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Novel Type of the Favorskii Rearrangement Combined with Aldol Reaction Leading to γ-Butyrolactone Derivatives

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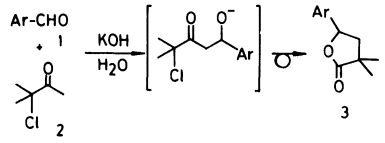
Reaction of Aromatic aldehydes or hetero-aromatic aldehydes with 3-chloro-3-methyl-2-butanone in ethanolic KOH at room temperature gave 3,3-dimethyl-5-aryltetrahydro-2-furanone as a major product. The reaction can be tentatively explained by the combination of Favorskii rearrangement and aldol reaction.

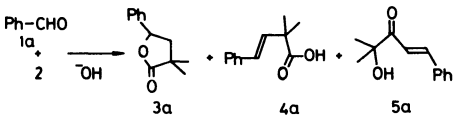
The Favorskii rearrangement has been known as a useful synthetic method of carboxylic acids or their derivatives by the skeletal rearrangement of α-halo ketones with nucleophilic bases.[1] This paper describes a novel type of the Favorskii rearrangement which involves an aldol reaction (KOH/EtOH) of aromatic aldehyde (**1**) with the enolate of 3-chloro-3-methyl-2-butanone (**2**), giving γ-butyrolactone derivative (**3**) as a major product in one-pot reaction (Scheme 1). In order to estimate the synthetic utility of the present reaction, the scope of reaction and the possible mechanism are discussed.

The reaction conditions and the product distribution were examined by the use of typical reaction of benzaldehyde (**1a**) wirh α-halo ketone (**2**) (Table 1). It is well-known that the Favorskii rearrangement is affected by many factors such as base, solvent, halogen, and so on.[1] For example, treatment of **2** with 40% aqueous NaOH gives pivalic acid, while



Scheme 1.

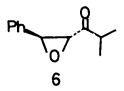
Table 1. Reaction of Benzaldehyde (**1a**) with Halo Ketone (**2**)



Reaction conditions	Yields/%		
	3a	**4a**	**5a**
40% $NaOH/H_2O$	32[a]	14	3
40% KOH/H_2O	25[a]	14	5
14% KOH/EtOH	50	14	5
14% $NaOH/H_2O$	0	0	80

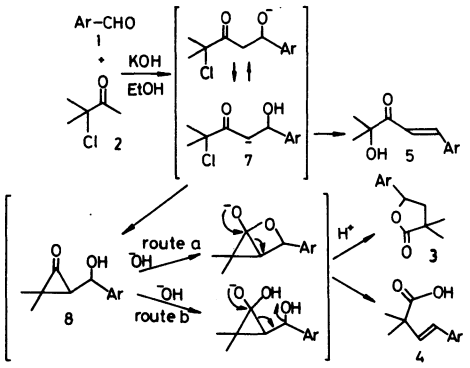
a) The decreased yield is due to the formation of pivalic acid, which was checked by ^1H NMR.

treatment with weak base such as 20% aqueous Na_2CO_3 affords 3-hydroxy-3-methyl-2-butanone, exclusively.[2] We also confirmed that the reaction of **2** with 14% aqueous or ethanolic KOH also yielded the hydroxy ketone. Thus, a mixture of compounds **1a** and **2** were treated with 40% aqueous NaOH (**1a**:**2**:NaOH=1:3.5:7)[3] at room temperature for 3 h to give 3,3-dimethyl-5-phenyltetrahydro-2-furanone (**3a**)[4] (32% yield), accompanied by 2,2-dimethyl-4-phenyl-3-butenoic acid (**4a**) (14% yield) and 4-hydroxy-4-methyl-1-phenyl-1-penten-3-one (**5a**)[5] (3% yield). It is quite interesting that the yield of lactone **3a** was improved up to 50% in the reaction with 14% ethanolic KOH, in spite of the fact that it is the hydrolytic conditions of **2**.[6] On the contrary, when the reaction was done in 14% aqueous NaOH, **5a**[7] was obtained exclusively in an excellent yield. In aqueous media with weak base, hydrolysis of **2** may occur readily in competition with the aldol reaction. Furthermore, the analogous reaction carried out with NaOEt in ether was found to give a mixture of **3a** (11% yield), **4a** (23% yield), and 1,2-epoxy-4-methyl-1-phenyl-3-pentanone (**6**) (28% yield).

