Reaction of Amino Acids with *o*-Acetylbenzoic Acid

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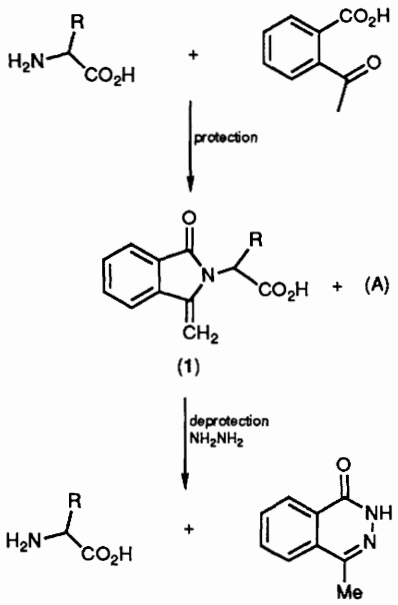
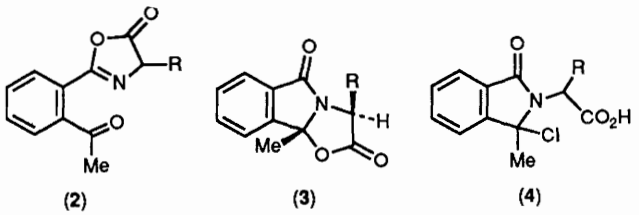
Novel benzo-fused bicyclic oxazolidinones are formed upon treatment of α-amino acids with *o*-acetylbenzoic acid; the crystal structure of one example has been determined.

Protecting group methodology is an important area in amino acid chemistry. Although the phthaloyl group has been widely utilized, the methylene analogue in (**1**) is less commonly used for the protection of the amino function (Scheme 1).[1] Panetta[2] reported the isolation of a major by-product (A) during the protecting step and characterized it as the oxazolone (**2**). We observed the formation of the same nonpolar by-product under various conditions with different amino acids in yields ranging from 2 to 42%. However, its structure elucidation needed further clarification. With valine as an example [*e.g.*, (**1c**)], the ^{13}C NMR of spectrum of the by-product (A) lacked a ketonic carbonyl signal but exhibited a characteristic peak at



		% Yield (1)	% Yield (A)
a;	Ala	59	2.7
b;	Phe	65	6.8
c;	Val	57	35
d;	Ile	23	42

Scheme 1



(2) (3) (4)

δ 97.4† which is low for an aryl-attached azalactone carbon resonance.[3] Moreover, dissolution of a pure sample of (**1c**) in chloroform at room temperature resulted in the slow formation of the crystalline by-product in quantitative yield. On the other hand, treatment with dry HCl in ether converted the by-product (A) cleanly back to the protected acid (**1c**) *via* the unstable chloro intermediate (**4**), which was not isolated.‡

† ^{1}H NMR ($CDCl_3$); δ 7.9—7.6 (m, 4H), 4.1 (d, *J* 10 Hz, 1H), 2.2—2.1 (m, 1H), 1.3 (d, *J* 6.5 Hz, 3H), and 1.2 (d, *J* 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.67, 172.41, 145.65, 133.88, 131.18, 130.78, 124.70, 123.08, 97.43, 63.54, 31.38, 26.09, 20.35, and 19.31. Other amino acid derivatives showed similar patterns.

‡ ^{1}H NMR spectroscopy clearly indicated the formation of (**4**) during the reaction and it decomposed smoothly to (**1**) upon heating at 70 °C. In general the stability of (**1**) is greatly enhanced when it is stored as the salt form. See also ref. 2.

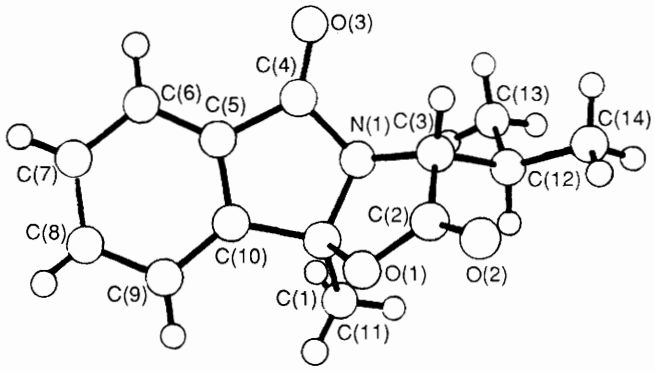


Figure 1. Perspective view of the crystal structure of (**3**).

Both manipulations are simple and require no purification. The preparative yield of (**1**) [or (A)] can therefore be enhanced by recycling the undesired product. Since (**1**) is not expected to be transformed into (**2**) easily, the facile acid-catalysed interconversion between (**1**) and (A) favours the identity of the by-product as the oxazolidinone (**3**) rather than the oxazolone (**2**).

An *X*-ray structure determination of the (±)-valine adduct confirmed the structure (**3**) (Figure 1).§ The facile formation of this unique oxazolidinone[4] is noteworthy and it represents a novel way of bis-protecting α-amino acids. It is also interesting to note that only a single diastereoisomer is isolated in which the R group adopts the *exo*-stereochemistry. This is most likely a result of thermodynamic control during lactone ring formation. Furthermore, the rigidity of the well known [3.3.0] system of these bis-protected amino acid derivatives allows them to serve as ideal templates for further elaboration at the α-position, for example, to prepare unnatural amino acid–peptide derivatives of predictable stereochemistry. This and other aspects of the chemistry of the oxazolidinone (**3**) will be reported accordingly elsewhere.

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References

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3 E. P. Prokof'ev, E. I. Karpeiskaya, G. V. Cheltsova, and T. B. Dantsig, *Izv. Akad. SSSR, Ser. Khim.*, 1980, 823. For leading references see: I. J. Turchi, 'Oxazoles,' in 'The Chemistry of Heterocyclic Compounds,' eds. A. Weissberger and E. Taylor, Wiley, New York, vol. 45, 1986.
4 For a related oxazolidinone see: V. Scartoni, F. Fiaschi, S. Catalano, I. Morelli, and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1547; P. Freytag, *Chem. Ber.*, 1915, 652.

§ *Crystal data* for (**3**): $C_{14}H_{15}N_1O_3$, space group $P\bar{1}$, a = 8.396(1), b = 10.733(2), c = 7.061(2) Å, α = 96.21(2), β = 93.49(2), γ = 100.68(1)°, D_c = 1.315 g cm^{-3} for U = 619.5(4) Å^3 and Z = 2. 2196 Unique reflections were measured on a Rigaku AFCOR diffractometer using Mo-K_α radiation, and the 1066 with $I > 3\sigma(I)$ were used in the refinement to R 0.045 and R_w 0.053. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.