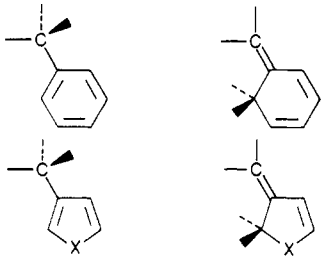


Destabilization due to the destruction of the aromatic rings during the course of cyclization increases the ground-state energy of the ring-closed form. The aromaticity explains well the trend of the relative stability.

We can conclude that the thermal stability of both isomers of the diarylethene-type photochromic compounds can be improved by introducing aryl groups that have low aromatic stabilization energy.

Registry No. **1a**, 108028-41-7; **1b**, 108028-40-6; **1c**, 117439-52-8; **1d**, 117439-53-9; **3a**, 108028-39-3; **3b**, 588-59-0; 1,2-di(3-pyrrolyl)ethene, 117439-51-7; 2,3-bis(2-cyano-5-methyl-3-pyrrolyl)-2-butene, 117439-54-0.

Facile Synthesis of L-Kynurenine

Francesco G. Salituro* and Ian A. McDonald

Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, Ohio 45215

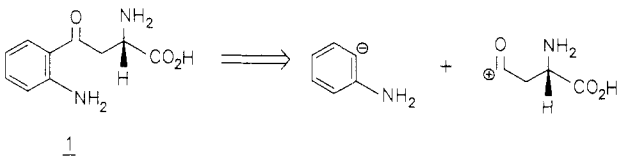
Received June 15, 1988

The aromatic amino acid L-kynurenine (**1**) is a key intermediate in the metabolism of L-tryptophan to nicotinic acid ribonucleotide via the commonly referred to kynurenine pathway. Quinolinic acid, a potent neurotoxic amino acid, is a late-stage intermediate in this pathway and has been implicated in brain diseases such as epilepsy and Huntington's chorea.[1] Lowering levels of quinolinic acid, therefore, may be an attractive means of treatment for these central nervous system disorders.

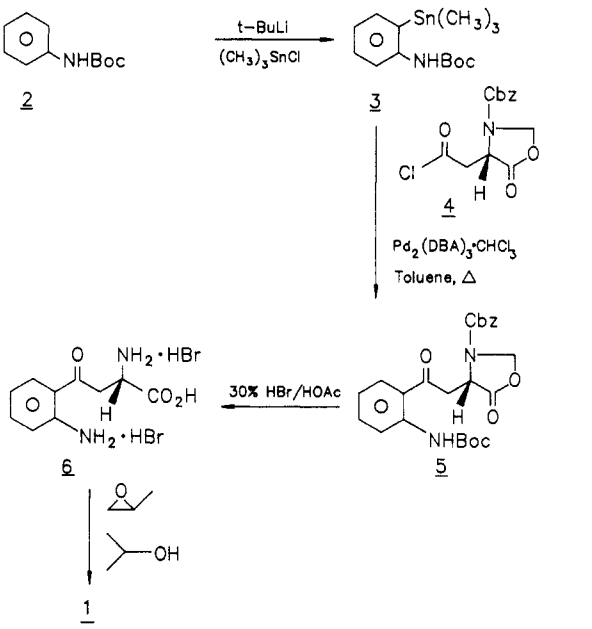
During the course of a research program directed toward the inhibition of various enzymes in this pathway, it became necessary to develop a general synthesis of L-kynurenine which would also allow for the facile preparation of various analogues. While several syntheses of L- and DL-kynurenine have been reported,[2] none were sufficiently versatile to accommodate the preparation of a variety of analogues. For example, tryptophan oxidation or acetamidomalonate addition to phenacyl bromides is impractical due to the difficulties encountered in the preparations of highly functionalized tryptophans and acetophenones, respectively, needed as starting materials.

