A Convenient Synthesis of Glycyl-(β-aryl)-dehydroalanines

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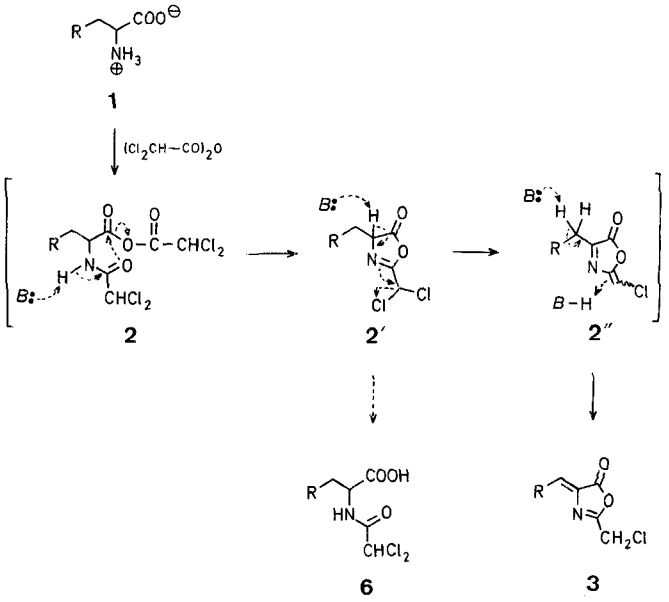
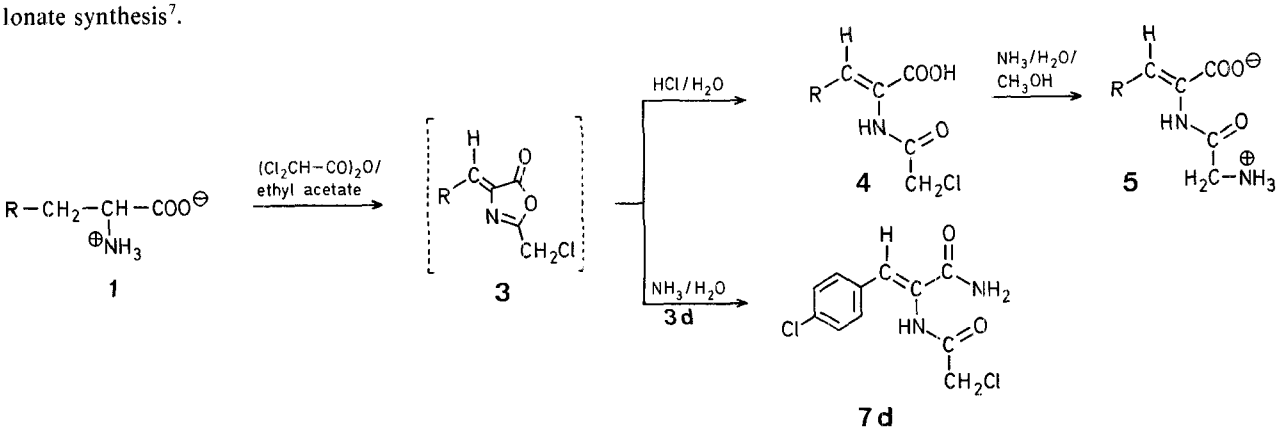
Since it was first reported in 1930, the synthesis of glycyldehydrophenylalanine **(5a)** has been the subject of only three publications[1,2,3]. There is interest in this structural unit because **5a** is a convenient substrate for a spectrophotometric assay of a dipeptidase[4] and because of general interest in dehydropeptides, some of which include a glycyldehydrophenylalanine unit[5]. The previously reported syntheses of **5a** are lengthy and low-yielding. In addition, the synthesis of substituted dehydrophenylalanines is not achievable by the reported methods, hence no substituted dipeptides have been reported. The *N*-chloroacetyl compound **(4b)** has been made[3] but we found it very difficult to obtain sufficient material of this compound. Because substituents on the aryl ring will have an influence on the absorption spectra of these dipeptides, a number of compounds **5** were synthesized. They may prove to be more sensitive and selective substrates for the assay of dipeptidases.

We describe herein a general, two-step process for making **5** from β-arylalanines. Because the chiral center of the arylalanine becomes an sp^2 carbon during the synthesis, racemic starting materials may be employed. This opens up the synthesis to any D,L-β-arylalanines, which are in turn readily available commercially, or in a few steps from the Erlenmeyer[6] or malonate synthesis[7].





