Substitution-Type Thermal 1,2-Rearrangement. Synthesis of Chiral β-Aryl(or Alkenyl) α-Oxo Nitrile Acetal

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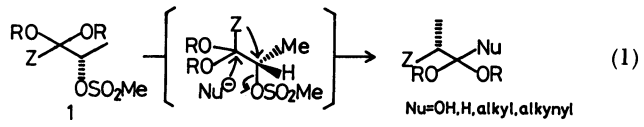
Synopsis. Title compound was synthesized via a substitution-type thermal 1,2-rearrangement accompanied by introduction of a cyano group, and derived into the corresponding aldehyde, alkanoic acid, and amide.

In the last five years, we have studied on 1.2-rearrangement accompanied by introduction of hydroxide,[1-3] hydride,[4] alkanide, and alkynide anion[5] to give chiral α-substituted alkanoic ester, aldehyde acetal, and ketone acetal, respectively. They were promoted by elimination of sulfonyloxy group caused by heating or activation with Lewis acids (Eq. 1).

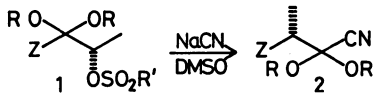


(1)

Now, we report a new thermal rearrangement accompanied by introduction of a cyano group.

Results and Discussion

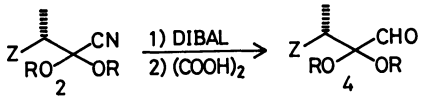
Since cyanide anion is a strong nucleophile compared with hydroxide anion, cyano group was expected to be introduced even when chiral α-sulfonyloxy ketone acetal (**1**) is treated with sodium cyanide in aqueous solution. In practice, however, the corresponding alkanoic ester (**3**, Fig. 1) was formed quantitatively instead of the desired β-substituted α-oxo nitrile acetal (**2**). Under reflux conditions in anhydrous methanol, **2** was yielded in 11%, but the main product was also **3**. It is concluded that the attack of a large excess of methanol has occurred predominantly. As the results, **1** was treated with two equivalents of sodium cyanide in anhydrous dimethyl sulfoxide to yield chiral α-oxo nitrile acetal (**2**) in a good yield (Eq, 2, Table 1).



(2)

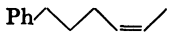
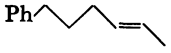
Obtained **2** was sensitive to light. Many by-products were generated in Entries 1—3, because the rate of migration of a phenyl group was extremely low. Taking into consideration of the reaction temperature and time, the migratory aptitudes are enhanced by the migrating groups in the order alkenyl≧*p*-methoxyphenyl>phenyl and by the acetal groups in the order dimethyl>trimethylene>2,2-dimethyltrimethylene.

α-Oxo nitrile acetal (**2**) can be transformed into the variety of the corresponding derivatives. At first **2** was treated with DIBAL (i-Bu_2AlH) to give an imino derivative quantitatively,[6] and then with oxalic acid dihydrate to give α,α-dialkoxy aldehyde (**4**) (Eq. 3,



(3)

Table 1. Introduction of a Cyano Group

Entry	Z	R	R'	Temp/°C	Time/h	Yield/%	$[\alpha]_D$/° (t/°C, c, in $CHCl_3$)
1	Ph-		Me	130	54	38	+ 7.5 (24, 0.77)
2	〃		〃	〃	48	29	+ 5.8 (22, 0.89)
3	〃	Me	Br-C_6H_4-	〃	24	43	+ 7.4 (22, 0.82)
4	MeO-C_6H_4-		Me	〃	18	90	+ 5.6 (24, 1.00)
5	〃		〃	〃	16	85	+10.9 (21, 1.06)
6	〃	Me	〃	110	12	86	− 2.3 (21, 1.06)
7			〃	130	9	84	+68.8 (17, 1.20)
8	〃		〃	120	20	93	+69.2 (17, 1.34)
9	〃	Me	〃	120	4	75	+38.0 (17, 1.13)
10			〃	130	11	76	+ 4.8 (20, 0.92)

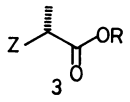


Fig. 1.

