SUPPORTING INFORMATION

A novel convenient synthesis of benzoquinazolines

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General Information. All commercial chemicals and solvents used were analytical grade and were used without further purification. Melting point (uncorrected) were determined using a Gallenkamp MFB-595-010M capillary melting point apparatus. Analytical thin layer chromatography (tlc) was performed on pre-coated silica gel plates (Merck 60-F-254, 0.25 mm), which were developed with a mixture of chloroform/ethanol (9/1). The ¹H-NMR and the ¹³C-NMR spectra were recorded on a Bruker 300-AMX spectrometer with TMS as an internal standard and DMSO-*d*₆ as solvent, unless otherwise indicated. Coupling constants are given in Hz and the relative peak areas and the decoupling experiments were in agreement with all assignments. Elemental analyses were performed on a Perkin-Elmer 2400 analyser. Mass spectra for final compounds were performed on a Applied Biosystem Mariner System 5220 with direct injection of the sample.

Analytical data for compounds **2b**¹, **4b**², **6b**³, and **7b**² were compared with literature data.

Ethyl (4-bromonaphthalen-2-yl)carbamate (**2a**)

A mixture of 4-bromo-2-naphthylamine (**1a**) (5.3 g, 23.9 mmol), ethyl chloroformate (4.6 mL, 47.8 mmol), and TEA (6.7 mL, 47.8 mmol) in anhydrous THF (200 mL) was stirred at room temperature for 1 hour. The solid was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and the organic phase was washed with water (2 x 100 mL). The organic phase was evaporated under reduced pressure to give **2a** (7.0 g, quantitative yield), as an oil: ¹H-NMR: δ 9.98 (s, 1 H, NH), 8.09 (d, J=1.3, 1 H, 3-H), 8.02-7.98 (m, 2 H, 1-H and 5-H or 8-H), 7.86-7.83 (m, 1 H, 5-H or 8-H), 7.58-7.50 (m, 2 H, 6-H and 7-H), 4.18 (q, J=7.1, 2 H, CH₂CH₃), 1.27 (t, J=7.1, 3 H, CH₂CH₃); anal. calcd. for C₁₃H₁₂BrNO₂: C, 53.08; H, 4.11; Br, 27.16; N, 4.76; found: C, 53.12; H, 4.08; Br, 27.09; N, 4.85.

Ethyl 6-bromo-3H-benzo[f]quinazolin-4-carboxylate (**3a**)

A mixture of **2a** (2.4 g, 8.2 mmol) and hexamethylenetetramine (7.6 g, 54.2 mmol) in TFA (10 mL) was refluxed for 1 hour. After cooling, the mixture was diluted with cold water (100 mL), neutralized with NaHCO₃ and extracted with EtOAc (3 x 50 mL). The organic phase was evaporated under reduced pressure and the residue was treated with cyclohexane (50 mL). The undissolved solid was filtered off and the solution was evaporated under reduced pressure to give **3a** (2.2 g, 81%): mp 103°C; ¹H-NMR: δ 9.18 (s, 1 H, 1-H), 8.49 (d, J=8.2, 1 H, 10-H), 8.23 (s, 1 H, 5-H), 8.18 (d, J=8.2, 1 H, 7-H), 7.77-7.69 (m, 2 H, 8-H and 9-H), 5.28 (s, 2 H, 3-H), 4.25 (q, J=7.0, 2 H, CH₂CH₃), 1.28 (t, J=7.0, 3 H, CH₂CH₃); anal. calcd. for C₁₅H₁₃BrN₂O₂: C, 54.07; H, 3.93; Br, 23.98; N, 8.41; found: C, 53.98; H, 3.95; Br, 24.00; N, 8.39.

6-Bromobenzo[f]quinazoline (**4a**)

From compound 3a. A mixture of **3a** (1.0 g; 3.0 mmol) in aqueous ethanolic (water/EtOH: 1/1) 10% KOH (150 mL) was refluxed for 1 hour. After cooling, K₃Fe(CN)₆ (5.0 g; 15.2 mmol) was added and the mixture was refluxed for 4 hour. After cooling, the mixture was diluted with water (300 mL), extracted with toluene (4 x 100 mL), and the organic phase was evaporated under reduced pressure. The residue was dissolved in the minimum amount of MeOH (25 mL) and diluted with water (75 mL). The precipitate was collected and washed with water to give **4a** (0.06 g; 8%):

mp 147°C; ¹H-NMR: δ 10.43 (s, 1 H, 1-H), 9.44 (s, 1 H, 3-H), 9.13 (br d, J=8.9, 1 H, 10-H), 8.40 (br d, J=8.9, 7-H), 8.34 (s, 1 H, 5-H), 7.98-7.95 (m, 2 H, 8-H and 9-H); ¹³C-NMR: δ 156.45, 155.38, 150.03, 130.33, 129.65, 129.53 (2C), 129.46, 128.66, 127.66, 123.27, 121.14; HRMS (ESI-TOF) for C₁₂H₈BrN₂ (M⁺+1): calcd.: 258.9452, found: 258.9865; anal. calcd. for C₁₂H₇BrN₂: C, 55.63; H, 2.72; Br, 30.84; N, 10.81; found: C, 55.66; H, 2.68; Br, 30.79; N, 10.87.