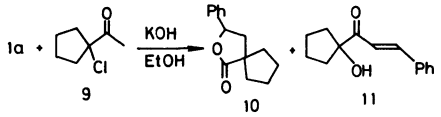


A conceivable mechanism of the present reaction (KOH/EtOH) is shown in Scheme 2, which involves the Favorskii rearrangement of initially formed aldol product **7**. It is possible that the cyclopropanone intermediate **8**[8] is cleaved either by the intramolecular alkoxide ion[9] (route a) or by hydroxide ion (route b). The by-product **5** may be formed either by hydrolysis of **7** or by the Claisen-Schmidt condensation of **1** with 3-hydroxy-3-methyl-2-butanone, which is formed initially in competition with the reaction of **1** with **2**. The present reaction is the first example of the Favorskii rearrangement which undergoes in combination with an aldol reaction.

Table 2 shows that this reaction (KOH/EtOH) can be adapted to a variety of aromatic aldehydes and hetero-aromatic aldehydes,[10] giving γ-butyrolactone derivatives **3b—g** as the major product. In addition, a



Scheme 2.



Scheme 3.

Table 2. Yields[a] of Reaction Products **3**, **4**, and **5**

Aldehyde **1** Ar		Products (Yields/%)					
		3		**4**		**5**	
1b	2-Chlorophenyl-	**3b**	(52)			**5b**	(27)
1c	4-Chlorophenyl-	**3c**	(54)	**4c**	(33)		
1d	2,4-Dichlorophenyl-	**3d**	(47)				
1e	3-Nitrophenyl-	**3e**	(42)	**4e**	(20)		
1f	3-Pyridyl-	**3f**	(29)				
1g	2-Furyl-	**3g**	(31)	**4g**	(16)		

a) In the reaction with 14% ethanolic KOH.

similar reaction of 1-(1-chlorocyclopentyl)ethanone (**9**)[11] with **1a** gave 3-phenyl-2-oxaspiro[4.4]nonan-1-one (**10**) (23% yield) and 1-(1-hydroxycyclopentyl)-3-phenyl-2-propen-1-one (**11**) (13% yield) (Scheme 3). Although the yields of the lactones **3a—g** and **10** were moderate to low and they were accompanied by the by-products such as **4**, **5**, or **11**, the present method has the advantage that the reaction can be done in one-pot in a very simple way.

Experimental

Melting points were measured on a Yamato Model MP-21 melting point apparatus and are uncorrected. Evaporative bulb-to-bulb distillation was done using a Büchi Kügelrohrofen. IR spectra were taken on a JASCO Model A-102 spectrometer. ^{1}H NMR spectra (60 MHz) were measured with a JEOL Model JNM-60 SI spectrometer and ^{13}C NMR spectra (25 MHz) were taken on a JEOL Model FX-100 spectrometer using Me_4Si as an internal standard. Analysis and preparative isolation by GLC were done with Hitachi Model 163 (SE-30 5 mmϕ×1.2 m, N_2 27 ml min^{-1}, oven temperature 130 °C) and Yanagimoto Model G-80 (Apiezone Glease L on 10% Chromosorb, N_2 50 ml min^{-1}, oven temperature 200 °C) gas chromatographs, respectively. The preparative TLC was carried out on silica gel (Kieselgel 60 PF_{254}, Merck A. G. Darmstadt). Elemental analysis was performed by Eiichiro Amano of our laboratory.

Typical Reaction of α-Halo Ketones with Aromatic Aldehydes in Ethanolic KOH. 3,3-Dimethyl-5-phenyltetrahydro-2-furanone (3a). To a solution of benzaldehyde (**1a**) (0.53 g, 5.0 mmol) and 3-chloro-3-methyl-2-butanone (**2**)[12] (2.11 g, 17.5 mmol) in ethanol (10 ml), was added a solution of KOH (1.96 g, 35 mmol) in ethanol (10 ml) over a period of 30 min at room temperature. After being stirred for 3 h at room temperature, ethanol was removed under reduced pressure. The residue was acidified with 10% HCl and then stirred for 30 min for completion of lactonization. The resulting organic layer was extracted with ether, washed with aqueous $NaHCO_3$ and then with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was subjected to vacuum distillation [bp 125—145 °C (2 mmHg) (1 mmHg=133.322 Pa)] to give 504 mg of a mixture of **3a**[4] (50%)[13] and **5a**[5,6] (5%)[13] which were separated by preparative GLC. Structural identification was done by comparison of their spectral data with those reported in the literature. The aqueous $NaHCO_3$ layer was acidified and the ether extract was treated in a similar way as described above to give 2,2-dimethyl-4-phenyl-3-butenoic acid (**4a**) (133 mg, 14%) after purification by preparative TLC (hexane–acetone, 3:1). **4a**: IR (neat) 3600—2300, 1685, 1600, 1580 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.40 (6H, s), 6.40 (2H, s), 7.30 (5H, br s), 10.80 (1H, br s); ^{13}C NMR ($CDCl_3$) δ=24.9 (q), 44.4 (s), 126.6 (d), 127.7 (d), 128.7 (d), 130.3 (d), 133.8 (d), 137.1 (s), 182.7 (s). Anal. ($C_{12}H_{14}O_2$) C, H.

