

SYNTHESIS OF SOME β -(1-BENZIMIDAZOLYL)- AND β -(1-BENZOTRIAZOLYL)-
 α -AMINO ACID DERIVATIVES

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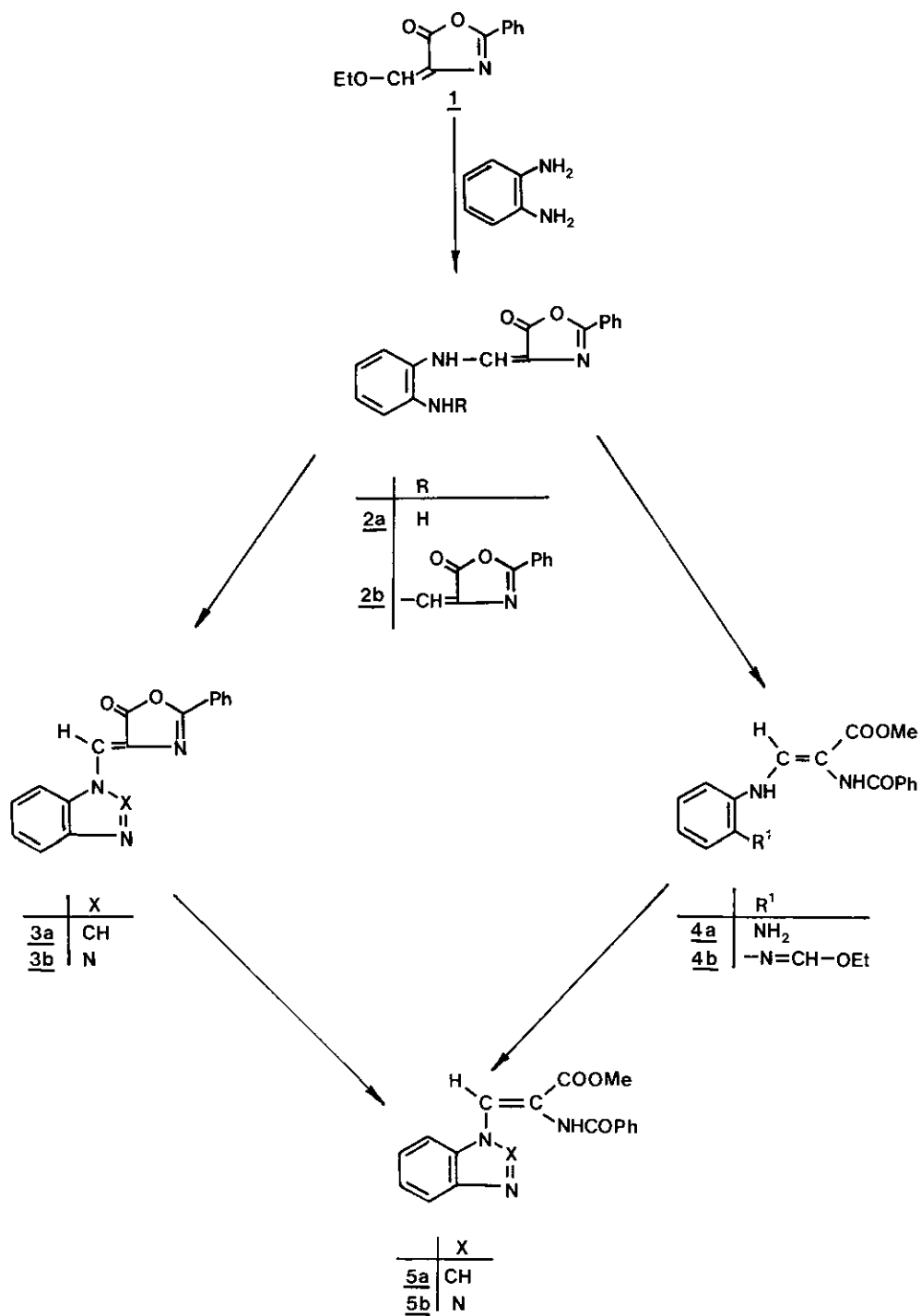
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Abstract - A convenient method for the preparation of methyl β -(1-benzimidazolyl)- and β -(1-benzotriazolyl)- α -benzoylaminoacrylates (5) from N-substituted o-phenylenediamine 2a is described. The synthesis of these two compounds proceeds either by ring opening of oxazolones 3 or by cyclization of acrylates 4.

