A Short-step Synthesis of 4-Hydroxyproline

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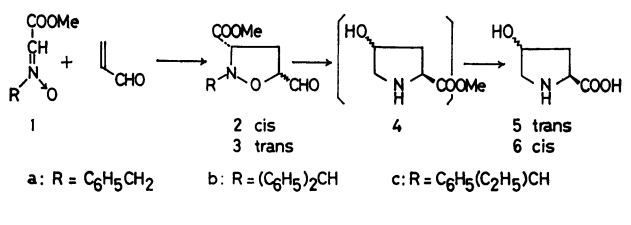
Synopsis. The reaction of *N*-benzyl-, *N*-diphenylmethyl-, or *N*-(1-phenylpropyl)-α-methoxycarbonylmethanimine *N*-oxide newly prepared with acrylaldehyde in benzene, followed by hydrogenolysis over palladium hydroxide and by acid hydrolysis, gave 4-hydroxyprolines.

After Leuchs synthesis[1] of 4-hydroxyprolines *via* a α-bromo-δ-chloro-γ-valerolactone, many procedures have been reported: one was a variant of the Leuchs method involving a α,δ-disubstituted γ-valerolactone intermediate,[2] others was a methods using a 2-amino-4-pentenoic acid derivative,[3] and the rest were along different routes.[4,5] All of these were based on the stepwise introduction of two asymmetric centers; the ratios of allohydroxyproline (**6**) to hydroxyproline (**5**) were near one. The predominant production of **6** was recognized in some cases,[2c,2e,4] but the overall yields were not high due to the rather long reaction sequences.

We wish to report here a new short-step synthesis of 4-hydroxyprolines (**5** and **6**). The method is comprised of 1,3-dipolar cycloaddition of *N*-alkyl-α-methoxycarbonylmethanimine *N*-oxide (**1**)[6] with acrylaldehyde, followed by the cleavage of the N–O bond and recyclization between the nitrogen and the aldehyde group to give a pyrrolidine ring. Two asymmetric centers can be introduced simultaneously at the stage of the cycloaddition.

The nitrones [**1**: **a**; *N*-benzyl-, **b**; *N*-diphenylmethyl-, and **c**; *N*-(1-phenylpropyl)-α-methoxycarbonylmethanimine *N*-oxides] were prepared according to the previous procedure.[6] NMR spectra of **1** showed the presence of both *E*- and *Z*-isomers.

The reaction of **1a** (E/Z=1.6) with acrylaldehyde in benzene for 24 h gave a mixture of two isomeric isoxazolidines (**2a** and **3a**; **2a**/**3a**=1.6); the structures were assigned by the comparison of their NMR spectra and pseudocontact shifts (0.057 equiv. of Eu-FOD) with those of the related compound.[6] The mixture thus obtained was subjected to the catalytic hydrogenolysis and the resulted crude ester **4** was hydrolyzed to give a mixture of **6** and **5** (**6**/**5**=1.61) in a 46% yield based on **1a**.



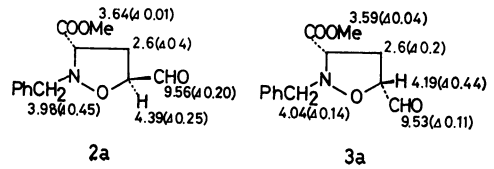


Table 1. The ratio of allo-Hyp(**6**)/Hyp(**5**) and yield in variation of nitrone and reaction type

		Nitrone		
		1a	**1b**	**1c**
Type I	**6**/**5**	1.61	3.66	1.43
	Yield/%	46	56	55
Type II	**6**/**5**	1.87	5.90	1.23
	Yield/%	32	71	65

When **1b** (E/Z=1.1) was used, a mixture of **6** and **5** (**6**/**5**=3.66) was obtained in a 56% yield.

The above results show that the E/Z ratio in $CDCl_3$ had not necessarily reflected on the ratio of **6**/**5**. This led to the finding[7] that nitrones (**1**), though they exist in a *Z*-form in a crystalline state, exhibit a novel *E*-*Z* equilibrium in a solution. Therefore, two types of reactions were performed in order to clarify the synthetic utility of the present method. In type I, the crystalline *Z*-nitrone was added to a solution of acrylaldehyde in benzene, while in type II, acrylaldehyde was added to a equilibrium mixture of *E*- and *Z*-nitrones in benzene.