Reaction of 1a with 2 in the Presence of NaOEt in Ether. To a solution of **1a** (382 mg, 3.6 mmol) and **2** (434 mg, 3.6 mmol) in ether (20 ml), was added NaOEt (294 mg, 4.3 mmol) at room temperature. After being stirred for 20 h at room temperature, the mixture was acidified with 10% HCl. The resulting mixture was treated in a manner similar to that described above and the crude products were firstly divided into neutral and acidic portions. The former was fractionated by column chromatography (hexane–ether, 20:1) to give **3a** (76 mg, 11%) and 1,2-epoxy-4-methyl-1-phenyl-3-pentanone (**6**) (192 mg, 28%): IR (neat) 1715 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.10 (3H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 2.74 (1H, m), 3.37 (1H, d, J=2 Hz, trans[14]), 3.85 (1H, d, J=2 Hz, trans[14]), 7.27 (5H, br s); ^{13}C NMR ($CDCl_3$) δ=17.3 (q), 18.1 (q), 37.0 (d), 58.4 (d), 61.9 (d), 125.6 (d), 128.6 (d), 128.9 (d), 135.3 (s). Anal. ($C_{12}H_{14}O_2$) C, H. The acidic portion was purified by TLC to give **4a** (156 mg, 23%).

γ-Butyrolactones **3b—g** and **10** were synthesized in the similar way to the typical reaction described above. Procedure for purification of the poroducts, their yields and physical properties are as follows.

5-(2-Chlorophenyl)-3,3-dimethyltetrahydro-2-furanone (3b). A neutral portion was subjected to vacuum distillation [bp 148—152 °C (2 mmHg)] and further purified by preparative TLC (hexane–acetone, 3:1) to give **3b** (R_f 0.50—0.58, 52% yield) and 1-(2-chlorophenyl)-4-hydroxy-4-methyl-1-penten-3-one (**5b**)[5] (R_f 0.25—0.40, 27% yield). **3b**: IR (neat) 1780, 1595, 1577 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.21 (3H, s), 1.33 (3H, s), 1.82 (1H, dd, J=10 Hz and 14 Hz), 2.66 (1H, dd, J=7 Hz and 14 Hz), 5.52 (1H, dd, J=7 Hz and 10 Hz), 7.6—

7.9 (4H, m). Anal. ($C_{12}H_{13}O_2Cl$) C, H.

5-(4-Chlorophenyl)-3,3-dimethyltetrahydro-3-furanone (3c). A neutral portion was purified by vacuum distillation [bp 148—150 °C (3 mmHg)] followed by preparative TLC (hexane–acetone, 3:1, R_f 0.1—0.26) to give **3c**: 54% yield, mp 56—57 °C (hexane–ether, 3:1); IR (KBr) 1780, 1605 cm^{-1}; ^1H NMR (CCl_4) δ=1.24 (3H, s), 1.30 (3H, s), 1.88 (1H, dd, J=7 Hz and 14 Hz), 2.42 (1H, dd, J=7 Hz and 14 Hz), 5.32 (1H, dd, J=7 Hz and 10 Hz), 7.27 (4H, br s). Anal. ($C_{12}H_{13}O_2Cl$) C, H. An acidic portion was purified by TLC (hexane–acetone, 3:1, R_f 0.26—0.37) to obtain 4-(4-chlorophenyl)-2,2-dimethyl-3-butenoic acid (**4c**): 33% yield, mp 145—147 °C (hexane–ether, 3:1); IR (KBr) 1690, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (6H, s), 6.42 (2H, s), 7.30 (4H, br s). Anal. ($C_{12}H_{13}O_2Cl$) C, H.

