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SUPPORTING INFORMATION

Title: Synthesis of Some 2,2':6',2"-Terpyridines Disubstituted in Positions 6 and 6" with Head-to-Tail Oriented Amino Acids and Dipeptides: A Simple Entry to a Reversible Inducer of Folding in Amino Acid Sequences
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Synthesis of *N*-4-iodobenzoyl amino acid ethyl esters 3a-c. *General Procedure:* To a stirred solution of amino acid ethyl ester hydrochloride (3 mmol) in DCM (7 mL), triethylamine (0.45 mL, 3.2 mmol) was added and the mixture was stirred 10 min at room temperature. In a second flask, to a solution of 4-iodobenzoic acid (744 mg, 3 mmol) in DCM (18 mL), EDC (690 mg, 3.6 mmol) and HOBt (486 mg, 3.6 mmol) were added in this order. After 10 min stirring ar room temperature, the content of the second flask was cannulated into the first flask cooled at 0 °C, and stirring was continued for 24 h at room temperature. The reaction was quenched by the addition of 1*N* aqueous HCl (10 mL), the organic layer was separated, and washed successively with saturated aqueous solutions of $NaHCO_3$ and NaCl. The organic layer was then dried and evaporated to afford the product that was purified by flash chromatography with a 9:1 hexane:AcOEt mixture as eluant.

***N*-4-iodobenzoyl glycine ethyl ester 3a** was obtained in 90% yield. It had m.p. 130-131 °C (lit.:[1] 129-131 °C) and NMR data in agreement with those reported.

(*L*)-*N*-4-iodobenzoyl alanine ethyl ester 3b was obtained in 98% yield. It had m.p. 90-91 °C; $[\alpha]_D$ 30.8 (*c* 0.23, in chloroform); IR (KBr): 3300, 3019, 1729, 1665, 1058 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.30 (t, *J* 7.0, 3H, $CH_2\underline{Me}$); 1.51 (d, *J* 7.0, 3H, $CH\underline{Me}$), 4.28 (q, *J* 7.0, 2H, $\underline{CH_2}Me$), 4.75 (q, *J* 7.0, 1H, $\underline{CH}Me$), 6.73 (bs, 1H, NH), 7.51 (part A of an AB system, *J* 8.5, 2H, aromatic protons), 7.80 (part B of an AB system, *J* 8.5, 2H, aromatic protons). Anal. Calcd. for $C_{12}H_{14}INO_3$: C, 41.50; H, 4.06; N, 4.03: Found: C, 41.59; H, 4.01; N, 3.98.

(*L*)-*N*-4-iodobenzoyl valine ethyl ester 3c was obtained in 98% yield. It had m.p. 72-73 °C; $[\alpha]_D$ 32.0 (*c* 0.44, in DCM); IR (KBr): 3300, 3025, 1730, 1670, 1057 cm^{-1}. ^{1}H-NMR ($CDCl_3$): d 0.91 (d, *J* 3.0, 3H, one Me of *i*-Pr group); 0.93 (d, *J* 3.0, 3H, one Me of *i*-Pr group), 1.24 (t, *J* 7.2, 3H, $CH_2\underline{Me}$), 2.15-2.25 (m, 1H, CH of *i*-Pr group), 4.10-4.25 (m, 2H, $\underline{CH_2}Me$), 4.66 (dd, *J* 3.0 and 8.0, 1H, $\underline{CH}NH$), 6.78 (bd, *J* 8.0, 1H, NH), 7.45 (part A of an AB sytem, *J* 8.0, 2H, aromatic protons), 7.68 (part B of an AB system, *J* 8.0, 2H, aromatic protons). Anal. Calcd. for $C_{14}H_{18}INO_3$: C, 44.82; H, 4.84; N, 3.73: Found: C, 44.66; H, 4.91; N, 3.89.

Synthesis of Boc amino acid *N*-4-iodophenylamides 4a-c. *General Procedure:* To a stirred solution of Boc amino acid (3 mmol) in DCM (13 mL), EDC (690 mg, 3.6 mmol) and HOBt (486 mg, 3.6 mmol) were added in this order. After 10 min stirring ar room temperature, the resulting mixture was cannulated into a flask containing 4-iodoaniline (657 mg, 3 mmol) in DCM (7 mL) cooled at 0 °C, and stirring was continued for 24 h at room temperature. The reaction was quenched by the addition of 1*N* aqueous HCl (10 mL), the organic layer was separated, and washed successively with saturated aqueous solutions of $NaHCO_3$ and NaCl. The organic layer was then dried and evaporated to afford the product that was purified by flash chromatography with a 7:3 hexane:AcOEt mixture as eluant.