	R		R
a		f	H_3C-
b	HO-	g	t-C_4H_9-
c	O_2N-	h	H_3CO-
d	Cl-	i	S
e	F-		

Our synthesis requires 2 molar equivalents of dichloroacetic anhydride, presumably to generate the reactive intermediate **2**, which cyclizes to oxazolinone **3**. Evidence that this is indeed the pathway follows:

- Hydrogen chloride (gas) is evolved as the reaction proceeds.
- Azlactones **3a, c, d, i** have been isolated in good yield.
- Amide **7d** has been trapped with ammonia.
- *N*-Dichloroacetyl derivatives **6** can be readily identified, in low yield, in the ^{1}H-N.M.R. spectra of crude reaction mixtures (particularly **6 h**).

Generally, it has been found convenient not to isolate **3** but rather to hydrolyze it *in situ*. The most convenient way to do this is to add water to the refluxing reaction mixture.

Although we have represented the dehydrocompounds in the (*Z*)-configuration, there is no proof of this, at present. However, it has been demonstrated that the Erlenmeyer azlactone synthesis leads invariably to the (*Z*)-geometry[8], and our synthesis is a modified Erlenmeyer method. Furthermore, ^{1}H-N.M.R. studies indicate that chemical shifts for the ethylenic proton in **4** and **5** are similar to those reported for (*Z*)-cinnamoyl compounds[9].

N-Chloroacetyl-p-chlorodehydrophenylalanine (4d); Typical Procedure:

p-Chlorophenylalanine (**1d**; 1.00 g, 5 mmol) and dichloroacetic anhydride (2.40 g, 10 mmol) are suspended in ethyl acetate (25 ml) with heating and stirring. After refluxing overnight (the time period for reflux can be cut to 0.5 h without a sacrifice in yield), the mixture is stirred at room temperature with 1 normal hydrochloric acid (5 ml). Analytically pure **4d** precipitates from the mixture; yield: 0.81 g (59%); m.p. 204–205 °C (dec). A further 0.37 g may be collected in two crops from the ethyl acetate; total yield: 1.18 g (86%).

Glycyl-p-chlorodehydrophenylalanine (5d); Typical Procedure:

N-Chloroacetyl-*p*-chlorodehydrophenylalanine (0.20 g, 0.73 mmol) is dissolved in methanol (5 ml) and conc. aqueous ammonia (5 ml). After 47 h, the solvent is evaporated and the residue suspended in water (10 ml), collected by suction, and dried to give **5d**; yield: 0.15 g (81%). An analytical sample may be prepared by recrystallization from water; m.p. 230 °C (dec).

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Table. Compounds **4, 5,** and **7** prepared

