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.
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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

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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

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(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

Table I. Characterization of Di- and Tripeptides

compound[a,b]	yield, %	mp, °C	α_D, deg (T, °C)	^{1}H NMR, δ[c]	mol formula	analytical data calcd/found C	H	N
PABz-Val-Val-OMe	71.7	186–7	+48 (24) (*c* 0.2, EtOAc)	1.0 (dd, 6, CH_3CH), 1.05 (d, 6, CH_3CH), 2.2 (octet, 2, CH_3CHCH), 3.76 (s, 3, CH_3O), 4.6 (dt, 2, $NHCHCH$), 6.6 (d, 1, *NH*CH), 7.0 (d, 1, N*H*CH), 7.5–8 (m, 9, aryl)	$C_{24}H_{30}N_4O_4$	65.73 65.62	6.90 6.88	12.78 12.82
PABz-D-Val-Val-OMe	70.6	175–7	−68 (24) (*c* 0.2, EtOAc)	1.0 (t, 6, CH_3CH), 1.15 (d, 6, CH_3CH), 2.3 (d quintet, 2, CH_3CHCH), 3.70 (s, 3, CH_3O), 4.65 (t, 1, $NHCHCH$), 4.75 (t, 1, $NHCHCH$)8 6.9 (d, 1, N*H*CH), 7.15 (d, 1, N*H*CH), 7.5–7.95 (m, 9, aryl)	$C_{24}H_{30}N_4O_4$	65.73 65.61	6.90 6.75	12.78 12.85
PABz-Phe-Phe-OMe	77.7	215–6	−47 (24) (*c* 0.2, EtOAc)	3.1 (m, 4, $CHCH_2$), 3.72 (s, 3, CH_3O), 4.85 (m, 2, $NHCHCH_2$), 6.25 (d, 1, N*H*CH), 6.8 (d, 1, N*H*CH), 7–8 (m, 19, aryl)	$C_{32}H_{30}N_4O_4$	71.88 71.70	5.67 5.66	10.48 10.48
PABz-D-Phe-Phe-OMe	77.9	172–4	+57.5 (24) (*c* 0.2, EtOAc)	3.1 (m, 4, $CHCH_2$), 3.66 (s, 3, CH_3O), 4.9 (m, 2, $NHCHCH_2$), 6.35 (d, 1, N*H*CH), 6.8 (d, 1, N*H*CH), 7–8 (m, 19, aryl)	$C_{32}H_{30}N_4O_4$	71.88 71.79	5.67 5.77	10.48 10.46
PABz-Ala-Ala-OMe	67.9	215–6.5	+77.0 (24) (*c* 0.2, DMF)	1.45 (d, 3, CH_3CH), 1.55 (d, 3, CH_3CH), 3.78 (s, 3, CH_3O), 4.6 (quintet, 1, $NHCHCH_3$), 4.75 (quintet, 1, $NHCHCH_3$), 6.6 (d, 1, N*H*CH), 6.95 (d, 1, N*H*CH), 7.2–8 (m, 9, aryl)	$C_{20}H_{22}N_4O_4$	62.80 62.51	5.81 5.77	14.65 14.59
PABz-D-Ala-Ala-OMe	54.4	155–6	−60.5 (24) (*c*, 0.2, EtOAc)	1.45 (d, 3, $CHCH_3$), 1.55 (d, 3,$CHCH_3$), 3.72 (s, 3, CH_3O), 4.6 (quintet, 1, $NHCHCH_3$), 4.75 (quintet, 1, $NHCHCH$), 7.2–8 (m, 9, aryl)	$C_{20}H_{22}N_4O_4$	62.80 62.80	5.81 5.81	14.65 14.65
Bz-Phg-Val-OMe	79.0	202–2.5	+36.5 (23) (*c* 0.2, EtOH)	0.9 (dd, 6, $CHCH_3$), 2.2 (heptet, 1, $CHCH_3$), 3.63 (s, 3, OCH_3), 4.5 (dd, 1, $CHCHMe_2$), 5.9 (d, 1, CHC_6H_5), 6.8 (d, 1, $NHCHMe_2$), 7.2–8.0 (m, 11, aryl, NH)	$C_{21}H_{24}N_2O_4$	68.46 68.65	6.56 6.52	7.60 7.68