Table 2. Synthesis of α,α-Dialkoxy Aldehyde (**4**)

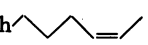
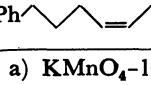
Z	R	Yield/%	$[\alpha]_D$/° (*t*/°C, *c*, in $CHCl_3$)
MeO-C_6H_4-		81	−15.7 (21, 1.00)
〃		71	−16.8 (20, 0.71)
〃	Me	78	− 7.0 (21, 0.99)
Ph 		80	+17.5 (22, 0.74)
〃		75	+ 9.3 (21, 0.97)
〃	Me	78	+15.3 (21, 0.84)

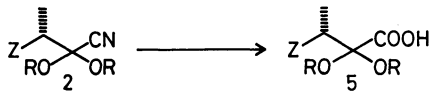
Table 3. Synthesis of α,α-Dialkoxy Carboxylic Acid (**5**)

Z	R	Yield/%	$[\alpha]_D$/° (*t*/°C, *c*, in $CHCl_3$)
MeO-C_6H_4		95[a]	−19.1 (24, 0.79)
〃		91[a]	−16.1 (22, 0.68)
Ph 		79[b]	+35.7 (21, 0.74)

a) $KMnO_4$-10% KOH. b) CrO_3-H_2SO_4-Acetone.

Table 2), which would be capable to be a useful building block for acyclic stereoselective synthesis of chiral compounds.

Aldehyde (**4**) was easily oxidized by treatment with $KMnO_4$-KOH[7] or Jones reagent in acetone to yield α,α-dialkoxy carboxylic acid (**5**) (Eq. 4, Table 3).



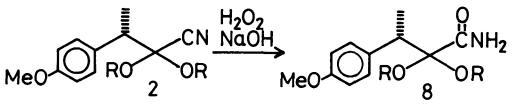
(4)

The absolute configuration of **2** was determined to be *S* from the sign of the specific rotation of the corresponding dithioacetal (**6**); $[\alpha]_D^{21} = -20.7°$ (*c* 0.34, $CHCl_3$), prepared from **5** in 88% yield by treatment with 1,3-propanedithiol in the presence of catalytic amount of $BF_3 \cdot OEt_2$ in dichloromethane at rt. An authentic **6**; $[\alpha]_D^{21} = -21.3°$ (*c* 0.35, $CHCl_3$), was prepared from (*S*)-aldehyde acetal (**7**)[4] by dithioacetalization, followed by lithiation and carboxylation with CO_2 (Fig. 2).

Table 4. Synthesis of α,α-Dialkoxy Amide (**8**)

R	Yield/%	$[\alpha]_D$/° (*t*/°C, *c*, in $CHCl_3$)
	95	−54.9 (22, 0.81)
Me	62	+ 8.8 (23, 0.64)

The enantiomeric excess was determined to be over 98% by HPLC analysis[8] of α,α-dimethoxy amide (**8**), which was prepared from **2** ($R = CH_2CMe_2CH_2$, $Z = MeOC_6H_4$) in 95% yield by treatment with 30% H_2O_2-NaOH in ethanol[9] (Eq. 5, Table 4).



(5)

Consequently, it was concluded that the optical purity of the starting material, ethyl (*S*)-lactate,[10] was remained through the rearrangenent and the follwing derivation.

Experimental

General Synthetic Procedure of α-Oxo Nitrile Acetal (2). Under an argon atmosphere, **1** (1.00 mmol) was dissolved in anhydrous dimethyl sulfoxide (10 ml) containing sodium cyanide (2.00 mmol) in a sealed tube. The mixture was heated in dark, and allowed to cool to rt. It was poured into a vigorously stirred ice-water, and extracted with ethyl acetate (30 ml×2). The residual syrup was purified by using silica-gel column chromatography (hexane-ethyl acetate-pyridine) to give **2** as a colorless oil.

