Supporting Information

for

Efficient Syntheses of 5-Aminoalkyl-1*H*-tetrazoles and of Polyamines Incorporating Tetrazole Rings

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General

Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. ¹H-NMR spectra were obtained at 400.13 MHz and ¹³C-NMR spectra at 100.62 MHz on a Bruker DPX spectrometer. CDCl₃ and tetramethylsilane (TMS) were used as the solvent and internal standard, respectively, unless otherwise stated. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. The assignments of the ¹H spectra are based on chemical shift arguments, analysis of coupling patterns and signal intensities whereas the ¹³C spectra were assigned taking into consideration chemical shift arguments.

Electron-spray ionization (ESI) mass spectra were recorded on a Micromass-Platform LC spectrometer using MeOH as solvent. The MALDI high-resolution MS (HR-MS) experiments were carried out in a MALDI-TOF-TOF A/B 4700 proteomics instrument.

Microanalyses were performed on a Carlo Erba EA 1108 CHNS elemental analyzer in the Center of Instrumental Analysis of the University of Patras.

Flash column chromatography (FCC) was performed on Merck silica gel 60 (230-400 mesh) and TLC on 60 Merck 60 F₂₅₄ films (0.2 mm) precoated on aluminium foil. Spots were visualized with UV light at 254 nm and the ninhydrin agent. All solvents (Merck) were dried and/or purified according to standard procedures prior to use. Anhydrous Na₂SO₄ was used for drying organic solvents, unless otherwise indicated, and subsequently solvents were routinely removed at ca. 40 °C under reduced pressure (water aspirator). All reagents employed in the present work were purchased from either Aldrich or Fluka and used without further purification with the exception of TFA-mediated deprotections, all other reactions were routinely carried out under an atmosphere of Ar.

General Experimental Procedures

Typical thionation: To a suspension of mono- or bisamide (1 mmol) in THF (5 ml) was added LR (0.55 mmol per amide bond) and the thus resulting mixture was stirred for further 2-12 h at ambient temperature or 0.5-3 h reflux in the case of **4**, **22** and **34** (Table 1 of the main article). Then the solvents removed under vacuum and the residue was subjected to flash column chromatography (FCC) using as eluents PhMe/EtOAc (various combinations from 6:4 to 95:5) to give the corresponding pure thioamides in 50-85% yields, with the only exception of **34** (25% yield, Table 1).

Typical tetrazole ring formation: To a suspension or a solution of mono- or bisthioamide (1 mmol) in THF (1-1.5 ml) were added DIAD and Ph₃P (1.5 mmol of each per amide bond), followed by the addition of Me₃SiN₃ (1.5 mmol per amide bond) 5 min later. The resulting slurry was stirred at ambient temperature for 1-24 h (Table 1 of the main article). Then, the solvents were removed under vacuum and the residue was subjected to FCC using as eluents PhMe/EtOAc (various combinations from 7:3 to 9:1) to give the corresponding pure tetrazole analogs in 50-90% yields (Table 1).

*Tetrazole rings formation in the aromatic amide **34**:* To a suspension of **34** (1 mmol) in THF (1.5 ml) were added DIAD and Ph₃P (2.5 mmol of each per amide bond), followed by the addition of Me₃SiN₃ (2.5 mmol per amide bond) 5 min later. The resulting slurry was stirred under reflux for 12 h. Then allowed to attain room temperature and concentrated under reduced pressure to leave an oily residue which was subjected to FCC, using as eluent PhMe/EtOAc 85:15, to give the corresponding bistetrazole derivative **36** in 75% yield.

Compound (6)

Foam; R_f (PhMe/ AcOEt 7:3) 0.48; ESI-MS (m/z) : 446.68 ($M+H^+$), 243.23 (Trt^+);

1H NMR: δ 7.38-7.11 (20H, m, Ph-*H*), 5.46 (2H, s, PhCH₂),

2.88 (2H, t, J 6.8 Hz, H-2), 2.51 (2H, t, J 6.8 Hz, H-1), 2.35 (1H, s, NH);

^{13}C NMR: 153.8 (C-3), 145.6, 133.2, 129.3, 129.0, 128.9, 128.5,

127.9, 127.4, 126.4 (Ph-C), 71.0 (Ph₃-C), 50.8 (PhCH₂), 41.0 (C-2), 24.8 (C-1) ppm

Compound (13)

White solid; R_f (PhMe/ AcOEt 8:2) 0.37; m.p. 216.5-217.5 °C;

ESI-MS (m/z) : 617.28 ($M+H^+$), 375.44 ($M+H^+-Trt$), 243.15 (Trt^+);

Anal. Calcd for C₄₂H₃₇N₂P (616.73): C, 81.79; H, 6.05; N, 4.54.

Found: C, 81.52; H, 6.01; N, 4.44.