Compound	Yield [%]	m.p. [°C]	Molecular formula[a]	U.V.[b] λ_{max} [nm] (logε)	^{1}H-N.M.R. (TMS)[c] δ [ppm]
4a	72	196–197° (dec)	$C_{11}H_{10}ClNO_3$ (239.7)	280 (4.18)	4.25 (s, 2H); 7.5 (m, 54); 9.70 (s, 1H); 12.70 (s, 1H)
4c	72	203–205° (dec)	$C_{11}H_9ClN_2O_5$ (284.7)	314 (4.04)	4.25 (s, 2H); 7.40 (s, 1H); 8.0 (m, 4H); 10.05 (s, 1H); 12.8 (s, 1H)
4d	86	204–205° (dec)	$C_{11}H_9Cl_2NO_3$ (274.1)	285 (4.27)	4.25 (s, 2H); 7.5 (m, 5H); 9.80 (s, 1H); 12.80 (s, 1H)
4e	85	186–188°	$C_{11}H_9ClFNO_3$ (257.6)	278 (4.18)	4.26 (s, 2H); 7.5 (m, 5H); 9.70 (s, 1H); 12.80 (s, 1H)
4f	75	209–212° (dec)	$C_{12}H_{12}ClNO_3$ (253.7)	288 (4.20)	2.30 (s, 3H); 4.25 (s, 2H); 7.30 (s, 1H); 7.4 (m, 4H); 9.79 (s, 1H); 12.70 (s, 1H)
4g	43	153–155°	$C_{15}H_{18}ClNO_3$ (295.8)	288 (4.28)	1.45 (s, 9H); 4.29 (s, 2H); 7.5 (m, 5H); 8.90 (s, 1H); 9.70 (s, 1H)
4h	45	202–204° (dec)	$C_{12}H_{12}ClNO_4$ (269.7)	300 (4.33)	3.80 (s, 3H); 4.25 (s, 2H); 7.3 (m, 4H); 7.38 (s, 1H); 9.65 (s, 1H); 12.70 (s, 1H)
4i	93	210–213° (dec)	$C_9H_8ClNO_3S$ (245.7)	308 (4.24)	4.25 (s, 2H); 7.5 (m, 4H); 9.65 (s, 1H); 12.70 (s, 1H)
5a	40	230° (dec)	$C_{11}H_{12}N_2O_3$ (220.2)	274 (4.18)	4.05 (s, 2H); 7.5 (m, 4H); 7.70 (s, 1H)
5d	81	230° (dec)	$C_{11}H_{11}ClN_2O_3$ (254.7)	280 (4.25)	4.05 (s, 2H); 7.5 (m, 4H); 7.70 (s, 1H)
5e	73	195° (dec)	$C_{11}H_{11}FN_2O_3$ (238.2)	273 (4.08)	4.10 (s, 2H); 7.5 (m, 5H)
5f	63	209° (dec)	$C_{12}H_{14}N_2O_3$ (234.2)	281 (4.23)	2.35 (s, 3H); 4.10 (s, 2H); 7.4 (m, 4H); 7.75 (s, 1H)
5h	74	215° (dec)	$C_{12}H_{14}N_2O_4$ (250.2)	292 (4.26)	3.80 (s, 3H); 4.10 (s, 2H); 7.4 (m, 5H)
5i	79	210° (dec)	$C_9H_{10}N_2O_3S$ (226.3)	303 (4.20)	4.15 (s, 2H); 7.5 (m, 3H); 8.12 (s, 1H)
7d	47	175° (dec)	$C_{11}H_{10}ClN_2O_2$ (273.1)	—	4.25 (s, 2H); 7.20 (s, 1H); 7.30 (s, 2H); 7.45 (m, 4H); 9.70 (s, 1H)

[a] The microanalyses (except for compounds **4c, 4g,** and **7d**) were in satisfactory agreement with the calculated values: C, ±0.40; H, ±0.16; N, ±0.40. Exceptions: **4c,** C, +0.45; **4g,** C, −0.41; **7d,** C, −0.46; these products retain traces of water.

[b] The U.V. spectra for **3a–3i** were obtained in 95% ethanol; those for **4a–4i** were obtained using 49.7 mmolar 3-morpholinopropanesulfonic acid at pH 7.1.

[c] The ^{1}H-N.M.R. spectra for compounds **3a–3f, 3h, 3i,** and **7d** were obtained in DMSO-d_6; the spectrum for **3g** was obtained in acetone-d_6; those of **4a–i** were obtained in DCl/D_2O.

***N*-Chloroacetyl-*p*-chlorodehydrophenylalaninamide (7d):**

4-(4-Chlorobenzylidene)-2-chloromethyl-5-oxo-4,5-dihydro-1,3-oxazole (Azlactone **3d**): *p*-Chlorophenylalanine (**1d**; 2.00 g, 10 mmol) is suspended in ethyl acetate (50 ml) and treated with dichloroacetic anhydride (4.80 g, 20 mmol). The mixture is heated at reflux for 1.5 h and the solvent is evaporated to yield a liquid and a solid. This mixture is treated with 5% sodium hydrogen carbonate solution (75 ml). The resultant solid is collected by suction and dried to give crude azlactone **3d**; yield: 2.52 g (98%).

The ^{1}H-N.M.R. spectrum is consistent with the structure proposed.

N-*Chloroacetyl*-p-*chlorodehydrophenylalaninamide* **(7d):** Azlactone **3d** (0.20 g, 0.8 mmol) is dissolved in dioxan (15 ml) and the solution treated with conc. aqueous ammonia (5 ml) for 10 min. The solvent is evaporated and the residue partitioned between ethyl acetate and aqueous 5% sodium hydrogen carbonate. The organic solution is dried with sodium sulfate and the ethyl acetate removed in vacuo to give analytically pure amide **7d**; yield: 0.10 g (47%); m.p. 175°C (dec).

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