

# Substitution-Type Thermal 1,2-Rearrangement. Synthesis of Chiral $\beta$ -Aryl(or Alkenyl) $\alpha$ -Oxo Nitrile Acetal

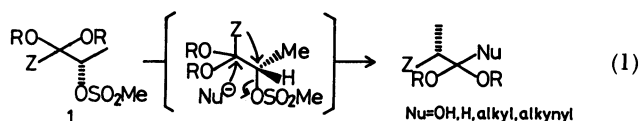
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**Synopsis.** Title compound was synthesized via a substitution-type thermal 1,2-rearrangement accompanied by introduction of a cyano group, and derived into the corresponding aldehyde, alkanolic acid, and amide.

In the last five years, we have studied on 1,2-rearrangement accompanied by introduction of hydroxide,<sup>1–3)</sup> hydride,<sup>4)</sup> alkanide, and alkynide anion<sup>5)</sup> to give chiral  $\alpha$ -substituted alkanolic 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).

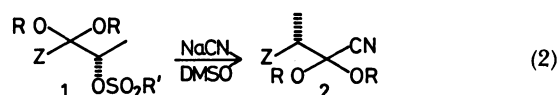


Now, we report a new thermal rearrangement accompanied by introduction of a cyano group.

## Results and Discussion

Since cyanide anion is a strong nucleophile compared with hydroxide anion, cyano group was expected to be introduced even when chiral  $\alpha$ -sulfonyloxy ketone acetal (**1**) is treated with sodium cyanide in aqueous solution. In practice, however, the corresponding alkanolic ester (**3**, Fig. 1) was formed quantitatively instead of the desired  $\beta$ -substituted  $\alpha$ -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  $\alpha$ -oxo nitrile acetal (**2**) in a good yield (Eq. 2, Table 1).



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  $\geq$  *p*-methoxyphenyl  $>$  phenyl and by the acetal groups in the order dimethyl  $>$  trimethylene  $>$  2,2-dimethyltrimethylene.

$\alpha$ -Oxo nitrile acetal (**2**) can be transformed into the variety of the corresponding derivatives. At first **2** was treated with DIBAL (*i*-Bu<sub>2</sub>AlH) to give an imino derivative quantitatively,<sup>6)</sup> and then with oxalic acid dihydrate to give  $\alpha,\alpha$ -dialkoxy aldehyde (**4**) (Eq. 3,

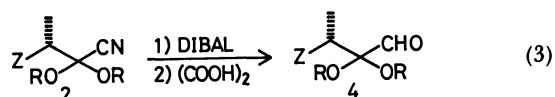


Table 1. Introduction of a Cyano Group

| Entry | Z                                           | R  | R'                                 | Temp/°C | Time/h | Yield/% | $[\alpha]_D^{20}$ (t/°C, c, in CHCl <sub>3</sub> ) |
|-------|---------------------------------------------|----|------------------------------------|---------|--------|---------|----------------------------------------------------|
| 1     | Ph-                                         |    | Me                                 | 130     | 54     | 38      | + 7.5 (24, 0.77)                                   |
| 2     | "                                           |    | "                                  | "       | 48     | 29      | + 5.8 (22, 0.89)                                   |
| 3     | "                                           | Me | Br-C <sub>6</sub> H <sub>4</sub> - | "       | 24     | 43      | + 7.4 (22, 0.82)                                   |
| 4     | MeO-C <sub>6</sub> H <sub>4</sub> -         |    | 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     | Ph-CH <sub>2</sub> -CH <sub>2</sub> -CH=CH- |    | "                                  | 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    | Ph-CH <sub>2</sub> -CH <sub>2</sub> -CH=CH- |    | "                                  | 130     | 11     | 76      | + 4.8 (20, 0.92)                                   |

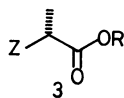


Fig. 1.

Table 2. Synthesis of  $\alpha,\alpha$ -Dialkoxy Aldehyde (4)

| Z                                              | R  | Yield/% | $[\alpha]_D^{20}$ ( $t/^\circ\text{C}$ , $c$ , in $\text{CHCl}_3$ ) |
|------------------------------------------------|----|---------|---------------------------------------------------------------------|
| $\text{MeO}-\text{C}_6\text{H}_4-$             |    | 81      | -15.7 (21, 1.00)                                                    |
| "                                              |    | 71      | -16.8 (20, 0.71)                                                    |
| "                                              | Me | 78      | -7.0 (21, 0.99)                                                     |
| $\text{Ph}-\text{CH}_2\text{CH}_2\text{CH}_2-$ |    | 80      | +17.5 (22, 0.74)                                                    |
| "                                              |    | 75      | +9.3 (21, 0.97)                                                     |
| "                                              | Me | 78      | +15.3 (21, 0.84)                                                    |