Bz-D-Phg-Val-OMe	73.3	230–30.5	−73.5 (23) (*c* 0.2, EtOH)	0.7 (dd, 6, $CHCH_3$), 2.1 (heptet, 1, $CHCH_3$), 3.68 (s, 3, OCH_3), 4.6 (dd, 1, $CHCHMe_2$), 5.8 (d, 1, CHC_6H_5), a6.7 (d, 1, $NHCHMe_2$), 7.2–8 (m, 11, aryl, NH)	$C_{21}H_{24}N_2O_4$	68.46 68.36	6.56 6.59	7.60 7.52
PABz-Phg-Val-OMe	83.4	142–3	+6.35 (23) (*c*, 0.2, EtOAc)	0.90 (dd, 6, $CHCH_3$), 2.2 (heptet, 1, $CHCH_3$), 3.66 (s, 3, OCH_3), 4.45 (dd, 1, $CHCHMe_2$), 5.8 (d, 1, $NHCHC_6H_5$), 6.3 (d, 1, $NHCHMe_2$), 7–8 (m, 15, aryl, NH)	$C_{27}H_{28}N_4O_4$	68.62 68.77	5.97 6.05	11.85 11.61
PABz-D-Phg-Val-OMe	80.7	168–9	−14.5 (23) (*c* 0.2, EtOAc)	0.7 (dd, 6, $CHCH_3$), 2.1 (heptet, 1, $CHCH_3$), 3.72 (s, 3, CH_3O), 4.6 (dd, 1, $CHCHMe_2$), 5.8 (d, 1, CHC_6H_5), 6.5 (d, 1, $NHCHMe_2$), 7.2–8.1 (m, 15, aryl, NH)	$C_{27}H_{28}N_4O_4$	68.62 68.60	5.97 5.91	11.85 11.74
PABz-Val-Phe-OMe	77.0	179–9.5	+24.5 (23) (*c* 0.2, EtOAc)	1.0 (dd, 6, $CHCH_3$), 2.2 (heptet, 1, $CHCH_3$), 3.1 (t, 2, $CH_2C_6H_5$), 3.75 (s, 3, CH_3O), 4.5 (t, 1, $NHCHCH_2C_6H_5$), 4.9 (q, 1, $CHCHMe_2$), 6.4 (d, 1, $NHCHCH_2C_6H_5$); 6.85 (d, 1, $NHCHMe_2$); 7–8 (m, 14, aryl)	$C_{28}H_{30}N_4O_4$	69.11 68.72	6.21 6.12	11.51 11.78
PABz-D-Val-Phe-OMe	80.4	215–5.2	−50 (23) (*c* 0.2, EtOAc)	0.9 (t, 6, $CHCH_3$), 2.2 (heptet, 1, $CHCH_3$), 3.2 (m, 2, $CH_2C_6H_5$), 3.71 (s, 3, CH_3O), 4.55 (t, 1, $CHCH_2C_6H_5$), 5.0 (q, 1, $CHCH_2C_6H_5$), 5.0 (q, 1, $CHCHMe_2$), 6.55 (d, 1, $NHCHCH_2C_6H_5$), 6.9 (d, 1, $NHCHMe_2$), 7–8.0 (m, 14, aryl)	$C_{28}H_{30}N_4O_4$	69.11 69.00	6.21 6.17	11.51 11.50
PAZ-Gly-Phe-$OCMe_3$	73.0	92 dec	+30.4 (22) (*c* 0.5, DMF)	1.45 (s, 9, CMe_3), 3.1 (d, 2, $C_6H_5CH_2$), 3.9 (m, 2, $NHCH_2$), 4.8 (q, 1, $CHCH_2$), 5.2 (s, 2, CH_2O), 5.4 (br s, 1, NH), 6.4 (d, 1, NH), 7.8–8.0 (m, 14, aryl)	$C_{29}H_{32}N_4O_5$	67.42 67.32	6.25 6.11	10.85 10.73
PAZ-Gly-Phe-OH[d]	80.0	182–4	+14.2 (22) (*c* 0.5, DMF)	3.1 (m, 3, $C_6H_5CH_2$), 3.9 (m, 2, $NHCH_2$), 4.9 (q, 1, $CHCH_2$), 5.5 (s, 2, CH_2O), 7.–8.0 (m, 16, aryl + NH)[e]	$C_{25}H_{24}N_4O_5$	65.21 64.95	5.25 5.29	12.17 12.01
PAZ-Gly-Phe-Ala-OMe	79.0	161–2	−8.0 (21) (*c* 0.5, EtOAc)	1.32 (d, 3, $CHCH_3$), 3.05 (d, 2, $CH_2C_6H_5$), 3.68 (s, 3, CH_3O), 3.91 (d, 2, $NHCH_2$), 4.5 (quintet, 1, $CHCH_2$), 4.8 (q, 1, $CHCH_3$); 5.16 (s, 2, CH_2O), 5.75 (m, 1, NH), 6.9 (d, 2, NH), 7.2–8.0 (m, 14, aryl)	$C_{29}H_{31}N_5O_6$	63.84 63.52	5.37 5.53	12.84 12.71

