Synthesis of Ethyl (*E*)-2-Formylamino-4-methoxy-3-butenoate and its 2-Alkyl Derivatives

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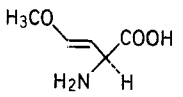
(2*S*)-(*E*)-2-Amino-4-methoxy-3-butenoic acid **(1)**, produced by *Pseudomonas aeruginosa* ATCC-7700[1], is an enzyme inhibitor for pyridoxal-phosphate depending enzymes[2] and an antibiotic agent[1]. Furthermore, it is of interest as a potential plant growth regulator[3]. Recently, the *N*-Cb-protected benzyl ester of **1** was prepared by a multistep synthesis starting with L-homoserine. Compound **1** is a key intermediate for the synthesis of rhizobitoxin[4] **(2)**.



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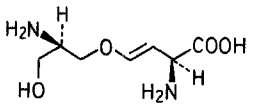

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This communication describes an efficient synthesis of the *N*-formyl ethyl ester **(8a)** of D,L-**1** and the introduction of alkyl groups into the 2-position to give the structural variants **8b–d** of **1**.

The sodium cyanide-catalyzed addition of ethyl isocyanoacetate **(3)** to methoxyacetaldehyde[5] **(4)** gives diastereoselectively ethyl *trans*-5-methoxymethyl-4,5-dihydro-1,3-oxazole-4-carboxylate **(5)**[6,7]. On treatment with potassium *t*-butoxide, base-induced ring opening of the oxazoline **5** takes place to give (after protonation) a 6 : 1-mixture of ethyl (*E*)- and ethyl (*Z*)-2-formylamino-4-methoxy-2-butenoate **(6)** in 66% yield. This mixture is isomerized to ethyl 2-formylamino-4-methoxy-3-butenoate **(8)** via "allyl deprotonation" and reprotonation

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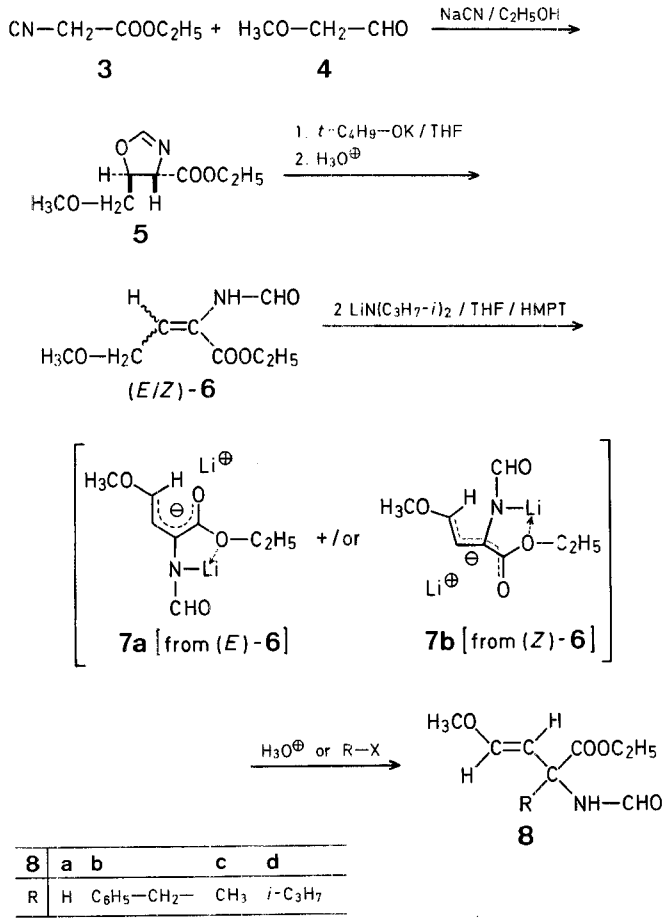
of the anions **7a** and **7b** (2 equivalents of lithium diisopropylamide in tetrahydrofuran, 5 equivalents of HMPT, followed by neutralization with trifluoroacetic acid)[8]. On chromatography, (*E*)-**8a** was isolated in 64% yield together with a 3 : 1 mixture of (*E*)-**6** and (*Z*)-**6**. The isomer (*Z*)-**8a** could not be detected in the crude product. On deprotonation-reprotonation of pure (*E*)-**6**, only (*E*)-**8a** and (*E*)-**6** could be isolated. Thus, from (*E*)-**6** the (2*E*,3*E*)-dianion **7a** and from (*Z*)-**6** the (2*Z*,3*E*)-dianion **7b** are formed on deprotonation. Both dianions react with alkyl halides in good yields (64–74%) to give the 2-alkyl derivatives **8b–d**. The *E*-configuration follows from the coupling constant $J_{3,4}=13$ Hz in the ^{1}H-N.M.R. spectrum.