From compound 2a. A mixture of **2a** (7.0 g, 23.8 mmol) and hexamethylenetetramine (23.4 g, 166.7 mmol) in TFA (150 mL) was refluxed for 1 hour. After cooling, the mixture was diluted with 4M HCl (800 mL), the undissolved solid was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in aqueous ethanolic (water/EtOH: 1/1) 10% KOH (700 mL), added with K₃Fe(CN)₆ (50.0 g, 151.9 mmol) and refluxed for 4 hours. After cooling, the mixture was diluted with water (700 mL), extracted with toluene (5 x 200 mL), and the organic phase was evaporated under reduced pressure. The residue was dissolved in the minimum amount of MeOH (50 mL) and diluted with water (150 mL). The precipitate was collected and washed with water to give **4a** (1.0 g, 16%).

Ethyl (naphthalen-2-yl)carbamate (2b)

A mixture of 2-naphthylamine (**1b**) (1.0 g, 7.0 mmol), ethyl chloroformate (1.4 mL, 14.0 mmol), and TEA (1.9 mL, 14.0 mmol) in anhydrous THF (100 mL) was stirred at room temperature for 1 hour. The solid was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with water (2 x 50 mL). The organic phase was evaporated under reduced pressure to give **2b** (1.5 g, quantitative yield); mp 95°C; ¹H-NMR: δ 9.82 (s, 1 H, NH), 8.06 (d, J=1.9, 1 H, 1-H), 7.82 (d, J=8.9, 1 H, 4-H), 7.81 (dd, J=6.9 and 1.2, 1 H, 5-H or 8-H), 7.77 (dd, J=6.9 and 1.2, 1 H, 5-H or 8-H), 7.53 (dd, J=8.9 and 1.9, 1 H, 3-H), 7.45 (td, J=6.9 and 1.2, 1 H, 6-H or 7-H), 7.36 (td, J=6.9 and 1.2, 1 H, 6-H or 7-H), 4.17 (q, J=7.1, 2 H, CH₂CH₃), 1.27 (t, J=7.1, 3 H, CH₂CH₃); anal. calcd. for C₁₃H₁₃NO₂: C, 72.54; H, 6.09; N, 6.51; found: C, 72.60; H, 6.02; N, 6.49.

Benzo[f]quinazoline (4b)

A mixture of **2b** (1.5 g, 7.0 mmol) and hexamethylenetetramine (6.9 g, 49.2 mmol) in TFA (50 mL) was refluxed for 1 hour. After cooling, the mixture was diluted with 4M HCl (500 mL), the insoluble residue was filtered off, and the solution was evaporated under reduced pressure. The solid was dissolved in aqueous ethanolic (water/EtOH: 1/1) 10% KOH (250 mL), added with K₃Fe(CN)₆ (17.5 g, 53.2 mmol) and refluxed for 4 hours. After cooling, the mixture was diluted with water (450 mL) and extracted with toluene (5 x 200 mL). The organic phase was evaporated under reduced pressure to give **4b** (1.2 g, 95%); mp 102°C; ¹H-NMR: δ 10.39 (s, 1 H, 1-H), 9.41 (s, 1 H, 3-H), 9.03 (d, J=8.6, 1 H, 10-H), 8.38 (d, J=9.1, 1 H, 6-H), 8.14 (d, J=7.4, 1 H, 7-H), 7.85 (d, J=9.1, 1 H, 5-H), 7.82 (dd, J=8.6 and 8.0, 1 H, 9-H), 7.76 (dd, J=8.0 and 7.4, 1 H, 8-H); ¹³C-NMR: 155.89; 155.01; 150.58; 135.93; 131.22; 128.88; 128.48; 128.28; 127.99; 125.82; 122.67; 121.46; HRMS (ESI-TOF) for C₁₂H₉N₂ (M⁺+1): calcd.: 181.0760, found: 181.0726; anal. calcd. for C₁₂H₈N₂: C, 79.98; H, 4.47; N, 15.55; found: C, 80.01; H, 4.44; N, 15.55.

