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Asymmetric Synthesis of Alanine by Alkylation of Optically Active *N*-Alkyl-*N*-formylaminoacetonitriles[1)]

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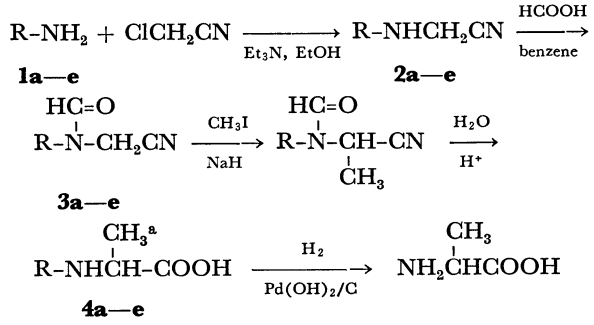
Synopsis. Optically active *N*-alkyl-*N*-formylaminoacetonitriles were prepared and the nitriles were alkylated with methyl iodide. The products were hydrolyzed and hydrogenolyzed to form optically active alanine. The optical yields of alanine ranged from 2 to 18%. The effects of the reaction temperature and of the asymmetric moieties on the optical yields were examined. The optical yields were also determined by the NMR spectra of the resulting diastereomers.

So far numerous asymmetric syntheses of α-amino acids have been reported.[2)] However, only a few papers deal with the asymmetric synthesis of α-amino acids by alkylation.[3)] An asymmetric synthesis of aspartic acid through β-lactams using optically active *N*-(alkylamino)acetonitriles[4)] has been reported.

In the present paper, sterically controlled synthesis of alanine from opitcally active *N*-alkyl-*N*-formylaminoacetonitriles(**3a**—**e**) by asymmetric alkylation with methyl iodide is described(Scheme 1). After hydrolysis and subsequent hydrogenolysis of the products, alanine was obtained. The *N*-(alkylamino)acetonitriles(**2a**—**e**) were prepared from racemic and optically active amines(**1a**—**e**) and chloroacetonitrile. The **2a**—**e** were converted in to the corresponding formylated compounds(**3a**—**e**). They were treated with sodium hydride and methyl iodide in DMF at various temperatures. The products were hydrolyzed with 6 M hydrochloric acid without isolation. The resulting *N*-alkyl-alanines(**4a**—**e**) were isolated by the use of a Dowex 50 column and were hydrogenolyzed with palladium hydroxide on charcoal to yield alanine. Yields of the synthesized alanine were in the range 2—66%, and the optical yields in the range 2—18%. When (*S*)-(—)-amines were used, (*R*)-(—)-alanine was obtained for all reaction temperatures. When α-methylbenzylamine was used, the optical yield of the resulting alanine was low. The use of 1-(1-naphthyl)-ethylamine slightly increased the optical yield of alanine. However, when α-ethylbenzylamine was used, the optical purity of alanine clearly increased. This suggests that the small(S) and the middle(M) groups among the large(L), M, and S groups of the asymmetric center might play an important role in the asymmetric synthesis.

The temperature effect on the optical yield was observed; the lower the reaction temperature, the higher the optical yield of alanine. However, the temperature effect was not so large. The results are summerized in Table 1.

In some cases, the optical yields of the asymmetric syntheses could be estimated by the NMR spectra of the resulting mixture of diastereomers.[5)] In the NMR spectrum of **4c**, the two sets of doublet signals observed are referred to (*S*-*R*) and (*S*-*S*) isomeric methyl protons (H_a, Scheme 1). The lower doublet



R: **a**, (±) Ph-CH(Me)-; **b**, (*S*)(—) Ph-CH(Me)-; **c**, (*S*)(—) Ph-CH(Et)-; **d**, (*R*)(+) Ph-CH(Et)-; **e**, (*S*)(—) $C_{10}H_7$-CH(Me)-

Scheme 1.

