Stereoselective Synthesis of β,γ-Unsaturated Ketones by Acid-Mediated Julia-Type Transformation from 2-(1-Hydroxyalkyl)-1-alkylcyclopropanols

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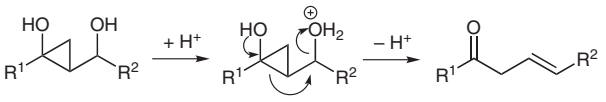
Received 11 March 2008

Abstract: An efficient transformation of 2-(1-hydroxyalkyl)-1-alkylcyclopropanols, obtained from α,β-unsaturated ketones, to β,γ-unsaturated ketones was achieved by trifluoroacetic acid (TFA)-mediated reaction.

Key words: β,γ-unsaturated ketone, methylene insertion, cyclopropanol, carbocation, stereoselective

In 1960, Julia reported acid-catalyzed isomerization of (1-hydroxyalkyl)cyclopropanes to (*E*)-homoallylic alcohols.[1] This reaction has been studied intensively and applied for various natural product synthesis.[2,3] When it was applied to 2-(1-hydroxyalkyl)-1-alkylcyclopropanols as starting materials, β,γ-unsaturated ketones were obtained via carbocation intermediate (Scheme 1).[4,5] This transformation, however, has not been studied well, because the starting materials are difficult to obtain. We had reported stereoselective and stereospecific cyclopropanations of α,β-epoxyketones with bis(iodozincio)methane to give 2-(1-hydroxyalkyl)-1-alkylcyclopropanols.[6] With these cyclopropane derivatives, we studied the transformation into β,γ-unsaturated ketones.



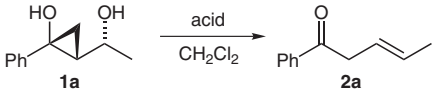
Scheme 1 Julia-type transformation of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol into (*E*)-β,γ-unsaturated ketone

As shown in Table 1, treatment of 2-(1-hydroxyethyl)-1-phenylcyclopropanol (**1a**) with a catalytic amount of various acids resulted in moderate *E*/*Z* selectivity (entries 1–3). Among them, TFA gave the best diastereoselectivity. Increasing the amount of TFA improved the yield and diastereoselectivity (entries 4 and 5). We found that treatment with five equivalents of TFA gave the desired β,γ-unsaturated ketone with high diastereoselectivity (entry 6).[7]

Other examples are shown in Table 2. Although a reaction of tertiary alcohol **1b** at 0 °C gave the desired product **2b** in 70%, it proceeded sluggishly (entry 1). The reaction at –78 °C, however, improved the yield (entry 2). Trisubstituted alkene **2d** was obtained with high diastereoselectivity from **1d** (entry 4). From bicyclic compound **1f**, ring-expanded (*E*)-cycloalkene **2f** was obtained in excellent yield (entry 6). In the case of a primary alcohol, such as **1g**, this acid-mediated transformation did not proceed efficiently because of the lack of stability of the primary cation intermediate (entry 7). Treatment of **1g** with mesyl chloride and pyridine,[8] however, gave the corresponding β,γ-unsaturated ketone **2g** in good yield (Scheme 2).

These substrates, 2-(1-hydroxyalkyl)-1-alkylcyclopropanols, are available from α,β-epoxyketones with bis(iodozincio)methane[6] in one step; α,β-epoxyketones can easily be prepared from α,β-unsaturated ketones with ba-

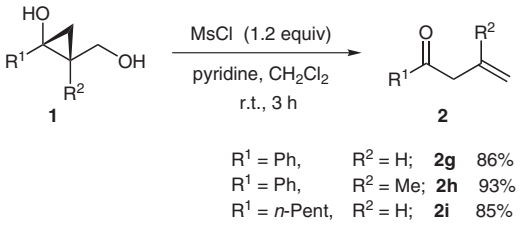
Table 1 Acid-Mediated Transformation of **1a** into **2a**



1a **2a**

Entry	Acid (equiv)[a]	Time (h)	Temp (°C)	Yield (%)[b]	*E*/*Z*[c]
1	TFA (0.2)	24	r.t.	67	75:25
2	TsOH (0.2)	6	r.t.	89	68:32
3	TfOH (0.2)	6	r.t.	76	62:38
4	TFA (1.0)	24	r.t.	90	88:12
5	TFA (2.0)	24	r.t.	90	92:8
6	TFA (5.0)	0.5	0	90	95:5

[a] TFA: trifluoroacetic acid, TsOH: *p*-toluenesulfonic acid, TfOH trifluoromethanesulfonic acid.
[b] Yield was determined by ^{1}H NMR using bromoform as internal standard.
[c] The *E*/*Z* ratio was determined by ^{1}H NMR analysis.



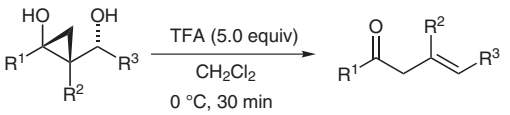
1 **2**

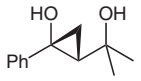
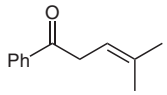
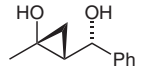
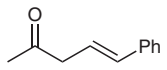
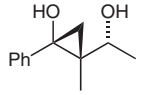
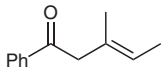
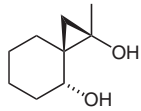
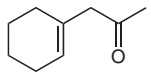
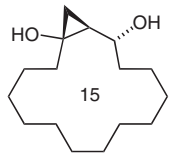
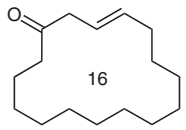
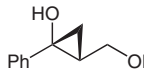
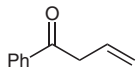
R^1 = Ph, R^2 = H; **2g** 86%
R^1 = Ph, R^2 = Me; **2h** 93%
R^1 = *n*-Pent, R^2 = H; **2i** 85%