(*S*)-3-(*p*-Methoxyphenyl)-2-oxobutanenitrile 2,2-Dimethyltrimethylene Acetal: IR (film) $\nu = 2230\ cm^{-1}$; ^1H NMR (CCl_4) $\delta = 0.78$ (s, 3H), 0.99 (s, 3H), 1.42 (d, $J = 7.2$ Hz, 3H), 3.05 (q, $J = 7.2$ Hz, 1H), 3.46 (d, $J = 11.4$ Hz, 2H), 3.72 (d, $J = 11.4$ Hz, 2H), 3.73 (s, 3H), 6.69 (d, $J = 9.0$ Hz, 2H), 7.58 (d, $J = 9.0$ Hz, 2H) ppm. HRMS; Found: *m/z* 275.1539. Calcd for $C_{16}H_{21}NO_3$: M^+, *m/z* 275.1522.

(3*S*,4*Z*)-3-Methyl-2-oxo-8-phenyl-4-heptenenitrile 2,2-Dimethyltrimethylene Acetal: IR (film) $\nu = 2230\ cm^{-1}$; ^1H NMR (CCl_4) $\delta = 0.83$ (s, 3H), 1.10 (d, $J = 6.3$ Hz, 3H), 1.17 (s, 3H), 1.5—2.2 (m, 4H), 2.58 (t, $J = 7.5$ Hz, 2H), 2.83 (dq, $J = 8.3$ Hz, $J = 6.3$ Hz, 1H), 3.48 (d, $J = 10.8$ Hz, 2H), 3.76 (d, $J = 10.8$ Hz, 2H), 5.1—5.7 (m, 2H), 6.9—7.3 (m, 5H) ppm. HRMS; Found: *m/z* 313.2018. Calcd for $C_{20}H_{27}O_2N$: M^+, *m/z* 313.2043.

General Synthetic Procedure of α,α-Dialkoxy Aldehyde (4). Into a solution of α-oxo nitrile acetal (**2**, 1.00 mmol) in toluene (10 ml), DIBAL (1.20 mmol, in hexane) was added at −78 °C. After 30 min, THF (10 ml) and oxalic acid dihydrate (5 mmol) were added at 0 °C. The mixture was extracted with ethyl acetate (30 ml×2). Obtained residue was purified by using silica-gel column chromatography to give **4** as a colorless oil.

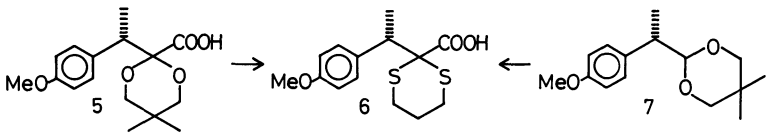


Fig. 2. Determination of the absolute configuration of **2**.

(*S*)-5,5-Dimethyl-2-formyl-2-[2-(*p*-methoxyphenyl)-propyl]-1,3-dioxane: IR (film) $\nu=1740\ cm^{-1}$; ^1H NMR (CCl_4) $\delta=0.65$ (s, 3H), 1.04 (s, 3H), 1.32 (d, $J=7.2$ Hz, 3H), 2.89 (q, $J=7.2$ Hz, 1H), 3.43 (m, 4H), 3.73 (s, 3H), 6.65 (d, $J=9.0$ Hz, 2H), 7.08 (d, $J=9.0$ Hz, 2H), 9.20 (s, 1H) ppm. HRMS; Found: m/z 278.1515. Calcd for $C_{16}H_{22}O_4$, M^+: m/z 278.1519.

(*S*)-5,5-Dimethyl-2-formyl-2-[(*Z*)-1-methyl-6-phenyl-2-hexenyl]-1,3-dioxane: IR (film) $\nu=1735\ cm^{-1}$; ^1H NMR (CCl_4) $\delta=0.68$ (s, 3H), 1.00 (d, $J=7.2$ Hz, 3H), 1.17 (s, 3H), 1.4—2.2 (m, 4H), 2.59 (t, $J=7.5$ Hz, 2H), 2.66 (dq, $J=9.5$ Hz, $J=7.2$ Hz, 1H), 3.2—3.5 (m, 4H), 5.1—5.5 (m, 2H), 6.9—7.3 (m, 5H), 9.36 (s, 1H) ppm. HRMS; Found: m/z 316.2026. Calcd for $C_{20}H_{28}O_3$, M^+: m/z 316.2036.