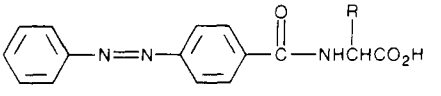
Table I (Continued)

compound[a,b]	yield, %	mp, °C	α_D, deg (T, °C)	^{1}H NMR, δ[c]	mol formula	analytical data calcd/found C	H	N
PAZ-Gly-D-Phe-Ala-OMe	87.0	129–30	+96 (21) (c 0.5, $CHCl_3$)	1.19 (d, 3, $CHCH_3$), 3.05 (d, 2, $CH_2C_6H_5$), 3.65 (s, 3, CH_3O), 3.90 (d, 2, $NHCH_2$), 4.5 (quintet, 1, $CHCH_2$), 4.8 (q, 1, $CHCH_3$), 5.16 (s, 2, CH_2O), 5.85 (br, 1, NH), 6.9 (d, 2 NH), 7.2–8.0 (m, 14, aryl)	$C_{29}H_{31}N_5O_6$	63.84 63.67	5.37 5.46	12.84 12.69
BOC-Gly-Phe-Ala-OMe[f]	65.1	119–20	−19.6 (21) (c 0.5, EtOAc)	1.35 (d, 3, $CHCH_3$), 1.45 (s, 9, CMe_3), 3.05 (m, 2, $CH_2C_6H_5$), 3.71 (s, 3, CH_3O), 3.79 (d, 2, $NHCH_2$), 4.50 (m, 1, $CHCH_2$), 4.83 (q, 1, $CHCH_3$), 5.3 (br 1, NH), 6.7–8.0 (br 2, NH), 7.2–7.4 (m, 5, aryl)	$C_{20}H_{29}N_3O_6$	58.95 58.72	7.17 7.11	10.31 10.24
BOC-Gly-D-Phe-Ala-OMe[g]	62.3	130–32	+9.45 (23) (c 2, CH_2Cl_2)	1.24 (d, 3, $CHCH_3$),1.45 (s, 9, CMe_3), 3.05 (m, 2, $CH_2C_6H_5$), 3.70 (s, 3, OCH_3), 3.79 (d, 2, $NHCH_2$), 4.5 (m, 1, $CHCH_2$), 4.85 (q, 1, $CHCH_3$), 5.1–6.8 (br, 1, NH), 7.2–7.4 (m, 5, aryl)	$C_{20}H_{29}N_3O_6$	58.95 58.79	7.17 7.09	10.31 10.24
Z-Gly-D-Phe-Ala-OMe[h]	83.0	133–34	+7.0 (21) (c 0.5, EtOAc)	1.21 (d, 3, $CHCH_3$), 3.05 (m, 2, $CH_2C_6H_5$), 3.67 (s, 3, CH_3O), 3.84 (d, 2, $NHCH_2$), 4.5 (quintet, 1, $CHCH_2$), 4.8 (q, 1, $CHCH_3$), 5.10 (s, 2, CH_2O), 5.6 (br, 1, NH), 6.6 (d, 1, NH), 7.2–7.35 (m, 10, aryl)	$C_{23}H_{27}N_3O_6$	62.57 62.64	6.17 6.08	9.52 9.36
FMOC-Gly-D-Phe-Ala-OMe[i]	81.0	183 dec	+7.0 (21) (c 0.5, EtOAc)	1.22 (d, 3, $CHCH_3$), 3.1 (m, 2, $CH_2C_6H_5$), 3.67 (s, 3, CH_3O), 3.85 (m, 2, $NHCH_2$), 4.15–4.6 (m, 4, $CHCH_2O$, $CHCH_2C_6H_5$), 4.75 (q, 1, $CHCH_3$), 6.65 (br, 1, NH), 7.1–7.85 (m, 15, aryl, 2 NH)	$C_{30}H_{31}N_3O_6$	68.03 67.84	5.91 5.97	7.93 8.05

[a] Protected dipeptide esters were synthesized by reaction of 1 mmol of the protected acid derivative and 1 mmol of amino acid ester hydrochloride in 10 mL of THF with 0.9 mmol of NEt_3 in the presence of 1 equiv each of either 1 mol of EEDQ or 1.1 mmol of DCC plus 1 mmol of *N*-hydroxybenzotriazole and allowing the reaction to proceed at room temperature for 21 h. Dilution with water and washing with 5% HCl and 0.5 M $NaHCO_3$ gave the peptide esters in the yields indicated. [b] Protected L,L tripeptide esters were synthesized by reaction of 1 mmol each of protected glycyl amino acid, alanine methyl ester hydrochloride, *N*-hydroxybenzotriazole, DCC, and NEt_3 in 10 mL of THF. After the mixture was allowed to stand overnight at 0 °C and at room temperature for 3 h, workup as in *a* gave the tripeptide esters. The BOC-DL-tripeptide diastereomer was made similarly. The remaining DL tripeptides (Z, FMOC, PAZ) were synthesized from the BOC derivative by TFA cleavage (50% in CH_2Cl_2) followed by acylation with the appropriate chloroformate. [c] In $CDCl_3$ unless otherwise indicated. [d] Obtained by cleavage of the corresponding *tert*-butyl ester in TFA–CH_2Cl_2 (1:1). [e] Spectrum taken in DMSO-d_6. [f] For preparation of BOC-Gly-Phe-OH, see: Ragnarsson, U.; Karlsson, S. M.; Hamberg, U. *Int. J. Pept. Protein Res.* **1975**, *7*, 307. [g] The intermediate, BOC-Gly-D-Phe-OH, obtained by catalytic hydrogenolysis of the corresponding benzyl ester (65.0%) had mp 142–143 °C: $[\alpha]^{20}_D$ −73.9° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9, CMe_3), 3.16 (d q, 2, $CHCH_2$), 3.75 (m, 2, $NHCH_2$), 4.8 (q, 1, NHC*H*), 6.05 (br s, 1, NH), 7.2–7.3 (m, 5, aryl). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.47; H, 6.85; N, 8.63. [h] For the corresponding L,L diastereomer, mp 125 °C (lit. mp 124–125 °C): $[\alpha]^{22}_D$ −29.3° (c 2, acetone) [lit. $[\alpha]^{25}_D$ −30.10° (c 2.06, acetone)], see: Goldschmidt, S.; Gupta, K. K. *Chem. Ber.* **1985**, *98*, 2831. The precursor (Z-Gly-Phe-OH) was obtained according to Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596. The NMR spectra of the two diastereomers were similar except for the position of the *C*-methyl doublets: LL δ 1.31 vs DL 1.21. [i] For the corresponding L,L diastereomer [mp 166–7 °C dec, $[\alpha]^{21}_D$ −4.3° (c 0.2, EtOAc)] and its precursor, Fmoc-Gly-Phe-OH [mp 204–206 °C, $[\alpha]^{21}_D$ +14.1° (c 1, DMSO)] obtained (70% yield) via reaction of Fmoc-Gly-Cl and H-Phe-OH, see: Kang, L.-L. M.S. Thesis, University of Massachusetts, Amherst, MA, 1985. In the NMR spectra both the *C*-Me doublets (LL δ 1.33; DL 1.22) and methyl ester peaks (LL δ 3.70; DL 3.67) were separated.