An attractive route to L-kynurenine would be a convergent synthesis based on the reaction of a suitably protected aniline analogue and an L-aspartic acid synthon (Scheme I). A procedure we felt would be the most synthetically versatile involves a Pd^0-catalyzed cross-coupling[3]

Scheme I



Scheme II



of *N*-(*tert*-butoxycarbonyl)-2-(trimethylstannyl)aniline (**3**) with (*S*)-3-(benzyloxycarbonyl)-5-oxo-4-oxazolidineacetyl chloride (**4**) leading to the desired, fully protected amino acid **5** in one step (Scheme II). Such a procedure should be general, allowing for the utilization of various aniline and aspartic acid analogues, and should proceed with full chiral retention.

Ortho metalation of *N*-(*tert*-butoxycarbonyl)aniline (**2**)[4] followed by quenching with trimethylstannyl chloride afforded **3** in 54% yield after flash chromatography (10% diethyl ether/hexane) as a colorless solid. The protected L-aspartic acid chloride derivative **4** was prepared from the corresponding acid[5] by using an excess of thionyl chloride in toluene. Coupling of **3** and **4** was carried out in the presence of 0.5 mol % of $Pd_2(DBA)_3{\cdot}CHCl_3$[6] in toluene at 70 °C for 3–4 h. Filtration over Celite and concentration in vacuo, followed by flash chromatography (25% EtOAc/hexane), gave **5** as a stiff foam in 79% yield. Complete deprotection of **5** was carried out in one step with 30% HBr/HOAc at room temperature for 15–20 min; addition of diethyl ether then precipitated the bis(hydrobromide salt) as a colorless solid. The supernatant was removed, and the residue was treated several times with more ether and then dried under vacuum to give **6** as a colorless powder in 83% yield.[7] The free amino acid could be prepared by treating **6** with a 6-fold excess of propylene oxide in 2-propanol whereupon L-kynurenine (**1**) was isolated as a light yellow powder in 90% yield. Spectral properties (IR, MS, ^1H NMR) were identical with those of an authentic sample.[8] The high-resolution mass

(1) (a) Mazzari, S.; Aldinio, C.; Beccaro, M.; Toffano, G.; Schwarcz, R. *Brain Res.* **1986**, *380*, 309–316. (b) Ben-Ari, Y.; Schwarcz, R. *Adv. Exp. Med. Biol.* **1986**, *203*, 709–711. (c) Schwarcz, R.; Speciale, C.; Okuno, E.; French, E. D.; Kohler, C. *Adv. Exp. Med. Biol.* **1986**, *203*, 697–707.

(2) (a) Warnell, J. L.; Berg, C. P. *J. Am. Chem. Soc.* **1954**, *76*, 1708. (b) Dalgliesh, C. E. *J. Chem. Soc.* **1952**, 137. (c) Nagasaka, T.; Ohki, S. *Chem. Pharm. Bull.* **1971**, *19*, 603–611. (d) Sakiyama, F.; Masuda, N.; Nakazawa, T.; Katsuragi, Y. *Chem. Lett.* **1978**, 893. (e) Ranganathan, S.; Ranganathan, D.; Singh, S.; Bhattacharyya, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1887.

(3) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524 and references therein.

(4) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.

(5) Itoh, M. *Chem. Pharm. Bull.* **1969**, *17*, 1679–1686.

(6) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253–266.

(7) Chars at 205–210 °C.

0022-3263/88/1953-6138$01.50/0

spectrum was also consistent with the assigned structure. HPLC analysis of either 1 or 6 showed a single symmetrical peak, coeluting with authentic L-kynurenine. Furthermore, HPLC analysis of synthetic 1 indicated an isomeric purity of 99%.[9]

In summary, this paper describes a straightforward synthesis of L-kynurenine from readily obtainable starting materials. More recently we have used this methodology to prepare a variety of kynurenine analogues, the synthesis and biological activity of which will be reported in a full paper.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian VXR-300 spectrometer; chemical shifts are reported in parts per million relative to a tetramethylsilane internal standard. IR spectra were recorded on a Perkin-Elmer 1800 spectrometer. High-resolution mass spectra were obtained on a VG ZAB2-SE mass spectrometer system.