1H NMR: δ 7.81 – 7.46 (21H, four m, Ph-*H*), 7.14 – 7.06 (9H, m, Ph-*H*), 4.05 (1H, d, J 6.8 Hz, H-1),

3.49 (1H, ddd, J 4.8, 9.6 and 11.2 Hz, H-4a), 2.86 (1H, dt, J 7.6 and 10.8 Hz, H-4b), 1.70 (1H, td, J 6.8 Hz, H-2a), 1.52 (1H, m, H-2b), 0.88 (2H, m, H-3);

^{13}C NMR: 187.8 (d, J 11.0 Hz, C-5), 146.0, 133.2 (d, J 9.7 Hz), 132.0, 129.6, 128.6 (d, J 12.2 Hz),

127.4 and 125.6 (Ph-C), 67.3 (Ph₃C), 67.1 (C-1), 50.1 (C-4), 32.1 (C-2), 24.7 (C-3) ppm

Compound (21)

White solid; R_f (PhMe/ AcOEt 7:3) 0.53; m.p. 134-135 °C;

ESI-MS (m/z) : 669.11 ($M+H^+$), 242.95 (Trt^+);

1H NMR: δ 7.44 – 7.14 (30H, m, Ph-*H*), 4.17 (2H, t, J 7.4 Hz, H-3), 2.94 (2H, unresolved t, H-2), 2.61 (2H, unresolved m, H-1), 2.17 (2H, unresolved m, H-6), 1.91 and 1.89 (4H, two t, J 7.6 Hz, H-4 and H-5), 1.47 (2H, unresolved t, NH);

^{13}C NMR: 153.4 (C-7), 145.9, 145.3, 128.5, 128.5, 128.0, 127.9, 126.5, 126.4 (Ph-C), 71.1 (Ph_3C), 46.9 (C-3), 42.9 (C-2), 41.3 (C-1), 27.5 (C-5 and C-4), 24.6 (C-6) ppm

Compound (28)

White solid; R_f (PhMe/ AcOEt 6:4) 0.42; m.p. 226-229 °C;

ESI-MS (m/z) : 766.62 ($M+H^+$), 243.23 (Trt^+);

1H NMR (DMSO- d_6): δ 7.32 – 7.15 (30H, m, Ph-*H*), 4.37 (4H, unresolved m, H-3 and H-3'), 3.17 (2H, t, J 7.4 Hz, NH), 3.07 (4H, t, J 60.0 Hz, H-2 and H-2'), 2.34 (4H, unresolved m, H-1 and H-1'), 1.82 (4H, unresolved m, H-4 and H-4');

^{13}C NMR (DMSO- d_6): 154.8 (C-5 and C-5'), 146.2, 128.7, 128.2, and 126.6 (Ph-C), 70.8 (Ph_3C), 46.1 (C-3 and C-3'), 42.3 (C-2 and C-2'), 26.6 (C-1 and C-1') and 23.8 (C-4 and C-4') ppm

Compound (32)

White solid; R_f (PhMe/ AcOEt 6:4) 0.25; m.p. 157.5-159.5 °C;

ESI-MS (m/z) : 826.62 ($M+H^+$), 848.66 ($M+Na^+$), 243.20 (Trt^+);

1H NMR : δ 7.40 – 7.16 (30H, m, Ph-*H*), 4.33 (4H, t, J 4.8 Hz, H-2 and H-2'), 3.67 (4H, t, J 4.8 Hz, H-1 and H-1'), 3.26 (4H, s, H-5 and H-5'), 2.99 (4H, t, J 6.4 Hz, H-4 and H-4'), 2.58 (4H, t, J 6.4 Hz, H-3 and H-3'), 2.36 (2H, br. s, NH);

^{13}C NMR: 154.9 (C-6 and C-6'), 145.7, 128.5, 127.9 and 126.4 (Ph-C), 70.3 (Ph_3C), 69.0 (C-4, C-4', C-4 and C-5'), 47.0 (C-3 and C-3'), 41.4 (C-2 and C-2') and 24.6 (C-1 and C-1') ppm

Compound (36)

Foam; R_f (PhMe/ AcOEt 7:3) 0.45; ESI-MS (m/z) : 876.76 ($M+H^+$), 243.20 (Trt^+);

1H NMR: δ 7.42 – 7.14 (38H, m Ph-*H*, Ar-*H*), 4.20 (2H s, H-8), 3.04 (4H, t, J 6.4 Hz, H-2), 2.58 (4H, t, J 6.4 Hz, H-1)

^{13}C NMR ($CDCl_3$): 153.8 (C-3), 145.3, 128.2, 127.6, 126.2 (Ph-C), 142.2 (C-4), 132.1 (C-7), 130.1 (C-5), 125.1 (C-6), 70.7 (Ph_3C), 41.2 (C-2), 40.8 (C-8), 24.9 (C-1) ppm