A number of naturally occurring nonproteinogenic heterocyclic α -amino acids such as, for example mimosine,¹ willardiine,² and lupinic acid,³ contain a nitrogen heterocyclic system attached to the amino acid moiety by ring nitrogen. Our interest in the synthesis of heterocyclic compounds led us to examine the synthetic possibilities for the preparation of some compounds of this type. In the present paper, we wish to describe the synthesis of some β -(1-benzimidazolyl)- and β -(1-benzotriazolyl)- α -amino acid derivatives.

It was reported that the reaction of 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone (1) with different primary amines afforded N-substituted aminomethylene oxazolones.⁴ It was also described that the reaction of the same compound with o-phenylenediamine gave 1,5-benzodiazepine system.⁵ Our strategy for the synthesis of N-heteroaryl- α -amino acid derivatives was based on the use of oxazolone 2a, a probable intermediate in the benzodiazepine synthesis mentioned above, as a starting compound. We prepared this key compound by the reaction of 1 with o-phenylenediamine in boiling ethanol. The use of two equivalents of 1 afforded N,N'-disubstituted derivative 2b, obtained also by the reaction between compound 2a and the ethoxymethylene derivative 1. (Scheme 1).

Two conventional methods were chosen for the cyclization of compound 2a. Treatment with triethyl orthoformate, which had been used extensively to prepare benz-



Scheme 1

imidazole nucleosides,⁶ gave 1-substituted benzimidazole 3a. On the other hand, reaction with nitrous acid, which is a classical method for the preparation of the benzotriazole system,⁷ afforded 3b. Both of these bicyclic derivatives underwent oxazolone ring opening in hot methanolic triethylamine solution to yield α,β -didehydroamino acid derivatives 5a and 5b.

As it turned out, 5a and 5b could be also prepared via acrylate 4a, obtained by treatment of oxazolone 2a with hot methanolic triethylamine solution. Attempted cyclization of the compound 4a in boiling triethyl orthoformate yielded instead the ethoxymethyleneamino derivative 4b, which was transformed into benzimidazole 5a by heating in diphenyl ether at 200°C. On the other hand, no difficulties were encountered in the preparation of benzotriazole 5b from 4a and nitrous acid.

The configuration of the double bond in these unsaturated oxazolones and didehydroamino acids was determined on the basis of ¹³C nmr spectroscopy. The magnitude of the vicinal coupling constants between the carbonyl carbon of an oxazolone and β -olefinic proton is in the range below 4 Hz,⁸ which is characteristic for the more stable (Z)-isomers.⁹ Since the configurational integrity is maintained during the solvolysis of oxazolones,⁹ we can conclude that the didehydroamino acids also have the (Z)-configuration of the double bond.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. Infrared spectra were taken on a Perkin-Elmer 727 B spectrometer. ¹H and ¹³C nmr spectra were recorded on a JEOL JNM FX-90 Q spectrometer with TMS as internal standard. Mass spectra were obtained on a CEC 21-110 B spectrometer. Elemental analyses were performed on a Perkin-Elmer CHN Analyser 240 C.

4-(2-Aminophenylamino)methylene-2-phenyl-5(4H)-oxazolone (2a).

A mixture of 1⁴ (2.172 g, 10 mmol), o-phenylenediamine (1.081 g, 10 mmol) and ethanol (60 ml) was heated under reflux for 30 min. Upon cooling the separated product was filtered (2.53 g, 91 %) and crystallized from methanol, mp 179-181°C. Anal.

Calcd for C₁₆H₁₃N₃O₂: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.63; H, 4.78; N, 14.87. ¹H Nmr (DMSO-d₆) δ : 5.30 (broad s, NH₂), 6.52-7.35 (m, 3'-H, 4'-H, 5'-H,

6'-H), 7.59 (m, three H of Ph, NHCH), 7.99 (m, two H of Ph), 9.87 (broad, NH).