TABLE 1. ASYMMETRIC SYNTHESIS OF ALANINE

Starting material **3**	Config. of asymmetric moiety	Temp (°C)	Synthesized Ala		DNP-Ala	
			Config.	Yield (%)[a)]	$[\alpha]_D^{25}$ (*c*)[b)]	Optical yield (%)[c)]
a	±	−15	±	62		
b	(*S*)(−)	−15	*R*	61	− 2.1(0.70)	2
c	(*S*)(−)	−15	*R*	66	−14.0(1.00)	10
		−25	*R*	60	−18.4(1.25)	13 [d)]
d	(*R*)(+)	−25	*S*	54	+20.0(1.05)	14 [d)]
		−45	*S*	2	+24.0(0.13)	17
e	(*S*)(−)	−15	*R*	23	− 7.8(0.83)	5
d	(*R*)(+)	−78	*S*	35	+26.8(0.35)	18 [e)]

a) Calculated from **3**. b) Specific rotation of DNP-alanine measured in 1 M NaOH. c) Defined ($[\alpha]_D$ obsed/$[\alpha]_D$ of the compound) × 100. DNP-(*S*)-(+)-alanine, $[\alpha]_D^{25}$ +143.9° (1 M NaOH). d) Also calculated from the NMR spectra of **4**. (Table 2). e) Lithium diisopropylamide (4.94 mmol), HMPA (4.94 mmol), and methyl iodide (2.47 mmol) treated with **3d** (2.47 mmol) in THF.

Table 2. Optical yields calculated from the NMR spectra of 4[a]

Starting material 3	Config. of asymmetric moiety	Reaction temp (°C)	δ of H^a (ppm)	Ratio	Optical[b] yield (%)
c	(*S*)(−)	−25	1.45(*S-S*) 1.55(*S-R*)	*S-R*/*S-S* =57/43	14
d	(*R*)(+)	−25	1.45(*R-R*) 1.55(*R-S*)	*R-S*/*R-R* =56/44	12

a) The NMR spectra measured in D_2O with a 60 MHz spectrometer using DSS as an internal standard. b) Defined as $[(S\text{-}R)-(S\text{-}S)/(S\text{-}R)+(S\text{-}S)]\times 100$, or $[(R\text{-}S)-(R\text{-}R)/(R\text{-}S)+(R\text{-}R)]\times 100$.

signal with larger area was assigned to the methyl proton (H_a) of (*S-R*) isomer, from which (*R*)-alanine was obtained by hydrolysis and hydrogenolysis. The optical yield was determined by the ratio of the doublet signals of the diastereomers. The optical yield of **4d**, was also determined in the same way. The optical yields of **4c,d** determined by the NMR spectra(Table 2) agreed with those determined by the specific rotation of 2,4-dinitrophenyl(DNP)-alanine (Table 1).

Experimental

The amino acid analyses were carried out with a Yanagimoto LC-5S instrument. The NMR spectra were obtained with Hitachi H-60 and R-24 A instruments. The specific rotations were measured with a JASCO ORD-CD 20 C spectropolarimeter using a 10 mm cell. The boiling points and melting points were uncorrected. The optically active amines used were as follows. **1b**($[\alpha]_D^{25}$ −41.3°, benzene),[6,7] **1c**($[\alpha]_D^{25}$ −21.0°, benzene),[7,8] **1d**($[\alpha]_D^{25}$ +23.3°, benzene),[7,8] **1e**($[\alpha]_D^{25}$ −90.9°, benzene).[9] *N*-alkylaminoacetonitriles (**2a—d**) were prepared as described.[4]