Scheme 2 Formation of β,γ-unsaturated ketones via mesylate elimination

SYNLETT 2008, No. 9, pp 1412–1414
Advanced online publication: 07.05.2008
DOI: 10.1055/s-2008-1067077; Art ID: U01808ST

Table 2 Examples of the Transformation of 2-(1-Hydroxyalkyl)-1-alkylcyclopropanols into (*E*)-β,γ-Unsaturated Ketones

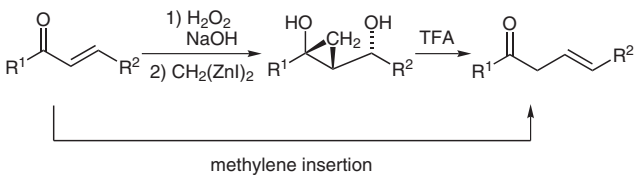


Entry	Substrate	Product	Yield (%)	*E*/*Z*[a]
1	 **1b**	 **2b**	70	
2[b]			>99	
3	 **1c**	 **2c**	96	*E* only
4	 **1d**	 **2d**	95	*E* only
5	 **1e**	 **2e**	86	
6	 **1f**	 **2f**	>99	*E* only
7[c]	 **1g**	 **2g**	35[d]	

[a] Stereochemistry was determined by NOE analysis.
[b] Reaction carries out at –78 °C.
[c] Reaction carried out at r.t. for 24 h.
[d] Corresponding α,β-unsaturated ketone was also obtained in 25%.

sic hydroperoxide. So the net transformation can be regarded as methylene insertion between a carbonyl group and an alkenyl group of α,β-unsaturated ketone (Scheme 3).

In conclusion, we showed the stepwise transformation of α,β-unsaturated ketones to (*E*)-β,γ-unsaturated ketones via cyclopropanation. Further applications for organic synthesis, especially natural product synthesis, are being studied in our laboratory.



Scheme 3 The entire transformation

General Procedure for the Transformation into β,γ-Unsaturated Ketone

To a solution of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol (0.5 mmol) in CH_2Cl_2 (2 mL), TFA (2.5 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min, then the solvent was removed under reduced pressure. The residue was purified by SiO_2 column chromatography (eluting with hexane–EtOAc) to give the corresponding β,γ-unsaturated ketone.

***cis*-2-(1-Hydroxyethyl)-2-methyl-1-phenylcyclopropanol (1d)**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.29–7.26 (m, 2 H), 7.18–7.14 (m, 2 H), 7.10–7.07 (m, 1 H), 4.03 (q, *J* = 7.0 Hz, 1 H), 2.73 (br s, 1 H), 2.62 (br s, 1 H), 1.29 (d, *J* = 7.0 Hz, 3 H), 0.83 (d, *J* = 5.5 Hz, 1 H), 0.80 (d, *J* = 5.5 Hz, 1 H), 0.70 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ = 141.2, 128.7, 128.3, 127.4, 70.6, 65.6, 32.0, 22.3, 19.6, 14.9. HRMS: *m/z* calcd for $C_{12}H_{16}O_2$: 192.1150; found: 192.1146.

(*E*)-3-Methyl-1-phenyl-3-penten-1-one (2d)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99–7.97 (m, 2 H), 7.57–7.53 (m, 1 H), 7.47–7.43 (m, 2 H), 5.39 (qqt, *J* = 7.0, 1.5, 1.5 Hz, 1 H), 3.47 (t, *J* = 1.0 Hz, 2 H), 1.69 (dt, *J* = 1.0, 1.0 Hz, 3 H), 1.64 (dtq, *J* = 7.0, 1.5, 1.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.8, 136.9, 132.9, 130.0, 128.5, 128.3, 123.6, 49.2, 16.2, 13.6. HRMS: *m/z* calcd for $C_{12}H_{14}O$: 174.1045; found: 174.1042.

(*E*)-3-Cyclohexadecen-1-one (2f)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.58–5.47 (m, 2 H), 3.03 (d, *J* = 6.5 Hz, 2 H), 2.49 (t, *J* = 7.0 Hz, 2 H), 2.09 (dt, *J* = 6.5, 6.0 Hz, 2 H), 1.59 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.42–1.21 (m, 18 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.4, 135.6, 123.2, 47.7, 40.9, 32.1, 28.2, 27.4, 27.2, 27.1, 26.9, 26.5, 26.2, 26.1, 25.6, 22.3. HRMS: *m/z* calcd for $C_{16}H_{28}O$: 236.2140; found: 236.2136.

1-Phenyl-3-buten-1-one (2g)

To a solution of 2-hydroxymethyl-1-phenylcyclopropanol (**1g**, 0.5 mmol) in CH_2Cl_2 (2 mL), pyridine (2 mmol), and MsCl (0.6 mmol) was added at r.t. The mixture was stirred at r.t. for 3 h, then sat. aq solution of $NaHCO_3$ was added. The organic layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by SiO_2 column chromatography eluting with hexane and EtOAc to give 1-phenyl-3-buten-1-one (**2g**, 86%, 0.43 mmol).

References and Notes

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(7) Treatment of diastereomixture of **2a** with 5 equiv of TFA at r.t. for 6 h did not change the *E*/*Z* ratio. An addition of 1 equiv of H_2O to this system did not also change the ratio. These experiments mean that the diastereoselectivity does not come from isomerization of the initial product.
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