Boc glycine *N*-4-iodophenylamide 4a was obtained in 60% yield. It had m.p. 183-184 °C; IR (KBr): 3349, 3270, 1690, 1057 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.48 (s, 9H, CMe_3), 3.91 (d, *J* 6.0, 2H, CH_2), 5.10 (bs, 1H, $CH_2N\underline{H}$), 7.28 (part A of an AB system, *J* 8.0, 2H, aromatic protons), 7.65 (part B of an AB system, *J* 8.0, 2H, aromatic protons), 8.15 (bs, 1H, $ArN\underline{H}$). Anal. Calcd. for $C_{13}H_{17}IN_2O_3$: C, 41.50; H, 4.55; N, 7.45: Found: C, 41.76; H, 4.78; N, 7.27.

(*L*)-Boc alanine *N*-4-iodophenylamide 4b was obtained in 89% yield. It had m.p. 168-169 °C (lit.:[2] 169-170° C) and IR and NMR data in agreement with those reported. $[\alpha]_D$ -56.6 (*c* 0.21, in chloroform); lit.: [2] $[\alpha]_D$ -45.0 (*c* 0.5, in chloroform).

(*L*)-Boc valine *N*-4-iodophenylamide 4c was obtained in 96% yield. It had m.p. 163-164 °C; $[\alpha]_D$ -12.5 (*c* 0.24, in chloroform); IR (KBr): 3437, 3310, 1674, 1058 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.01-1.05 (m, 6H, 2 Me of *i*-Pr group), 1.48 (s, 9H, CMe_3), 2.10-2.22 (m, 1H, CH of *i*-Pr group), 4.12 (bt, 1H, $C\underline{H}NH$), 5.32 (bd, 1H, $CHN\underline{H}$), 7.25 (part A of an AB system, *J* 8.0, 2H, aromatic protons), 7.52 (part B of an AB system, *J* 8.0, 2H, aromatic protons), 8.70 (bs, 1H, $ArN\underline{H}$). Anal. Calcd. for $C_{16}H_{23}IN_2O_3$: C, 45.94; H, 5.54; N, 6.70: Found: C, 46.16; H, 5.61; N, 6.51.

Synthesis of (*L*)-*N*-4-iodobenzoylGlyAlaOMe 7. To a stirred solution of commercially available HGlyAlaOMe hydrochloride (493 mg, 2.5 mmol) in chloroform (15 mL), triethylamine (0.365 mL, 2.63 mmol) was added and the mixture was stirred 15 min at room temperature. In a second flask, to a solution of 4-iodobenzoic acid (620 mg, 2.5 mmol) in chloroform (10 mL), EDC (576 mg, 3.0 mmol) and HOBt (405 mg, 3.0 mmol) were added in this order. After 20 min stirring ar room temperature, the content of the second flask was cannulated into that of the first flask cooled at 0 °C, and stirring was continued for 65 h at room temperature. The reaction was quenched by the addition of 1*N* aqueous HCl (10 mL), the organic layer was separated, and washed successively with saturated aqueous solutions of $NaHCO_3$ and NaCl. The organic layer was then dried and evaporated to afford the product that was purified by flash chromatography with a 95:5 DCM:MeOH mixture as eluant. The product (917 mg, 94% yield) was obtained as a white solid. It had m.p. 187-189 °C; $[\alpha]_D$ -26.0 (*c* 0.35, in MeOH); IR (KBr): 3293, 1742, 1637, 1057 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.48 (d, *J* 7.2, 3H, CH$\underline{Me}$), 3.79 (s, 3H, OMe), 4.21 (d, *J* 5.1, 2H, CH_2), 4.67 (q, *J* 7.2, 1H, C$\underline{H}$Me), 6.91 (bd, *J* 7.0, 1H, CH-N$\underline{H}$), 7.24 (bt, *J* 5.0, 1H, CH_2-N$\underline{H}$), 7.59 (part A of an AB system, *J* 8.5, 2H, aromatic protons), 7.82 (part B of an AB system, *J* 8.5, 2H, aromatic protons). ^{13}C-NMR ($CDCl_3$): δ 18.1 (CH$\underline{Me}$), 43.5 (CH_2), 48.3 ($\underline{CH}$Me), 52.6 (OMe), 98.9 (C-I) , 128.7 (2 aromatic C-H), 132.9 (aromatic $\underline{C}$-CONH), 137.8 (2 aromatic C-H), 166.9 ($\underline{C}$O-NHCH_2), 168.4 ($\underline{C}$O-NHCH), 173.0 (COO). Anal. Calcd. for $C_{13}H_{15}IN_2O_4$: C, 40.02; H, 3.87; N, 7.18: Found: C, 39.89; H, 3.77; N, 7.30.