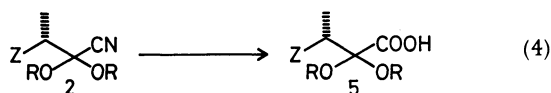
Table 3. Synthesis of  $\alpha,\alpha$ -Dialkoxy Carboxylic Acid (5)

| Z                                              | R | Yield/%         | $[\alpha]_D^{20}$ ( $t/^\circ\text{C}$ , $c$ , in $\text{CHCl}_3$ ) |
|------------------------------------------------|---|-----------------|---------------------------------------------------------------------|
| $\text{MeO}-\text{C}_6\text{H}_4$              |   | 95 <sup>a</sup> | -19.1 (24, 0.79)                                                    |
| "                                              |   | 91 <sup>a</sup> | -16.1 (22, 0.68)                                                    |
| $\text{Ph}-\text{CH}_2\text{CH}_2\text{CH}_2-$ |   | 79 <sup>b</sup> | +35.7 (21, 0.74)                                                    |

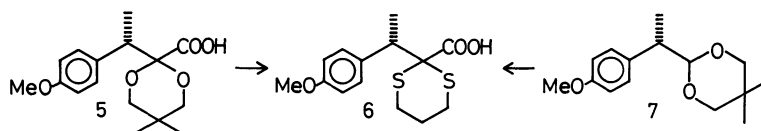
a)  $\text{KMnO}_4$ -10%  $\text{KOH}$ . b)  $\text{CrO}_3$ - $\text{H}_2\text{SO}_4$ -Acetone.

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  $\text{KMnO}_4$ - $\text{KOH}$ <sup>7</sup> or Jones reagent in acetone to yield  $\alpha,\alpha$ -dialkoxy carboxylic acid (5) (Eq. 4, Table 3).

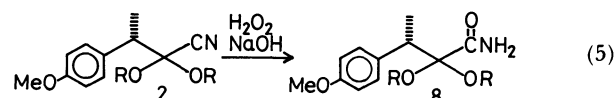


The absolute configuration of **2** was determined to be *S* from the sign of the specific rotation of the corresponding dithioacetal (**6**);  $[\alpha]_D^{20} = -20.7^\circ$  ( $c$  0.34,  $\text{CHCl}_3$ ), prepared from **5** in 88% yield by treatment with 1,3-propanedithiol in the presence of catalytic amount of  $\text{BF}_3 \cdot \text{OEt}_2$  in dichloromethane at rt. An authentic **6**;  $[\alpha]_D^{20} = -21.3^\circ$  ( $c$  0.35,  $\text{CHCl}_3$ ), was prepared from (*S*)-aldehyde acetal (**7**)<sup>4</sup> by dithioacetalization, followed by lithiation and carboxylation with  $\text{CO}_2$  (Fig. 2).

Fig. 2. Determination of the absolute configuration of **2**.Table 4. Synthesis of  $\alpha,\alpha$ -Dialkoxy Amide (8)

| R  | Yield/% | $[\alpha]_D^{20}$ ( $t/^\circ\text{C}$ , $c$ , in $\text{CHCl}_3$ ) |
|----|---------|---------------------------------------------------------------------|
|    | 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<sup>8</sup>) of  $\alpha,\alpha$ -dimethoxy amide (**8**), which was prepared from **2** ( $\text{R} = \text{CH}_2\text{CMe}_2\text{CH}_2$ ,  $\text{Z} = \text{MeOC}_6\text{H}_4$ ) in 95% yield by treatment with 30%  $\text{H}_2\text{O}_2$ - $\text{NaOH}$  in ethanol<sup>9</sup>) (Eq. 5, Table 4).



Consequently, it was concluded that the optical purity of the starting material, ethyl (*S*)-lactate,<sup>10</sup> was remained through the rearrangement and the following derivation.

## Experimental

**General Synthetic Procedure of  $\alpha$ -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  $\times$  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)  $\nu = 2230 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CCl}_4$ )  $\delta = 0.78$  (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  $\text{C}_{16}\text{H}_{21}\text{NO}_3$ :  $M^+$ ,  $m/z$  275.1522.

**(3*S*,4*Z*)-3-Methyl-2-oxo-8-phenyl-4-heptenenitrile 2,2-Dimethyltrimethylene Acetal:** IR (film)  $\nu = 2230 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CCl}_4$ )  $\delta = 0.83$  (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  $\text{C}_{20}\text{H}_{27}\text{O}_2\text{N}$ :  $M^+$ ,  $m/z$  313.2043.