N,N'-Bis[(2-phenyl-5-oxo-4,5-dihydro-1,3-oxazol-4-ylidene)methyl]-o-phenylenediamine (2b).

A) A mixture of 2a (279 mg, 1 mmol) and 1 (217 mg, 1 mmol) in ethanol (4 ml) was heated under reflux for 2 h. Upon cooling the separated product was filtered (350 mg, 78 %) and crystallized from ethanol, mp 226-229°C. Anal. Calcd for C₂₆H₁₈N₄O₄: C, 69.32; H, 4.03; N, 12.44. Found: C, 69.37; H, 4.04; N, 12.46. ¹H Nmr (DMSO-d₆) δ: 7.16-8.11 (m, two Ph, two CHNH, 3'-H, 4'-H, 5'-H, 6'-H), 10.20 (broad, two NH).

B) A mixture of 1 (217 mg, 1 mmol) and o-phenylenediamine (54 mg, 0.5 mmol) in ethanol (3 ml) was heated under reflux for 3 h. Upon cooling the separated product was filtered (184 mg, 82 %). The obtained product was found to be identical in all respects with the compound obtained as described under A.

(Z)-4-(1-Benzimidazolyl)methylene-2-phenyl-5(4H)-oxazolone (3a).

A mixture of 2a (250 mg, 0.9 mmol) and triethyl orthoformate (4 ml) was heated under reflux for 2 h. Upon cooling the separated product was filtered (230 mg, 80 %) and crystallized from ethanol, mp 227-240°C. Anal. Calcd for C₁₇H₁₁N₃O₂: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.80; H, 3.92; N, 14.27. ¹H Nmr (DMSO-d₆) δ: 7.32-7.86 (m, three H of Ph, 4'-H, 5'-H, 6'-H), 8.13 (m, two H of Ph, CH, 7'-H), 9.36 (s, 2'-H).

(Z)-4-(1-Benzotriazolyl)methylene-2-phenyl-5(4H)-oxazolone (3b).

To a suspension of 2a (279 mg, 1 mmol) in aqueous hydrochloric acid (18 %, 3 ml), a solution of sodium nitrite (100 mg, 1.4 mmol) in H₂O (2 ml) was added dropwise under stirring at 0°C. The reaction mixture was stirred for an additional 2 h at room temperature. The separated product was filtered (172 mg, 59 %) and crystallized from ethanol, mp 178-179°C. Anal. Calcd for C₁₆H₁₀N₄O₂: C, 66.20; H, 3.47; N, 19.30. Found: C, 66.44; H, 3.59; N, 19.33. ¹H Nmr (DMSO-d₆) δ: 7.48-7.89 (m, three H of Ph, 5'-H, 6'-H), 8.02-8.24 (m, two H of Ph, 4'-H), 8.41 (s, CH), 8.80 (m, 7'-H).

Methyl (Z)-3-(2-Aminophenyl)amino-2-benzoylaminopropenoate (4a).

A mixture of 2a (170 mg, 0.61 mmol), triethylamine (0.2 ml, 1.4 mmol) and ethanol

(5 ml) was heated under reflux for 8 h. Upon cooling the separated product was filtered (66 mg, 35 %) and crystallized from ethanol, mp 210-211°C. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.63; H, 5.64; N, 13.48. 1H Nmr (DMSO- d_6) δ : 3.61 (s, OMe), 5.01 (broad s, NH_2), 6.46-7.00 (m, 3'-H, 4'-H, 5'-H, 6'-H), 7.35-8.14 (m, Ph, NHCH), 9.13 (s, NH).

Methyl (Z)-2-Benzoylamino-3[(2-ethoxymethyleneamino)phenyl]aminopropenoate (4b).

A mixture of 4a (200 mg, 0.64 mmol) and triethyl orthoformate (5 ml) was heated under reflux for 0.5 h. Upon cooling the separated product was filtered (218 mg, 92 %) and crystallized from ethanol, mp 179-181°C. Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.52; H, 5.84; N, 11.48. 1H Nmr (DMSO- d_6) δ : 0.88 (t, CH_2CH_3), 3.69 (s, OMe), 3.88 (q, $J=7.1$ Hz, CH_2CH_3), 6.78-8.21 (m, Ph, NHCH, CH, 3'-H, 4'-H, 5'-H, 6'-H), 9.94 (s, NH).