phenomenon, for whatever reason, were real and related to the rigid elongated structure of the additives, the implications would be far-reaching. An obvious extension envisions the incorporation of such structural elements into classic protecting groups, coupling agents, auxiliary bases, etc.[6]

In an attempt to probe the effects reported in the Jeschkeit, Strube, Przybylski, Miecznickowska, and Kupryszewski (JSPMK) paper, we first examined some *p*-phenylazobenzoyl derivatives of amino acids **1** in view of their ready availability[7] and direct relationship to the acid component of the Young test. Use of such aroyl derivatives has the added advantage that the diastereomeric dipeptide methyl esters are easily recognizable by the different methyl ester peaks visible in their ^{1}H NMR spectra.[8]



1

Previously, coupling between *N*-benzoylvaline and valine methyl ester via DCC or EEDQ in THF was reported[8a,c] to lead to a diastereomeric mixture containing 48 and 22%

(6) Long before the work of JSPMK, Schwyzer and co-workers had investigated *p*-phenylazo-substituted benzyloxycarbonyl amino-protecting groups for their color-bearing properties and Losse and Barth had studied analogous phenol-based active esters. In these studies the question of racemization relative to non-azo bearing systems was not explicitly studied. See: (a) Schwyzer, R.; Sieber, P.; Zatsko, K. *Helv. Chim. Acta* **1958**, *41*, 491. (b) Tun-Kyi, A.; Schwyzer, R. *Helv. Chim. Acta* **1976**, *59*, 1642. (c) Barth, A.; Losse, G. *Z. Naturforsch.* **1964**, *19b*, 264. (d) Barth, A. *Justus Liebigs Ann. Chem.* **1965**, *683*, 216. Incorporation of a Schwyzer system into the present tests is detailed in Table III.

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Table II. Loss of Chirality in Coupling of ArCO-X_{aa}-OH + H-X_{bb}-OMe[a]

run	Ar[b]	solv	X_{aa}	X_{bb}	method	yield,[c] %	amount DL,[d] %
1[e]	Bz	THF	Val	Val	EEDQ	76.5, 74.2	8.0, 7.6
2	Bz	DMF	Val	Val	EEDQ	61.8, 60.5	34.3, 31.4
3[f]	PABz	THF	Val	Val	EEDQ	89.9, 91.7	6.4, 6.8
4[f]	PABz	DMF	Val	Val	EEDQ	61.1, 58.9	7.5, 7.8
5[f,g]	PABz	THF	Val	Val	DCC	88.9, 89.5	20.0, 18.0
6	Bz	THF	Phe	Phe	EEDQ	94.5, 96.4	<1, <1
7	Bz	DMF	Phe	Phe	EEDQ	86.2, 84.5	<1, <1
8	Bz	THF	Phe	Phe	DCC	50.0, 52.0	48, 56
9	PABz	THF	Phe	Phe	EEDQ	94.2, 96.2	<1, <1
10	PABz	DMF	Phe	Phe	EEDQ	88.5, 84.5	<1, <1
11	PABz	THF	Phe	Phe	DCC	46.0, 50.0	47.0, 52.0
12	Bz	THF	Ala	Ala	EEDQ	69.4, 68.5	<1, <1
13	Bz	DMF	Ala	Ala	EEDQ	55.6, 62.5	0.8, 0.7
14	PABz	DMF	Ala	Ala	EEDQ	61.5, 60.2	2.4, 2.8
15	PABz	THF	Val	Phe	EEDQ	66.9, 68.9	<1, <1
16	PABz	DMF	Val	Phe	EEDQ	60.2, 58.8	<1, <1
17	Bz	THF	Phg	Val	EEDQ	84.2, 82.1	<1, <1
18	Bz	DMF	Phg	Val	EEDQ	58.9, 59.2	<1, <1
19	PABz	THF	Phg	Val	EEDQ	83.7, 82.8	<1, <1
20	PABz	DMF	Phg	Val	EEDQ	76.1, 74.4	<1, <1