Analytical thin-layer chromatography was performed by using 0.25-mm silica gel glass-backed plates. All flash chromatography was performed on 230–400-mesh silica gel from E. Merck.

***N*-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)aniline (3).** *N*-(*tert*-Butoxycarbonyl)aniline[4] (3 g, 15.54 mmol) was dissolved in dry THF (30 mL) at −78 °C under an atmosphere of nitrogen. To this solution was added *tert*-butyllithium (1.7 M in pentane, 32.6 mmol) via an addition funnel. The yellow solution was stirred at −78 °C for 15 min and then for 2 h at −20 °C. Trimethyltin chloride (3.1 g, 15.54 mmol) in THF (20 mL) was then added, and the solution was stirred for 1–2 h. The reaction mixture was then quenched with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (10% diethyl ether/hexane) to yield a clear oil, which solidified upon standing, affording 3 as a colorless solid (3 g, 8.4 mmol, 54%): mp 64–65 °C; NMR ($CDCl_3$) δ 0.32 (s, 6 H), 1.5 (s, 9 H), 6.28 (br m, 1 H), 7.08–7.18 (m, 1 H), 7.28–7.36 (m, 1 H), 7.36–7.42 (m, 1 H), 7.46–7.56 (m, 1 H). Anal. Calcd for $C_{14}H_{23}NO_2Sn$: C, 47.23; H, 6.51; N, 3.93. Found: C, 47.35; H, 6.66; N, 3.89.

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidineacetyl Chloride (4). (*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidineacetic acid[5] (1.18 g, 4.2 mmol) in a 1:1 mixture of thionyl chloride and toluene (10 mL) was stirred at room temperature for 4 h. The solvents were evaporated, and the resulting oil was dried under vacuum. The crude material was used without further purification: NMR ($CDCl_3$) δ 3.40–3.75 (m, 2 H), 4.30 (m, 1 H), 5.00–5.45 (m, 4 H), 7.30 (m, 5 H).

Synthesis of Protected L-Kynurenine (5). Stannane 3 (1.5 g, 4.2 mmol) and acid chloride 4 (4.2 mmol) were dissolved in toluene (50 mL). To this solution was added $Pd_2(DBA)_3{\cdot}CHCl_3$[6] (40.5 mg, 0.1 mmol), and the mixture was heated to 70 °C for 3–4 h; the reaction mixture turned black within about 20 min. The mixture was cooled, and the catalyst was removed by filtration over Celite. The filtrate was concentrated in vacuo and then diluted with ethyl acetate (50 mL). The resulting solution was washed consecutively with saturated bicarbonate, water, and saturated NaCl, then dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate/hexane). Pure product was obtained as a stiff colorless foam (1.5 g, 3.3 mmol, 79%): mp 58–60 °C; $[\alpha]^{20}_D$ = +153° (*c* = 1.0, CH_3OH); NMR ($CDCl_3$) δ 1.52 (s, 9 H), 3.50–4.35 (m, 2 H), 4.45 (m, 1 H), 5.10–5.25 (m, 2 H), 5.50–5.65 (m, 2 H), 7.12 (m, 1 H), 7.25–7.40 (m, 5 H), 7.55–7.60 (m, 1 H), 7.60–7.90 (m, 1 H), 8.61 (m, 1 H), 10.61 (br m, 1 H, exchangeable). Anal. Calcd for $C_{24}H_{26}N_2O_7$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.13; H, 5.89; N, 5.91.