Methyl (Z)-3-(1-Benzimidazolyl)-2-benzoylamino propenoate (5a).

A) A mixture of 3a (340 mg, 1.2 mmol), triethylamine (0.6 ml, 4.3 mmol) and methanol (4 ml) was heated under reflux for 2.5 h. The reaction mixture was then concentrated to 1.5 ml. Upon cooling the separated product was filtered (166 mg, 44 %) and crystallized from ethanol-diethyl ether (1:1), mp 196-197°C. Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.49; H, 4.73; N, 13.28. 1H Nmr (DMSO- d_6) δ : 3.81 (s, OMe), 7.22-8.00 (m, Ph, 4'-H, 5'-H, 6'-H, 7'-H), 8.15 (s) and 8.54 (s) (CH, 2'-H), 10.14 (broad s, NH), ms m/z : 321 (M^+).

B) A mixture of 4b (100 mg, 0.27 mmol) and diphenyl ether (3 ml) was heated at 200°C for 2 h. Upon cooling the separated product was filtered (45 mg, 51 %) and crystallized from ethanol. The obtained product was found to be identical in all respects with the compound obtained as described under A.

Methyl (Z)-3-(1-Benzotriazolyl)-2-benzoylamino propenoate (5b).

A) A mixture of 3b (300 mg, 1.03 mmol), triethylamine (0.8 ml, 5.7 mmol) and methanol (4 ml) was heated under reflux for 2.5 h. The reaction mixture was then concentrated to 2 ml and cooled. The separated product was filtered (125 mg, 37 %). The filtrate was then evaporated to dryness and the residue was suspended in diethyl ether (5 ml). Upon filtration some more of the product was obtained (20 mg, 6 %). The combined product was then crystallized from ethanol, mp 176-177°C. Anal.

Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.40; H, 4.42; N, 17.12. 1H Nmr (DMSO- d_6) δ : 3.86 (s, OMe), 7.38-7.77 (m, three H of Ph, 5'-H, 6'-H), 7.84-8.22 (m, two H of Ph, 4'-H, 7'-H), 8.35 (s, CH), 10.25 (s, NH).
ms m/z : 322 (M^+).

B) To a suspension of 4a (120 mg, 0.4 mmol) in aqueous hydrochloric acid (18 %, 2 ml), a solution of sodium nitrite (100 mg, 1.4 mmol) in water (2 ml) was added dropwise under stirring at 0°C. The reaction mixture was stirred for an additional 45 min at room temperature. The separated product was filtered (115 mg, 93 %) and crystallized from ethanol. The obtained product was found to be identical in all respects with the compound obtained as described under A.

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REFERENCES AND NOTES

1. E.Klinsberg, "Pyridine and Its Derivatives", Pt 1, Interscience, New York, 1962, p. 111, and references cited therein.
2. D.J.Brown, "The Pyrimidines", Suppl. I, Wiley-Interscience, New York, 1970, p. 198, and references cited therein.
3. I.G.Wagner and J.Musso, Angew.Chem., 1983, 95, 822.
4. J.W.Cornforth, "The Chemistry of Penicillin", H.T.Clarke, J.R.Johnson, and R.Robinson, Eds., Princeton University Press, 1949, p. 743.
5. H.Kristen, K.Peseke, C.Vogel, and H.Braueniger, Ger.(East) 116.827, Chem.Abstr., 1976, 85, P 5704x.
6. L.B.Townsend and G.R.Revankar, Chem.Rev., 1970, 70, 389.
7. F.R.Benson and W.L.Savell, Chem.Rev., 1950, 46, 1.
8. The signals of the carbonyl carbon in the coupled nuclear Overhauser enhanced ^{13}C nmr spectra are doublets or degenerated doublets at 167.5 ppm (1, DMSO- d_6 , $J < 4$ Hz), 167.0 ppm (2a, DMSO- d_6 , $J = 2.6$ Hz), and 167.1 ppm (3b, $CDCl_3$, $J = 3.7$ Hz).
9. E.P.Prokof'ev and E.I.Karpeiskaya, Tetrahedron Lett., 1979, 737, and references cited therein.

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