(S)-(−)-N-α-Ethylbenzyl-N-formylaminoacetonitrile (3c). Compound **2c**(4.77 g, 27.4 mmol) and formic acid (6.30 g, 0.137 mol) were dissolved in 100 ml of dry benzene. The solution was stirred at room temperature for 2 h and then refluxed for 3 h with use of a Dean Stark distillation tube. After the reaction was over, the benzene solution was washed with 3% sodium hydrogencarbonate. The benzene solution was dried with anhydrous sodium sulfate and the solvent was evaporated. Compound **3c** was obtained by distillation under reduced pressure, yield, 3.42 g, 61.8%, bp 142—143 °C/1 Torr, $[\alpha]_D^{25}$ −99.3° (*c* 0.826, benzene). After distillation the nitrile **3c** crystallized. This was recrystallized from ethanol; mp, 56—57 °C, Found: C, 71.37; H, 6.91; N, 13.94%. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%. IR(KBr): 2950, 1655, and 1390 cm^{-1}; δ($CDCl_3$): 1.05(3H, t, *J*=7.2 Hz), 2.15(2H, quintet, *J*=7.2 Hz), 2.94(2H, ABq, *J*=17.4 Hz), 4.59(1H, t, *J*=7.2 Hz), 7.39(5H, s), 8.45(1H, s). Other nitriles were prepared in a similar way. The physical properties were as follows: **3a**; bp 156—157 °C/2 Torr, Found: C, 69.93; H, 6.48; N, 14.95%. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88%. **3b**; bp 157—158 °C/2 Torr, $[\alpha]_D^{25}$ −63.7°(*c* 0.97, benzene). Found: C, 70.12; H, 6.45; N, 14.82%. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88%. **3d**; bp 164—165 °C/3 Torr, $[\alpha]_D^{25}$ +103.1°(*c* 0.62, benzene); Found: C, 71.28; H, 6.98; N, 13.88%. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%. **3e**; bp 195—197 °C/1 Torr, $[\alpha]_D^{25}$ −76.1°(*c* 0.18, benzene). Found: C, 75.49; H, 5.99; N, 11.72%. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%.

N-[(S)-α-Ethylbenzyl]-(R)-alanine (4c). The formylated nitrile **3c**(0.510 g, 2.52 mmol) and methyl iodide(0.526 g, 3.71 mmol) were dissolved in 15 ml of anhydrous DMF. The solution was cooled to −25 °C and sodium hydride(0.140 g, 2.74 mmol, 47%, suspension in mineral oil) was added with stirring. The reaction mixture was stirred for 24 h at −25 °C. After the reaction was over the solvent was evaporated at 30 °C under reduced pressure. The residue was refluxed with 20 ml of 6 M hydrochloric acid for 20 h. After evaporation of hydrochloric acid, the hydrolyzate was applied on a Dowex 50 column(H^+ form). The column was eluted with 3 M aqueous ammonia and the solution was evaporated to dryness under reduced pressure. A part of **4c** was dissolved in 3 M hydrochloric acid and the solvent was removed under reduced pressure to crystallize **4c** hydrochloride. The salt was subjected to NMR analysis δ(D_2O): 0.80(3H, t, *J*=7.2 Hz), 1.45(3H, d, *J*=7.2 Hz), 1.55(3H, d, *J*=7.2 Hz), 2.10(2H, quintet, *J*=7.2 Hz), 7.50(5H, s).

(R)-Alanine (5). Compound **4c** was dissolved in a mixture of water(10 ml) and ethanol(10 ml) and was hydrogenolyzed with palladium hydroxide on charcoal(0.5 g) for 24 h at 1 atm. After the reaction was over the catalyst was removed by filtration. A part of the solution was diluted appropriately and analyzed with an automatic amino acid analyzer to determine the yield of alanine(60%). A part of alanine was converted to 2,4-dinitrophenyl(DNP)-alanine in the usual way,[4] and the resulting DNP-alanine was purified with use of a celite column treated with a citrate-phosphate buffer(pH 4 and pH 7).[10] The DNP-alanine was further confirmed by thin layer chromatography using ether-AcOH-H_2O(100 : 1 : 1 v/v) solvent system. DNP-(*R*)-alanine, $[\alpha]_D^{25}$ −18.4°(*c* 1.25, 1 M NaOH); optical purity 13%.

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