(*S*)-2-Carboxy-5,5-dimethyl-2-[2-(*p*-methoxyphenyl)-propyl]-1,3-dioxane (5): Colorless oil: IR (film) $\nu=1729\ cm^{-1}$; ^1H NMR (CCl_4) $\delta=0.67$ (s, 3H), 0.96 (s, 3H), 1.32 (d, $J=7.2$ Hz, 3H), 3.43 (br m, 4H), 3.73 (s, 3H), 6.65 (d, $J=8.4$ Hz, 2H), 7.12 (d, $J=8.4$ Hz, 2H), 10.17 (br s, 1H) ppm. HRMS; Found: m/z 249.1502. Calcd for $C_{15}H_{21}O_3$, M^+-COOH: m/z 249.1491.

(*S*)-2-Carboxy-5,5-dimethyl-2-[(*Z*)-1-methyl-6-phenyl-2-hexenyl]-1,3-dioxane (5): Colorless oil: IR (film) $\nu=$ 3070, 1715 cm^{-1}; ^1H NMR (CCl_4) $\delta=0.70$ (s, 3H), 1.04 (d, $J=6.9$ Hz, 3H), 1.19 (s, 3H), 1.4—2.2 (m, 4H), 2.55 (t, $J=$ 7.5 Hz, 2H), 2.86 (dq, $J=9.0$ Hz, $J=6.9$ Hz, 1H), 3.2—3.7 (m, 4H), 5.1—5.5 (m, 2H), 6.9—7.3 (m, 5H), 10.92 (br s, 1H) ppm. HRMS; Found: m/z 287.1998. Calcd for $C_{19}H_{27}O_2$, M^+-COOH: m/z 287.2009.

(*S*)-2-Carboxy-2-[2-(*p*-methoxyphenyl)propyl]-1,3-dithiane (6): Colorless oil: IR (film) $\nu=1720\ cm^{-1}$; ^1H NMR ($CDCl_3$) $\delta=1.57$ (d, $J=7.2$ Hz, 3H), 1.8—2.2 (m, 2H), 2.5—2.9 (m, 2H), 2.9—3.3 (m, 2H), 3.53 (q, $J=7.2$ Hz, 1H) 3.79 (s, 3H), 6.83 (d, $J=9.0$ Hz, 2H), 7.33 (d, $J=$ 9.0 Hz, 2H), 10.23 (br s, 1H) ppm. HRMS; Found: m/z 253.0715. Calcd for $C_{13}H_{17}OS_2$, M^+-COOH: m/z 253.0722.

(*S*)-2-Carbamoyl-5,5-dimethyl-2-[2-(*p*-methoxyphenyl)propyl]-1,3-dioxane (8): Colorless oil: IR (film) $\nu=1685\ cm^{-1}$, ^1H NMR ($CDCl_3$) $\delta=0.68$ (s, 3H), 1.01 (s, 3H), 1.40 (d, $J=6.9$ Hz, 3H), 3.00 (q, $J=6.9$ Hz, 1H), 3.77 (s, 3H), 5.86 (br s, 1H), 6.02 (s, 1H), 6.76 (d, $J=8.4$ Hz, 2H), 7.21 (d, $J=8.4$ Hz, 2H) ppm. HRMS; Found: m/z 249.1517. Calcd for $C_{15}H_{21}O_3$, M^+-CONH_2: m/z 249.1491.

References

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5) Y. Honda, E. Morita, and G. Tsuchihashi, *Chem. Lett.*, **1986**, 277.

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8) Chiralcel OB offered from Daicel Chemical Industries, LTD. was used; MeOH/H_2O=9/1 (v/v), flow rate 0.4 ml min^{-1}, k'_S=8.10, $\alpha=k'_R/k'_S$=1.64.

9) J. G. Wallace, "Hydrogen peroxide in organic chemistry", E. I. Du Pont Co., 42 (1962).

10) Determined to be over 98% ee by HPLC measurement of the corresponding (*R*)-MTPA ester by using Develosil (Nomura Chemical Co., LTD.); hexane/dichloromethane/methanol=6/1/0.007 (v/v/v), flow rate 0.4 ml min^{-1}, k'_S= 3.24, $\alpha=k'_R/k'_S$=1.21. Methyl (*R*)-lactate is also available (Aldrich, >98% ee), which can be converted into (*R*)-**2**.