5-(2,4-Dichlorophenyl)-3,3-dimethyltetrahydro-2-furanone (3d). A neutral portion was purified by vacuum distillation [bp 180—200 °C (0.2 mmHg)] and preparative TLC (hexane–acetone, 3:1) to give **3d**: 47% yield, IR (neat) 1785, 1592, 1561 cm^{-1}; ^1H NMR (CCl_4) δ=1.27 (3H, s), 1.32 (3H, s), 1.82 (1H, dd, J=10 Hz and 13 Hz), 2.59 (1H, dd, J=6 Hz and 13 Hz), 5.60 (1 H, dd, J=6 Hz and 10 Hz), 7.1—7.6 (3H, m). Anal. ($C_{12}H_{12}O_2Cl_2$) C, H.

3,3-Dimethyl-5-(3-nitrophenyl)tetrahydro-2-furanone (3e). A neutral portion was purified by preaparative TLC (hexane–acetone, 2:1) to give **3e**: 42% yield; mp 82—84 °C (CCl_4); IR (KBr) 1768, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (3H, s), 1.60 (3H, s), 2.05 (1 H, dd, J=10 Hz and 13 Hz), 2.62 (1H, dd, J=6 Hz and 13 Hz), 5.54 (1H, dd, J=6 Hz and 10 Hz), 7.3—8.4 (4 H, m). Anal. ($C_{12}H_{13}O_4N$) C, H. An acidic portion was refined in a similar way to afford **4e**: 20% yield; mp 105—106 °C (hexane–ether, 1:1); IR (KBr) 3720—2300, 1708, 1615, 1528 cm^{-1}; ^1H NMR (CCl_4) δ=1.45 (6H, s), 6.53 (2H, s), 6.7—8.5 (4H, m), 10.10 (1H, br s). Anal. ($C_{12}H_{13}O_4N$) C, H.

3,3-Dimethyl-5-(3-pyridyl)tetrahydro-2-furanone (3f). A neutral portion was purified by vacuum distillation [bp 160-170 °C (2 mmHg)] and preparative TLC (hexane–acetone, 1:1) to give **3f**: 29% yield; mp 78—79 °C (hexane–ether, 2:1); IR (neat) 1770, 1620, 1615 cm^{-1}; ^1H NMR (CCl_4) δ=1.26 (3H, s), 1.8—2.8 (2H, m), 5.40 (1H, dd, J=6 Hz and 9 Hz), 7.1—8.8 (4H, m). Anal. ($C_{11}H_{13}O_2N$) C, H.

5-(2-Furyl)-3,3-dimethyltetrahydro-2-furanone (3g). A neutral portion was distilled under vacuum [bp 130—135 °C (4 mmHg)] and separated by preparative TLC (hexane–acetone, 3:1) to give **3g** (R_f 0.57, 31% yield) and 1-(2-furyl)-4-hydroxy-4-methyl-1-penten-3-one (**5g**)[5] (R_f 0.50, 16% yield). **3g**: IR (neat) 1768, 1604 cm^{-1}; ^1H NMR (CCl_4) δ=1.29 (6H, s), 2.30 (2H, d, J=8 Hz), 5.29 (1H, t, J=8 Hz), 6.33 (2H, br s), 7.35 (1H, br s); ^{13}C NMR ($CDCl_3$) δ=24.4 (q), 24.9 (q), 40.3 (s), 41.2 (t), 71.0 (d), 110.0 (d), 110.7 (d), 143.7 (d), 150.8 (s), 181.1 (s). Anal. ($C_{10}H_{12}O_3$) C, H.

3-Phenyl-2-oxaspiro[4.4]nonan-1-one (10). A neutral portion was fractionated by preparative TLC (hexane–acetone, 3:1, three times developments) to afford **10** (R_f 0.38—0.44, 23% yield) and 1-(1-hydroxycyclopentyl)-3-phenyl-2-penten-1-one (**11**) (R_f 0.44—0.51, 13% yield). **10**: IR (neat) 1770, 1650, 1610 cm^{-1}; ^1H NMR (CCl_4) δ=1.1—1.9 (8 H, m), 1.9—2.7 (2H, m), 5.27 (1H, dd, J=7 Hz and 9 Hz), 7.25 (5H, s). Anal. ($C_{14}H_{16}O_2$) C, H. **11**: IR (neat) 3480, 1680, 1640, 1610, 1575, 1555 cm^{-1}; ^1H NMR (CCl_4) δ=1.3—2.2 (8H, m), 3.7 (1H, br s), 6.87 (1H, d, J=16 Hz), 7.1—7.8 (5H, m), 7.76 (1H, d, J=16 Hz). Anal. ($C_{14}H_{16}O_2$) C, H.

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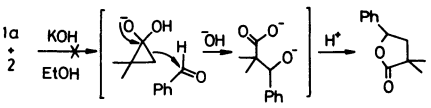

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