L-Kynurenine (1). Compound 5 (100 mg, 0.22 mmol) was stirred in 30% HBr in acetic acid (2 mL) for 20 min at ambient temperature. Diethyl ether (25 mL) was then added to precipitate the bis(hydrobromide salt) as a colorless solid. The ether layer was decanted, and the procedure was repeated several times to remove as much HBr as possible. The last traces of ether were removed in vacuo, and the colorless solid was thoroughly dried. This material was dissolved in 2-propanol (10 mL) and treated with propylene oxide (1.32 mmol). L-Kynurenine precipitated as a light yellow powder (41 mg, 0.2 mmol, 90%): mp 155–160 °C dec (lit.[2a] mp 191 °C dec), recrystallized from aqueous ethanol). The ^{1}H NMR and IR spectra were identical with those of an authentic sample except for the presence of trace amounts of 2-propanol. HRMS calcd for $C_{10}H_{12}N_2O_3$: M + H 209.0926. Found: M + H 209.0915.

HPLC analysis was performed on a VYDAC C-18 300-Å reverse-phase column eluting with a gradient of acetonitrile containing 0.1% trifluoroacetic acid (A) and water containing 0.1% trifluoroacetic acid (B). A gradient of 0–20% A in B over a 30-min period elutes L-kynurenine in 15.2 min.

Registry No. 1, 2922-83-0; 2, 3422-01-3; 3, 114552-32-8; 4, 111197-44-5; 5, 117269-80-4; 6, 117269-81-5; (*S*)-3-(benzyloxycarbonyl)-5-oxo-4-oxazolidineacetic acid, 23632-66-8.

(8) Sigma Chemical Co.
(9) Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591–596.

Peptide Coupling in the Presence of So-Called Liquid Crystal Formers

Louis A. Carpino,* Hann Guang Chao, Fatemeh Nowshad, and Hitesh Shroff

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

Received December 30, 1987

No completely general solution to the problem of racemization during peptide segment coupling has yet been devised.[1] In cases where segment condensations are initiated by a coupling agent, e.g. dicyclohexylcarbodiimide, various additives, most often derivatives of hydroxylamine, have routinely been used to eliminate or reduce loss of chirality at the activated carboxylic acid site. Recently a report appeared announcing a new family of additives to suppress racemization, namely "compounds belonging to prototypes of thermotropic liquid crystal structures, i.e., azoxybenzene, azobenzene, and 4,4′-dimethoxyazoxybenzene..."[2] A varied group of such compounds was said to protect strongly against racemization in three model systems: the couplings represented by the Anderson[3] and Young[4] tests and an NMR-visualized[5] coupling of *N*-(benzyloxycarbonyl)glycylphenylalanine with alanine methyl ester.

We were attracted to this report for several reasons, not the least being the fact that there appeared to be no obvious rationale for the protective effects observed. The conditions chosen for the coupling reactions (dilute solutions with 10 mol% of additive present) preclude the operation of true liquid crystal effects. Nevertheless, if the

(1) Reviews: (a) Kemp, D. S. In *The Peptides*; Gross, E., Meienhofer, J., Eds.; Academic: New York, 1979, Vol. 1, p 315. (b) Kovacs, J. *Ibid.* 1980, Vol. 2, Part A, p 485; (c) Benoiton, N. L. *Ibid.* 1983, Vol. 5, Part B, p 217.
(2) Jeschkeit, H.; Strube, M.; Przybylski, J.; Miecznickowska, H.; Kupryszewski, G., *J. Prakt. Chem.* **1984**, *326*, 638.
(3) (a) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 1338. (b) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1958**, *80*, 2902. (c) Anderson, G. W.; Young, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 5307.
(4) Williams, M. W.; Young, G. T. *J. Chem. Soc.* **1963**, 881.
(5) Compare (a) Halpern, B.; Chew, L. F.; Weinstein, B. *J. Am. Chem. Soc.* **1967**, *89*, 501. (b) Halpern, B.; Nitecki, D. E.; Weinstein, B. *Tetrahedron Lett.* **1967**, 3075. (c) Weinstein, B.; Pritchard, A. E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1015.

0022-3263/88/1953-6139$01.50/0