The results are summarized in Table 1. The **6**/**5** ratio was the highest when **1b** was subjected to the type II condition. Stereoselectivity (**6**/**5**=5.90) and overall yield (71%) for the production of **5** and **6** are superior to hitherto reported procedures.[2-5] On the other hand, the stereoselective production of **5** was not specified in the present method.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi 215 grating spectrophotometer and the NMR spectra were measured with a JEOL MH-100 spectrophotometer, using TMS as the internal standard. The amino acid chromatograms were taken on a Dionex D-500 Mark II analyzer using a column of DC-6A (1.75ϕ× 480 mm) at 41 °C with an elution buffer Li-A (pH 2.75).

Preparation of Nitrones. Nitrones (**1a**, **1b**, and **1c**) were prepared by condensation of methyl glyoxylate with a corresponding *N*-alkylhydroxylamine.

1a: Mp 90—92 °C (colorless prisms from benzene); ν(KBr): 1727, 1570, 1220, and 1205 sh cm^{-1}; δ ($CDCl_3$, E/Z=1.6): 7.6—7.1 (m, C_6H_5 and =CH), 5.70 (s, N-CH_2- of *E*-form), 4.98 (s, N-CH_2- of *Z*-form), 3.77 (s, $COOCH_3$, *Z*), and 3.78 (s, $COOCH_3$, *E*); E/Z=3.3 (C_6D_6). Found: C, 61.87; H, 5.65; N, 7.18%. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.65; N, 7.24%.

1b: Mp 131.5—132.5 °C (colorless needles from benzene); ν (KBr): 1725, 1700, 1550 br, 1215, and 1205 cm^{-1}; δ ($CDCl_3$, E/Z=1.1): 8.2 (s, =CH, *E*), 7.5—7.2 (m), 6.28 (s, N-CH, *Z*), and 3.71 (s, $COOCH_3$, *E*+*Z*); E/Z=1.7 (C_6D_6). Found: C, 71.50; H, 5.52; N, 5.13%. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20%.

1c: Mp 72.5—74.5 °C (colorless prisms which formed slowly from benzene); ν (KBr): 1730, 1550 br, 1220 sh, 1210,

and 1170 cm^{-1}; δ ($CDCl_3$, E/Z=0.95): 7.7—7.2 (m, C_6H_5 and =CH), 6.86 (dd, J=10 and 6 Hz, N-CH, Z), 4.83 (dd, J=10 and 6 Hz, N-CH, E), 3.84 (s, $COOCH_3$, E), 3.80 (s, $COOCH_3$, Z), 2.7—1.9 (m, $C\underline{H}_2CH_3$, $E+Z$), 0.97 (t, J=7 Hz, $CH_2C\underline{H}_3$, Z), and 0.94 (t, J=7 Hz, $CH_2C\underline{H}_3$, E); E/Z= 1.9 (C_6D_6). Found: C, 65.13; H, 6.78; N, 6.31%. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33%.

Preparation of **6** *and* **5**. Typical procedures of both types were as follows:

Type I: To a solution of acryladehyde (1.5 mmol) in benzene (4 ml), was added **1a** (0.5 mmol), in one portion. The mixture was stirred at room temperature for 24 h. The removal of benzene and the excess of acryladehyde *in vacuo* at 25 °C gave an oily mixture of **2a** and **3a** (100%, **2a**/**3a**= 1.6). Without further purification, the mixture thus obtained was dissolved in methanol (20 ml) and then hydrogenated over palladium hydroxide (85 mg) under a hydrogen atmos phere (3 atm) for 24 h, After removal of the catalyst, the filtrate was concentrated to give **4** (127 mg), which was subsequently refluxed with 1 mol dm^{-3} HCl (5 ml) for 4.5 h. After decolorizing with activated carbon, the solution was concentrated to give pale yellow crystals (103 mg). The ratio of stereoisomers and the yield from **1a** were determined by amino acid analysis (**6**/**5**=1.61, yield 46%).

Type II: A solution of **1b** (0.26 mmol) in benzene (5 ml) was left at room temperature for 3 h. To the solution was added acrylaldehyde (0.8 mmol) in one portion and the mixture was stirred at room temperature for 24 h. The removal of benzene and excess of acryladehyde *in vacuo* at 25 °C gave a colorless oily mixture of **2b** and **3b** (100%, **2b**/**3b**=4.4). The mixture of **2b** and **3b** (87 mg) was subjected to catalytic hydrogenolysis and acid hydrolysis under similar conditions as in Type I, giving a crystalline mixture of **6** and **5** (**6**/**5**=5.90, yield 71% from **1b**).

In the case of **1a** or **1c**, the solution in benzene was left for 3 h or 2 d, respectively, before the addition of acryladehyde.

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