[a] To a stirred solution of 1 mmol of the amino acid ester hydrochloride at 0 °C in 10 mL of THF or DMF was added 0.9 mmol of NEt_3 followed by 1 mmol of the protected amino acid followed by 1 mmol of EEDQ or DCC. After being allowed to come to room temperature, the mixture was stirred for 21 h and treated with 10 mL of water and 30 mL of CH_2Cl_2, and the layers were separated. After being washed twice with 10-mL portions each of 10% HCl and 1 M $NaHCO_3$, the solution was dried ($MgSO_4$) and evaporated to give the dipeptide ester in the yields recorded. Formation of the DL diastereomer was recorded for the crude product. [b] Bz = benzyl, PABz = *p*-phenylazobenzoyl. [c] Separate figures for two independent runs. [d] Obtain by ^1H NMR analysis at 200 or 300 MHz with the detection limit being approximately 1% (see the Experimentanl Section). The separate figures are for two independent runs. [e] Coupling of equimolar amounts of Bz-Val-OH with H-Val-OMe in THF in the presence of 1 equiv each of NEt_3, DCC, and *p,p'*-azoxyanisole gave a 1:3 ratio of the LL and DL diastereomeric dipeptide esters. This may represent the 1:3 oxazolone-derived mixture of diastereomers.[8c] [f] Significant contamination of one diastereomer by the other in this case can be detected visually by TLC analysis. Merck silica gel 60 F254 aluminum-backed plates were used as received with elution by 35% ethyl acetate in hexane. A 47-mm plate was developed several times in succession. At least three runs were necessary to effect clear separation which amounted to 2.5 mm affter six developments. These couplings were also carried out in the presence of either 10 mol % or a full equivalent of azobenzene and *p,p'*-azoxyanisole. The amount of DL diastereomer formed did not differ from that observed in the absence of the additive. [g] In this run 1 mmol of *N*-hydroxybenzotriazole was used as additive. When free valine methyl ester was used in place of its hydrochloride, thereby allowing the triethylamine to be eliminated, the yields were 88.9, 90.2%; the amount of DL 10.2, 9.8%.

of the DL form, respectively. We confirmed this loss of chirality for EEDQ coupling in THF (7.6–8.0% DL) and DMF (31–34% DL) and extended the test to include (*p*-phenylazobenzoyl)valine. Surprisingly, and in apparent agreement with the JSPMK report, EEDQ coupling to valine methyl ester in DMF led to significantly less racemization (6–7% DL) than for the benzoyl analogue (31–34%). However, in THF the extent of racemization was comparable in the two systems (6–8%) and couplings of the azo derivative carried out by means of either DCC or Woodward's Reagent K were accompanied by extensive racemization (18–20% and 40–45%, respectively). Clearly there is no significant difference between azo- and non-azo-based *N*-acyl amino acids in these reactions (Table II). Similarly, and more to the point regarding the value of such compounds as additives, when azobenzene or *p,p'*-azoxyanisole were present during a selected group of these coupling reactions, there was no significant change in the amount of DL diastereomer formed.

These results led us to reinvestigate some of the very same coupling reactions described by the JSPMK group. Regrettably the results have been uniformly negative, at least in the case of the additives azobenzene and azoxyanisole.[9,10] To the extent possible the experimental details described in the earlier work were carefully followed. It remains to be seen whether some unknown variable not obvious from the printed description is responsible for our inability to repeat the work as reported.

With alanine or phenylalanine methyl ester and EEDQ as coupling agent we observed no significant racemization (<1%) in the coupling of either *N*-benzoyl or *N*-*p*-phenylazobenzoyl derivatives of alanine, phenylalanine, or even the highly sensitive[11] α-phenylglycine (Table II). Similar results were obtained for the coupling of Z-, BOC, FMOC- and PAZ-glycine derivatives of phenylalanine with alanine methyl ester with either EEDQ or, under certain conditions, the mixed anhydride technique (Table III). For DCC and mixed anhydride couplings of Z-protected derivatives under drastic conditions racemization occurred, but our results differed from those of the JSPMK group (Table III, footnote *e*).

Our results are summarized in Tables I–III. Table I includes characterization data for all new di- and tripeptides obtained during the course of this work. Although incidental to the present study, the data in Table III confirm previous observations[12] that *t*-BOC-protected amino acid derivatives are slightly less susceptible to racemization than analogous Z-protected systems. The FMOC and PAZ functions appear to fall between the other two in this regard, although the differences are not substantial. The EEDQ couplings involving the formation of protected valylvaline derivatives with which we began this study and which show less racemization for the *p*-

(9) A third additive listed by JSPMK, *trans*-stilbene, was studied less extensively than azobenzene and *p,p'*-azoxyanisole. NMR studies showed no effect of either 10 molar % or a full equivalent of this additive on the coupling of either Z-Gly-Phe-OH or Bz-Phe-OH with alanine methyl ester using DCC in THF.

(10) Recently the use of azobenzene as additive in a BOP-Cl mediated coupling of Z-Gly-Phe-OH and H-Val-OMe in THF was said to have "no effect at all" as a racemization suppressor. See: Van der Auwera, C.; Van Dame, S.; Anteunis, M. J. O. *Int. J. Pept. Protein Res.* **1987**, *29*, 464.