Synthesis of (*L*)-AcAlaGly 4-iodophenylamide 8.

Step 1: Synthesis of (L)-BocAlaGly 4-iodophenylamide. To a stirred solution of commercially available (*L*)-BocAlaGlyOH (492 mg, 2 mmol) in chloroform (10 mL), EDC (458 mg, 2.4 mmol) and HOBt (270 mg, 2.4 mmol) were added in this order. After 15 min stirring ar room temperature, the resulting mixture was added to a flask containing 4-iodoaniline (438 mg, 2 mmol) in chloroform (10 mL) cooled at 0 °C, and stirring was continued for 65 h at room temperature. The reaction was quenched by the addition of 1*N* aqueous HCl (10 mL), the organic layer was separated, and washed successively with saturated aqueous solutions of $NaHCO_3$ and NaCl. The organic layer was then dried and evaporated to afford the product that was purified by flash chromatography with a 95:5 DCM:MeOH mixture as eluant. The product (865 mg, 97% yield) was obtained as a white solid. It had m.p. 202-204 °C; $[\alpha]_D$ 16.0 (*c* 0.35, in MeOH). ^1H-NMR ($CDCl_3$): δ 1.43 (d, *J* 6.0, 3H, $\underline{CHMe}$), 1.44 (s, 9H, CMe_3), 4.14 (m, 3H, C$\underline{H}$ and C$\underline{H_2}$), 5.05 (d, *J* 5.0, 1H, Boc-N$\underline{H}$), 6.92 (bs, 1H, CH_2-N$\underline{H}$), 7.47 (part A of an AB system, *J* 8.5, 2H, aromatic protons), 7.67 (part B of an Ab system, *J* 8.5, 2H, aromatic protons), 8.72 (s, 1H, Ar-N$\underline{H}$). ^{13}C-NMR ($CDCl_3$): δ 17.6 (CH$\underline{Me}$), 28.3 (C$\underline{Me_3}$), 44.1 ($\underline{C}H_2$), 51.4 (CH), 81.1 ($\underline{C}Me_3$), 87.6 (C-I), 122.0 (2 aromatic C-H), 137.6 (2 aromatic C-H), 139.3 (C-NHCO), 156.0 (CHNH-COO), 167.2 (NHCOCH$_2$), 173.4 (NHCOCH), 173.5. Anal. Calcd. for $C_{16}H_{22}IN_3O_4$: C, 42.96; H, 4.96; N, 9.39. Found: C, 43.11; H, 4.79; N, 9.36.

Step 2: Boc deprotection. To a solution of (*L*)-BocAlaGly 4-iodophenylamide (194 mg, 0.434 mmol) in DCM (2.7 mL), TFA (1.3 mL, excess) was added. After 1 h stirring at room temperature, TLC showed the absence of the starting product. The mixture was cooled at 0 °C and a saturated aqueous solution of $NaHCO_3$ was added dropwise until pH 8. The organic layer was separated, and the aqueous layer was extracted three times with 5 mL portions of DCM. The combined organic phases were dried and concentrated under vacuum to afford the crude product that was used as such in step 3.

Step 3: N-acetylation. To a stirred suspension of the crude product of step 2 in 2*M* NaOH (0.315 mL) cooled at 0 °C, acetic anhydride (0.315 mL, 2.8 mmol) was added. After 15 min stirring, the suspension was treated with 1*N* sulfuric acid until pH 1. The mixture was extracted with DCM containing a few drops of MeOH. The combined organic phases were dried and concentrated under vacuum to afford the product (543 mg, 70% overall yield on steps 1 to 3) as a pale yellow solid. It had m.p. 233-234 °C; $[\alpha]_D$ 11.2 (*c* 0.15, in MeOH). IR (nujol): 3322, 3292, 1631 cm^{-1}. ^{1}H-NMR (CD_3OD): δ 1.37 (d, *J* 7.2, 3H, CHMe), 2.00 (s, 3H, Me-CO), 3.96 (d, *J* 4.9, 2H, CH$_2$), 4.30 (q, *J* 7.2, 1H, CH), 7.46 (part A of an AB system, *J* 8.7, 2H, aromatic protons), 7.61 (part B of an AB system, *J* 8.7, 2H, aromatic protons). ^{13}C-NMR (CD_3OD): δ 17.4 (CHMe), 30.7 (Me-CO), 44.1 (CH$_2$), 51.2 (CH), 88.0 (C-I), 123.1 (2 aromatic CH), 138.8 (2 aromatic CH), 139.4 (C-NHCO), 169.7 (NH-CO-CH$_2$), 173.7 (NHCOCH), 175.9 (MeCO). Anal. Calcd. For $C_{16}H_{22}IN_3O_4$: C, 42.96; H, 4.96; N, 9.39. Found: C, 43.11; H, 4.79; N, 9.36.