8	a	b	c	d
R	H	C_6H_5—CH_2—	CH_3	i-C_3H_7

Low-pressure chromatography (1.5 at) was performed on silica gel (230–400 mesh). Technical-grade methoxyacetaldehyde[5] (**4**) was purified by distilling the 79% water/methanol solution (10 g) of **4** with chloroform (100 g) at 760 torr to remove water and methanol, discarding a forerun, and distilling **4** at 90 °C; the purity of **4** is then 95% (according to ^{1}H-N.M.R. analysis). Compound **4** trimerizes on standing.

Ethyl *trans*-5-Methoxymethyl-4,5-dihydro-1,3-oxazole-4-carboxylate (5):

Methoxyacetaldehyde (**4**; 8.15 g, 0.11 mol) is added to a stirred solution of ethyl isocyanoacetate (**3**; 11.3 g, 0.1 mol) in dry ethanol (65 ml) containing sodium cyanide[6] (0.6 g), under a nitrogen atmosphere. Stirring is continued for 15 h at room temperature and the solvent then removed in vacuo. Tetrachloromethane (125 ml) is added to the residue, the mixture is cooled at 0 °C for 1 h and then filtered, and the filtrate is distilled in vacuo; yield: 12.65 g (68%); b.p. 78 °C/0.1 torr.

$C_8H_{13}NO_4$	calc.	C 51.33	H 7.00
(187.2)	found	51.49	7.07

I.R. (film): $\nu=1735$ (C=O), 1625 cm^{-1} (N=C).

^{1}H-N.M.R. (CCl_4/TMS): $\delta=6.88$ (d, $J=2$ Hz, 2-H); 4.77 (dd, $J=8$ Hz, 4 Hz, 5-H); 4.43 (dd, $J=8$ Hz, 2 Hz, 4-H); 3.59 (d, $J=4$ Hz, CH_2); 3.44 (s, OCH_3); 4.28, 1.38 ppm (q or t, $J=7$ Hz, CH_2—CH_3).

Ethyl 2-Formylamino-4-methoxy-2-butenoate [(*E*/*Z*)-6]:

A solution of compound **5** (7.48 g, 40 mmol) in tetrahydrofuran (30 ml) is added dropwise to a stirred solution of potassium *t*-butoxide (4.92 g, 44 mmol) in dry tetrahydrofuran (60 ml) at 0–5 °C. Stirring is continued for 30 min at room temperature and the solvent then removed in vacuo. A mixture of acetic acid (2.64 g, 44 mmol) and water (40 ml) is added to the residue and the mixture is extracted with dichloromethane (3 × 25 ml). The organic extract is dried with magnesium sulfate and the solvent is evaporated in vacuo. The residue is chromatographed on silica gel using ether as eluent; yield of **6**: 4.9 g (66%); R_f: 0.17; *E*/*Z* ratio = 6 : 1.

$C_8H_{13}NO_4$	calc.	C 51.33	H 7.00
(187.2)	found	51.07	6.89

I.R. (film): $\nu=3280$ (NH); 1660–1720 (ss) (C=O, C=C); 1500 cm^{-1} (amide II).

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta=8.31$, 8.23 [s, CHO, (*Z*)-**6**, (*E*)-**6**]; 8.15 (s, NH); 7.36, 6.69 [t, $J=5$ Hz, =CH, (*Z*)-**6**, (*E*)-**6**]; 4.0–4.5 (m, 4H, CH_2O, CH_2—CH_3); 3.37 (s, OCH_3); 1.36, 1.32 ppm [t, $J=7$ Hz, CH_2—CH_3, (*Z*)-**6**, (*E*)-**6**].

Pure (*E*)-**6** may be obtained by repeated chromatography of the last fractions of the initial chromatography.

Ethyl (*E*)-2-Formylamino-4-methoxy-3-butenoate [(*E*)-8a]:

A 1.55 normal solution of butyllithium in hexane (2.6 ml, 4 mmol) is added to a stirred solution of diisopropylamine (0.56 ml, 4 mmol) in dry tetrahydrofuran (10 ml) at −78 °C. After a few minutes, an ice-cold solution of compound **6** (0.374 g, 2 mmol) and HMPT (1.8 g, 10 mmol) in tetrahydrofuran (2 ml) is added at −78 °C and stirring is continued for 30 min. Then, trifluoroacetic acid (0.31 ml, 4 mmol) is added (without cooling) and the solvent is removed in vacuo. The residue is shaken with dichloromethane (20 ml) and water (15 ml). The aqueous layer is separated and again extracted with dichloromethane (15 ml). The combined organic layers are dried with magnesium sulfate, the solvent is evaporated in vacuo, and the residue is chromatographed on silica gel using ether as eluent; yield of (*E*)-**8a**: 0.24 g (64%); $R_f=0.10$.

$C_8H_{13}NO_4$	calc.	C 51.33	H 7.00
(187.2)	found	51.10	7.05

I.R. (film): $\nu=3300$ (NH); 1740 (C=O); 1650–1680 (amide I, C=C—O); 1510 cm^{-1} (amide II).