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Table III. Loss of Chirality in Coupling of X-Gly-Phe-OH + H-Ala-OMe[a]

run	X[b]	additive[c]	yield,[d] %	amount DL,[d] %
1	Z		57, 63	26, 27[e]
2	Z	azo	61, 67	29, 20[e]
3	Z	azox	68, 65	30, 23[e]
4	BOC		52, 67	17, 21
5	BOC	azo	58, 69	18, 20
6	BOC	azox	50, 71	14, 21
7	FMOC		46, 53	19, 22
8	FMOC	azo	53, 61	24, 21
9	FMOC	azox	51, 60	17, 19
10	PAZ		50, 57	15, 17
11	PAZ	azo	57, 69	17, 14
12	PAZ	azox	56, 70	21, 20

[a] All couplings were carried out by adding at 0 °C first 1.1 equiv of NEt_3 and then 1.1 equiv of DCC to a solution of 0.5 mmol of X-Gly-Phe-OH, 0.5 mmol of H-Ala-OMe·HCl and, if used, 0.05 mmol of the additive in 5 mL of DMF. After 30 min at 0 °C and 20 h at room temperature, the Z derivative was worked up exactly as described in the JSPMK paper. In the other three cases, the workup was modified by column chromatography to collect the set of LL and DL diastereomers together in one fraction which was used to determine the yield and relative amount of DL isomer by ^1H NMR analysis. When EEDQ was substituted for DCC as coupling agent, no detectable amount of the DL diastereomer (<1%) was observed in any one of the 12 runs (yields 60–84%) with or without additive. [b] Z = $C_6H_5CH_2OCO$; BOC = Me_3COCO; FMOC = 9-$C_{13}H_9$-CH_2OCO; PAZ = p-$C_6H_5N{=}N$-$C_6H_4CH_2OCO$. [c] In each case 10 mol % of additive was used: azo = azobenzene; azox = p,p'-azoxyanisole. [d] The figures given are for two independent runs. [e] JSPMK report the following extent of DL diastereomer formation in THF solution: (a) no additive, 12%; (b) azo, 3.4%; (c) azox, 0%. In our hands in the same solvent, results were (two runs): (a) 17, 13.5; (b) 10, 8.4%; (c) 11, 11%. For the mixed anhydride technique JSPMK report (a) 26%, (b) 3%, and (c) 0%. In our hands under the conditions described no racemization was observed with or without additive. When the reaction was carried out similarly except at room temperature with a 6-min activation period, the results were (two runs): (a) 36, 38%; (b) 41, 45.7%; (c) 38, 38.7%. Yields of dipeptide ester were in the range 69–75%.

phenylazo relative to the parent benzoyl system remain anomalous and subject to further study.

Experimental Section[13]

***N*-(*p*-Phenylazobenzoyl)-α-phenylglycine.** A solution of 1.51 g of α-phenylglycine and 3 g of Na_2CO_3 in 50 mL of water and 10 mL of dioxane was stirred at room temperature, and a solution of 2.45 g of *p*-phenylazobenzoyl chloride[14] in 10 mL of dioxane was added in one portion. After being stirred for 60 min the mixture was poured into 300 mL of water and extracted with 30 mL of CH_2Cl_2. The aqueous layer was acidified with concentrated HCl, and the precipitated orange solid was filtered, washed with water, and recrystallized twice from ethanol to give 2.79 g (77.7%) of the acid as shiny orange crystals: mp 189–190 °C; ^1H NMR ($CDCl_3$) δ 5.9 (d, 1 C*H*NH), 7–9 (m, 15, aryl, NH); $[\alpha]^{23}_D$ +38.0° (*c* 0.1, EtOH). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.76; N, 11.69. Found: C, 69.95; H, 4.68; H, 11.77.

***N*-(*p*-Phenylazobenzoyl)-D-α-phenylglycine** was prepared as described for the L isomer in 81.4% yield as bright orange crystals: mp 189–190 °C; ^1H NMR ($CDCl_3$) δ 5.9 (d, 1, C*H*NH), 7–9 (m, 15, aryl, NH); $[\alpha]^{23}_D$ −36° (*c* 0.1, EtOH). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.76; N, 11.69. Found: C, 70.12; H, 4.92; N, 11.48.

(13) Melting points and boiling points are uncorrected. Infrared spectra were determined on Perkin-Elmer 237B and 1310 instruments and ^1H NMR spectra on Varian XL-200 (200 MHz) and XL-300 (300 MHz) spectrometers with Me_4Si as internal standard. Thin-layer chromatography was performed on aluminum-backed Merck silica gel 60 F254 plates. Separations by flash chromatography were achieved with Merck silica gel 9385 (230–400 mesh). Elemental annayses were carried out by the University of Massachusetts Microanalytical Laboratory under the direction of Greg Dabkowski.

(14) Eastman Kodak Co., Rochester, NY.