References

1) S.C. Conway, R.B. Perni, *Synthetic Comm.* **1998**, *28*, 1539-1545.

2) K. Maeda, N. Kamiya, E. Yashima, *Chem. Eur. J.* **2004**, *10*, 4000-4010.

nucleus	#	Δδ		nucleus	#	Δδ
H	3/3"	-0.37		C	2/2"	-8.5
H	4/4"	0.22		C	3/3"	0.2
H	5/5"	0.22		C	4/4"	2.4
H	3'/5'	-0.19		C	5/5"	2.5
H	4'	0.39		C	6	-0.5
H	10	0.19		C	2'/6'	-5.5
H	10"	0.18		C	3'/5'	1.2
H	11	-0.37		C	4'	4.2
H	11"	-0.25		C	7	-1.5
				C	7"	-3.9
				C	8	-0.8
				C	8"	6.0
				C	9	und.
				C	9"	-2.0

Table 1. Relevant chemical shift differences (Δδ, in ppm) observed upon complexation of tpy **6a** with Zn(OTf)$_2$.

#	δ	Δδ		#	δ	Δδ		#	δ	Δδ
3	8.47	-0.20		10	7.57	-0.06		NHa	9.21	0.27
3'	8.55	0.02		10"	7.64	-0.14		NHb	7.67	0.52
3"	8.55	-0.16		11	7.64	-0.24		NHc	7.50	0.50
4	8.25	0.25		11"	7.83	-0.11		NHd	7.97	0.51
4'	8.43	0.30		14	4.10[a]	0.18		NHe	7.45	0.45
4"	8.55	0.51		14"	4.20[b]	0.17				
5	7.90	0.21		16	4.37	0.27				
5'	8.55	0.02		16"	4.55	-0.10				
5"	7.95	0.20		17	1.26	-0.10				
				17"	1.32	0.06				
				19	2.04	0.01				
				19"	3.77	0.07				

Table 2. Relevant ^{1}H chemical shifts (δ, in ppm) and chemical shift differences (Δδ, in ppm) observed upon protonation of compound **10** to **10**/H_2^{2+} in CD_3CN. [a] AB system centered at 4.10 ppm; *J* 5.5 Hz. [b] AB system centered at 4.20 ppm; *J* 4.0 Hz.

#	δ	Δδ		#	δ	Δδ
3	123.7	2.9		2	153.1	-3.0
3'	124.9	3.1		2'	152.8	-1.8
3"	123.8	2.6		2"	151.5	-4.5
4	141.6	2.9		6	143.1	0.4
4'	143.1	2.7		6'	150.3	-4.4
4"	143.1	4.5		6"	141.6	-0.5
5	130.8	2.5		7	84.9	-3.9
5'	125.5	3.7		7"	89.1	-2.0
5"	130.8	2.3		8	97.8	8.4
10	134.0	1.0		8"	92.8	4.5
10"	133.1	0.9		9	116.9	0.8
11	120.9	1.3		9"	125.7	1.1
11"	128.8	0.5		12	141.6	1.2
14	44.4	1.0		12"	135.8	0.8
14"	43.7	1.0		13	170.0	1.3
16	51.2	1.9		13"	168.9	2.8
16"	49.8	1.8		15	175.9	6.7
17	17.5	-0.6		15"	171.3	-2.2
17"	17.5	0.0		18	173.8	3.5
19	22.7	-0.3		18"	174.0	0.5
19"	53.0	0.8				

Table 3. Relevant ^{13}C chemical shifts (δ, in ppm) and chemical shift differences (Δδ, in ppm) observed upon protonation of compound **10** to **10**/H_2^{2+} in CD_3CN.