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

**(S)-5,5-Dimethyl-2-formyl-2-[2-(p-methoxyphenyl)propyl]-1,3-dioxane:** IR (film)  $\nu=1740\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CCl}_4$ )  $\delta=0.65$  (s, 3H), 1.04 (s, 3H), 1.32 (d,  $J=7.2\text{ Hz}$ , 3H), 2.89 (q,  $J=7.2\text{ Hz}$ , 1H), 3.43 (m, 4H), 3.73 (s, 3H), 6.65 (d,  $J=9.0\text{ Hz}$ , 2H), 7.08 (d,  $J=9.0\text{ Hz}$ , 2H), 9.20 (s, 1H) ppm. HRMS; Found:  $m/z$  278.1515. Calcd for  $\text{C}_{16}\text{H}_{22}\text{O}_4$ ,  $\text{M}^+$ :  $m/z$  278.1519.

**(S)-5,5-Dimethyl-2-formyl-2-[(Z)-1-methyl-6-phenyl-2-hexenyl]-1,3-dioxane:** IR (film)  $\nu=1735\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CCl}_4$ )  $\delta=0.68$  (s, 3H), 1.00 (d,  $J=7.2\text{ Hz}$ , 3H), 1.17 (s, 3H), 1.4–2.2 (m, 4H), 2.59 (t,  $J=7.5\text{ Hz}$ , 2H), 2.66 (dq,  $J=9.5\text{ Hz}$ ,  $J=7.2\text{ Hz}$ , 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  $\text{C}_{20}\text{H}_{28}\text{O}_3$ ,  $\text{M}^+$ :  $m/z$  316.2036.

**(S)-2-Carboxy-5,5-dimethyl-2-[2-(p-methoxyphenyl)propyl]-1,3-dioxane (5):** Colorless oil: IR (film)  $\nu=1729\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CCl}_4$ )  $\delta=0.67$  (s, 3H), 0.96 (s, 3H), 1.32 (d,  $J=7.2\text{ Hz}$ , 3H), 3.43 (br m, 4H), 3.73 (s, 3H), 6.65 (d,  $J=8.4\text{ Hz}$ , 2H), 7.12 (d,  $J=8.4\text{ Hz}$ , 2H), 10.17 (br s, 1H) ppm. HRMS; Found:  $m/z$  249.1502. Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_3$ ,  $\text{M}^+-\text{COOH}$ :  $m/z$  249.1491.

**(S)-2-Carboxy-5,5-dimethyl-2-[(Z)-1-methyl-6-phenyl-2-hexenyl]-1,3-dioxane (5):** Colorless oil: IR (film)  $\nu=3070, 1715\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CCl}_4$ )  $\delta=0.70$  (s, 3H), 1.04 (d,  $J=6.9\text{ Hz}$ , 3H), 1.19 (s, 3H), 1.4–2.2 (m, 4H), 2.55 (t,  $J=7.5\text{ Hz}$ , 2H), 2.86 (dq,  $J=9.0\text{ Hz}$ ,  $J=6.9\text{ Hz}$ , 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  $\text{C}_{19}\text{H}_{27}\text{O}_3$ ,  $\text{M}^+-\text{COOH}$ :  $m/z$  287.2009.

**(S)-2-Carboxy-2-[2-(p-methoxyphenyl)propyl]-1,3-dithiane (6):** Colorless oil: IR (film)  $\nu=1720\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=1.57$  (d,  $J=7.2\text{ Hz}$ , 3H), 1.8–2.2 (m, 2H), 2.5–2.9 (m, 2H), 2.9–3.3 (m, 2H), 3.53 (q,  $J=7.2\text{ Hz}$ , 1H), 3.79 (s, 3H), 6.83 (d,  $J=9.0\text{ Hz}$ , 2H), 7.33 (d,  $J=9.0\text{ Hz}$ , 2H), 10.23 (br s, 1H) ppm. HRMS; Found:  $m/z$  253.0715. Calcd for  $\text{C}_{13}\text{H}_{17}\text{OS}_2$ ,  $\text{M}^+-\text{COOH}$ :  $m/z$  253.0722.

**(S)-2-Carbamoyl-5,5-dimethyl-2-[2-(p-methoxyphenyl)**

**yl)propyl]-1,3-dioxane (8):** Colorless oil: IR (film)  $\nu=1685\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=0.68$  (s, 3H), 1.01 (s, 3H), 1.40 (d,  $J=6.9\text{ Hz}$ , 3H), 3.00 (q,  $J=6.9\text{ Hz}$ , 1H), 3.77 (s, 3H), 5.86 (br s, 1H), 6.02 (s, 1H), 6.76 (d,  $J=8.4\text{ Hz}$ , 2H), 7.21 (d,  $J=8.4\text{ Hz}$ , 2H) ppm. HRMS; Found:  $m/z$  249.1517. Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_3$ ,  $\text{M}^+-\text{CONH}_2$ :  $m/z$  249.1491.

## References

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