***N*-(*p*-Phenylazobenzoyl)phenylalanine.** The procedure described for α-phenylglycine was used in the case of phenylalanine although the workup had to be changed due to the insolubility of the sodium salt of the acid in aqueous media. The salt that precipitated during the reaction was filtered and suspended in water. Acidification with concentrated HCl (Congo Red) followed by stirring for 30 min, filtration, and air-drying gave, after recrystallization from ethanol, the free acid in a yield of 65%: mp 183–184 °C; $[\alpha]^{23}_D$ −84.0° (*c* 0.2, EtOH); ^1H NMR ($CDCl_3$) δ 3.35 (m, 2, C$H_2C_6H_5$), 5.0 (dt, 1, NHC*H*), 7.0–8.0 (m, 15, aryl, NH). Anal. Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.14; N, 11.26. Found: C, 70.67; H, 5.12; N, 11.25.

***N*-(*p*-Phenylazobenzoyl)valine *tert*-Butyl Ester.** A solution of 2 g of H-Val-$OCMe_3$·HCl in 40 mL of CH_2Cl_2 was treated with 1.92 g of NEt_3 followed by 2.45 g of *p*-phenylazobenzoyl chloride,[14] and the solution was stirred at room temperature for 1 h. Extraction with 5% HCl (2 × 10 mL), 1 M $NaHCO_3$ (2 × 10 mL) and water followed by drying ($MgSO_4$) and removal of solvent gave 3.2 g (87.9%) of the pure *tert*-butyl ester: mp (hexane) 107–108.5 °C; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3, CH_3CH), 1.04 (d, 3, CH_3CH), 1.51 (s, 9, *tert*-Bu), 2.3 (m, 1, CHMe_2), 4.7 (dd, 1, NHC*H*), 6.75 (d, 1, N*H*CH), 7.52–7.97 (m, 9, aryl); $[\alpha]^{23}_D$ +58.5° (*c* 0.2, EtOH). Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.25; H, 7.15; N, 11.02. Found: C, 69.10; H, 7.02; N, 10.96.

***N*-(*p*-Phenylazobenzoyl)valine** was obtained in 85.9% yield by the method described above for the corresponding α-phenylglycine derivative or by treatment of the corresponding *tert*-butyl ester with 30–50% TFA in CH_2Cl_2 for several hours at room temperature (70–80%). Recrystallization from ethanol or nitromethane gave orange crystals: mp 158.5–160 °C (lit.[7] mp 157–159 °C); $[\alpha]^{25}_D$ +39.0° (*c* 1, EtOH).

Quantitative ^1H NMR Analysis of Diastereomers via Differentiated Methyl Ester Peaks. In cases where the methyl ester peaks are different contamination of the LL dipeptide diastereomer by about 1% of the DL form can readily be detected at 200 or 300 MHz by the NMR technique. A calibration curve prepared by weighing out exact quantities of *N*-(*p*-phenyazobenzoyl)-D-valyl-L-valine methyl ester and mixing with the L,L isomer in $CDCl_3$ in order to obtain solutions containing 2, 3, 4, and 5% of the DL form gave the following percentages as measured by duplicate integrations on an XL-200 instrument: 1.45, 2.62, 3.54, and 4.77%. On the recording chart, 1% contamination was easily visible but difficult to measure accurately with the average scan rate used (NT ~ 16). In the range 0.5–1% a ^{13}C satellite method[15] gave acceptable results, the 1% standard solution giving a value of 0.86% DL isomer (XL-300 instrument, NT = 200).

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Registry No. Azo, 103-33-3; Azox, 1562-94-3; PABz-Cl, 104-24-5; PABz-Val-OBu-*t*, 117370-39-5; H-Phg-OH, 2935-35-5; H-D-Phg-OH, 875-74-1; H-Phe-OH, 63-91-2; H-Val-OBu-*t*·HCl, 13518-40-6; H-Val-OH, 72-18-4; PABz-Phg-OH, 117370-40-8; PABz-D-Phg-OH, 117370-41-9; PABz-Phe-OH, 117370-42-0; PABz-Val-OH, 117370-43-1; Bz-Val-OH, 5699-79-6; Bz-Phe-OH, 2566-22-5; Bz-Ala-OH, 2198-64-3; PABz-Ala-OH, 117370-44-2; Bz-Phg-OH, 7352-07-0; Z-Gly-Phe-OH, 1170-76-9; BOC-Gly-Phe-OH, 4530-37-4; Fmoc-Gly-Phe-OH, 117370-45-3; PAz-Gly-Phe-OH, 117370-46-4; H-Ala-OMe·HCl, 2491-20-5; H-Val-OMe·HCl, 6306-52-1; H-Phe-OMe·HCl, 7524-50-7; H-Val-OMe, 4070-48-8; Bz-Val-Val-OMe, 13795-37-4; Bz-D-Val-Val-OMe, 13795-36-3; PABz-Val-Val-OMe, 117370-47-5; PABz-D-Val-Val-OMe, 117370-48-6; Bz-Phe-Phe-OMe, 60728-18-9; Bz-D-Phe-Phe-OMe, 80657-82-5; PABz-Phe-Phe-OMe, 117370-49-7; PABz-D-Phe-Phe-OMe, 117370-50-0; Bz-Ala-Ala-OMe, 56047-49-5; PABz-Ala-Ala-OMe, 117370-51-1; PABz-Val-Phe-OMe, 117370-