^{1}H-N.M.R. (CCl_4/TMS): $\delta=8.05$ (s, CHO); 7.17 (d, $J=7$ Hz, NH); 6.58 (d, $J=12$ Hz, O—CH=); 4.5–5.0 (m, HC=, HC—N); 4.15 (q, $J=7$ Hz, CH_2); 3.52 (s, OCH_3); 1.29 ppm (t, $J=7$ Hz, CH_2—CH_3).

The forefraction gives (*E*/*Z*)-**6** (3 : 1); yield: 67 mg (18%); $R_f=0.17$.

With pure (*E*)-**6** as starting material, only (*E*)-**8a** and (*E*)-**6** are formed in a ratio 3 : 1; (*Z*)-**6** could not be detected in the product.

Ethyl (*E*)-2-Alkyl-2-formylamino-4-methoxy-3-butenoates [(*E*)-8b, c, d]; General Procedure:

A 1.55 normal solution of butyllithium in hexane (2.6 ml, 4 mmol) is added to a stirred solution of diisopropylamine (0.56 ml, 4 mmol) in dry tetrahydrofuran (10 ml) at −78 °C. After a few minutes, an ice-cold solution of compound **6** (0.374 g, 2 mmol) and HMPT (1.8 g, 10 mmol) in tetrahydrofuran (2 ml) is added at −78 °C and stirring is continued for 30 min. Then, a solution of the alkyl halide (2 mmol) in tetrahydrofuran (2 ml) is added and stirring is continued for 1 h at −78 °C. The cooling bath is removed, acetic acid (0.12 ml, 2 mmol) is added, and the solvent is removed in vacuo. The residue is shaken with dichloromethane (20 ml) and water (15 ml). The aqueous layer is separated and again extracted with dichloromethane (15 ml). The combined organic layers are dried with magnesium sulfate, the solvent is evaporated in vacuo, and the residual product **8** is chromatographed on silica gel using ether as eluent.

Ethyl (E)-*2-Benzyl-2-formylamino-4-methoxy-3-butenoate* [(*E*)-**8b**] is prepared using benzyl bromide (0.24 ml, 2 mmol); yield: 0.413 g (74%); $R_f = 0.26$.

$C_{15}H_{19}NO_4$	calc.	C 64.97	H 6.91
(277.3)	found	65.13	6.87

I.R. (film): $\nu = 3300$ (NH); 1720 (C=O); 1650–1680 cm^{-1} (amide I, C=C).

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 7.93$ (s, CHO); 7.09 (m, C_6H_5); 6.5 (NH); 6.40 (d, $J = 13$ Hz, O—CH=); 4.95 (d, $J = 13$ Hz, HC=); 4.16 (q, $J = 7$ Hz, CH_2—CH_3); 3.50 (s, CH_3); 3.68, 3.21 (AB, $J_{AB} = 14$ Hz, CH_2); 1.31 ppm (t, $J = 7$ Hz, $CH_2\underline{CH_3}$).

Ethyl (E)-*2-Formylamino-4-methoxy-2-methyl-3-butenoate* [(*E*)-**8c**] is prepared using methyl iodide (0.13 ml, 2 mmol); yield: 0.265 g (66%); $R_f = 0.13$.

$C_9H_{15}NO_4$	calc.	C 53.72	H 7.51
(201.2)	found	54.00	7.49

I.R. (film): $\nu = 3280$ (NH); 1740 (C=O); 1660–1690 (amide I, C=C); 1510 cm^{-1} (amide II).

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 8.00$ (s, CHO); 7.10 (NH); 6.51 (d, $J = 13$ Hz, O—CH=); 4.96 (d, $J = 13$ Hz, HC=); 4.19 (q, $J = 7$ Hz, CH_2); 3.56 (s, OCH_3); 1.67 (s, CH_3); 1.32 ppm (t, $J = 7$ Hz, CH_2—CH_3).

Ethyl (E)-*2-Formylamino-2-isopropyl-4-methoxy-3-butenoate* [(*E*)-**8d**] is prepared using 2-iodopropane (0.22 ml, 2.2 mmol); yield: 0.315 g (69%); m.p. 68 °C; $R_f = 0.12$.

$C_{11}H_{19}NO_4$	calc.	C 57.63	H 8.35
(229.3)	found	57.79	8.42

I.R. (KBr): $\nu = 3290$ (NH); 1725 (C=O); 1685 (amide I); 1660 (C=C); 1520 cm^{-1} (amide II).

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 8.14$, 8.19 (s or d, $J = 14$ Hz, CHO); 6.48 (d, $J = 13$ Hz, O—CH=); 6.36 (d, $J = 14$ Hz, NH); 5.19, 4.96 (d, $J = 13$ Hz, CH=); 4.22 (q, $J = 7$ Hz, CH_2); 3.56 (s, OCH_3); 2.32 (hept, $J = 7$ Hz, CH); 1.32, 1.25 (each d, $J = 7$ Hz, CH_3); 0.95, 0.92 ppm (each t, $J = 7$ Hz, CH_2—$\underline{CH_3}$).

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