0, 2.0 Hz, 1 H), 5.20 (s, 2 H), 4.37–4.34 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 147.4, 135.9, 128.5, 128.2, 128.1, 119.8, 66.2, 61.9 ppm.

Acknowledgment

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

References and Notes

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(3) The following patent shows the same type of reaction in Table 1 without showing diastereoselectivity of the reaction. See: (a) Kato, H. JP 2008143880, **2008**. (b) Kato, H. JP 2008143881, **2008**.
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(6) The reaction was monitored by ^{1}H NMR for 2 h using CD_2Cl_2 as solvent. Through the whole reaction, *Z*-form was not detected in the product.
(7) From a ^{1}H NMR analysis, **4** was considered to have *Z*-configuration. Alkenoic proton was detected at δ = 6.34 ppm. See experimental procedure.
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