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Alkynyliodonium Tetrafluoroborates as a Good Michael Acceptor for an Azido Group. A Stereoselective Synthesis of (*Z*)-(β-Azidovinyl)iodonium Salts

Masahito Ochiai,* Munetaka Kunishima, Kaoru Fuji, and Yoshimitsu Nagao*

Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

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Alkynylphenyliodonium salts **1** are highly reactive and formally tetraphilic (Cα, Cα′, Cβ, and I) toward the attack of nucleophiles.[1] We have reported an efficient cyclopentene annulation utilizing **1** via the tandem Michael–carbene insertion (MCI) reaction. It was suggested that the reaction involved the formation of unstable iodonium ylides **2** by the conjugate addition of soft nucleophiles such as carbanions generated from 1,3-dicarbonyl compounds. Elimination of iodobenzene from **2** is a rapid process under basic conditions and results in formation of alkylidenecarbenes **3**, which undergo intramolecular 1,5-carbon–hydrogen insertion to give cyclopentenes.[2] However, if the unstable ylides **2** react with electrophiles at the Cα atom much faster than the reductive elimination of iodobenzene, the reaction would offer a new route to the synthesis of functionalized vinyliodonium salts **4**. Recently Stang and Kitamura reported the Michael type reaction of (β-phenylethynyl)iodonium tosylate (**1**: R = C_6H_5, X = OTs) with sodium azide in the presence of triethylsilane as a proton source in dichloromethane, which produces the corresponding (β-azidovinyl)iodonium tosylate. The reaction, however, is strongly dependent upon the nature of R groups and in some cases formation of alkylidenecarbene-derived insertion products results in a major pathway.[3]

Vinyliodonium salts behave similarly to the highly activated species of vinyl iodides because of the high leaving ability of the iodine(III) substituents. They serve as a useful precursor for the synthesis of a variety of functionalized olefins including α-cyano and α-nitro olefins, vinyl sulfides, vinyl halides, and α,β-unsaturated esters and also undergo Friedel–Crafts vinylation of aromatic compounds under mild conditions.[4-6] However, the synthetic method of vinyliodonium salts is very limited.[4,7] We report herein a stereoselective synthesis of (*Z*)-(β-azidovinyl)iodonium salts **5** via the Michael-type addition of an azido group to readily available alkynyliodonium salts **1**.

Scheme I

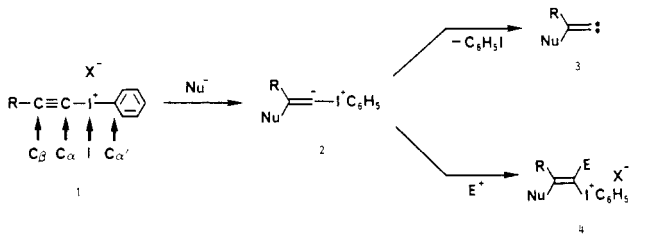
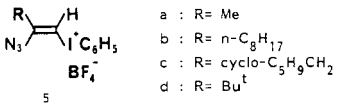


Table I. Synthesis of (*Z*)-(β-Azidovinyl)iodonium Tetrafluoroborates 5

1 (R)[a]	5	yield, %[b]	NOE, %[c]
1a (Me)	**5a**	79	10.3
1b (n-C_8H_{17})	**5b**	91	7.5
1c (c-$C_5H_9CH_2$)	**5c**	87	8.9
1d (t-Bu)	**5d**	50	
1d[d]	**5d**	72	

[a] X = BF_4. [b] Isolated yield. [c] See text. [d] 3 molar equiv of trimethylsilyl azide and water were used.



When propynylphenyliodonium tetrafluoroborate (**1a**) was treated with trimethylsilyl azide (1.2 equiv) in dichloromethane in the presence of water (1.2 equiv) at −78 °C to room temperature under an atmosphere of nitrogen, Michael-type addition of an azido group to the electron-deficient β-carbon atom took place and (*Z*)-phenyl(2-azidopropenyl)iodonium tetrafluoroborate (**5a**) was obtained as a pale yellow oil in 79% yield. The results for the synthesis of (*Z*)-(β-azidovinyl)iodonium tetrafluoroborates **5** are shown in Table I. In the case of (β-*tert*-butylethynyl)iodonium tetrafluoroborate (**1d**),[1e] the yield of **5d** (50%) was somewhat lower than those of **5a–c**, most probably because of the large steric requirement of the bulky *tert*-butyl group for the conjugate addition of an azido group. Use of 3 equiv of trimethylsilyl azide and water increased the yield of **5d** up to 72%. Purification of **5** was carried out by decantation (with hexane) and/or recrystallization. Some of the vinyliodonium salts **5** are labile at room temperature and should be kept in a refrigerator.

The addition reactions were completely stereoselective to the limits of NMR detection at 100 MHz. The *Z* stereochemistry of **5a–c** was easily established by observation of a large nuclear Overhauser effect (NOE) enhancement between the vinylic and allylic protons: 7.5–10.3% NOE enhancement of vinylic protons of **5a–c**

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