Ethyl (4-bromonaphthalen-1-yl)carbamate (6a)

A mixture of 4-bromo-1-naphthylamine (**5a**) (7.1 g, 32.0 mmol), ethyl chloroformate (12.2 mL, 128.0 mmol), and TEA (17.8 mL, 128.0 mmol) in anhydrous THF (300 mL) was refluxed for 1 hour. After cooling, the solid was filtered off and the solution was evaporated under reduced pressure. The residue was treated with EtOAc (200 mL) and washed with water (2 x 100 mL). The organic phase was evaporated under reduced pressure to give **6a** (9.4 g, quantitative yield); mp 143°C; ¹H-NMR (CDCl₃): δ 8.28 (dd, J=8.2 and 2.1, 1 H, 8-H), 7.88 (dd, J=8.2, J=2.1, 1 H, 5-H), 7.77 (s, 2 H, 2-H and 3-H), 7.65-7.55 (m, 2 H, 6-H and 7-H), 6.90 (br s, 1 H, NH), 4.28 (q, J=7.1, 2 H, CH₂CH₃), 1.35 (t, J=7.1, 3 H, CH₂CH₃); anal. calcd. for C₁₃H₁₂BrNO₂: C, 53.08; H, 4.11; Br, 27.16; N, 4.76; found: C, 52.98; H, 4.10; Br, 27.20; N, 4.80.

6-Bromobenzo[h]quinazoline (7a)

A mixture of **6a** (4.9 g, 16.7 mmol) and hexamethylenetetramine (16.4 g, 117.0 mmol) in TFA (100 mL) was refluxed for 1 hour. After cooling, the mixture was diluted with HCl 4M (800 mL), the insoluble residue was filtered off, and the solution was evaporated under reduced pressure. The solid was dissolved in aqueous ethanolic (water/EtOH: 1/1) 10% KOH (500 mL), added with $K_3Fe(CN)_6$ (40.0 g, 121.5 mmol) and refluxed for 4 hours. After cooling, the mixture was diluted with water (700 mL), extracted with toluene (5 x 300 mL), and the organic phase was evaporated under reduced pressure. The residue was dissolved in the minimum amount of MeOH (50 mL) and diluted with water (150 mL). The precipitate was collected and washed with water to give **7a** (1.0 g, 23%); mp 115°C; 1H -NMR: δ 9.58 (s, 1 H, 4-H), 9.52 (s, 1 H, 2-H), 9.26 (d, $J=7.7$, 1 H, 10-H), 8.50 (s, 1 H, 5-H), 8.36 (d, $J=7.7$, 1 H, 7-H), 8.07 (t, $J=7.7$, 1 H, 8-H or 9-H), 7.97 (t, $J=7.7$, 1 H, 8-H or 9-H); ^{13}C -NMR: δ 158.12; 155.64; 148.39; 132.71; 131.58; 130.03; 128.64; 127.09; 126.95; 124.30; 123.04; 122.24; HRMS (ESI-TOF) for $C_{12}H_8BrN_2$ (M^++1): calcd.: 258.9865; found: 258.9467; anal. calcd. for $C_{12}H_7BrN_2$: C, 55.63; H, 2.72; Br, 30.84; N, 10.81; found: C, 55.57; H, 2.69; Br, 30.90; N, 10.84.

Ethyl (naphthalen-1-yl)carbamate (6b)

A mixture of 1-naphthylamine (**5b**) (1.0 g, 7.0 mmol), ethyl chloroformate (2.7 mL, 28.0 mmol), and TEA (3.9 mL, 28.0 mmol) in anhydrous THF (100 mL) was refluxed for 1 hour. After cooling, the solid was filtered off and the solution was evaporated under reduced pressure. The residue was treated with EtOAc (100 mL) and washed with water (2 x 50 mL). The organic phase was evaporated under reduced pressure to give **6b** (1.5 g, 99%); mp 79°C; 1H -NMR ($CDCl_3$): δ 7.89-7.85 (m, 3 H, 2-H, 4-H and 5-H), 7.67 (d, $J=8.2$, 1 H, 8-H), 7.58-7.43 (m, 3 H, 3-H, 6-H and 7-H), 4.29 (q, $J=7.2$, 2 H, $\underline{CH_2CH_3}$), 1.35 (t, $J=7.2$, 3 H, $\underline{CH_2CH_3}$); anal. calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51; found: C, 72.58; H, 6.06; N, 6.58.

Benzo[h]quinazoline (7b) and ethyl (4-formylnaphthalen-1-yl)carbamate (8)

A mixture of **6b** (1.5 g, 7.0 mmol) and hexamethylenetetramine (6.9 g, 49.0 mmol) in TFA (50 mL) was refluxed for 1 hour. After cooling, the mixture was diluted with HCl 4M (500 mL), the precipitate was collected to give **8** (0.8 g, 47%), and the solution was evaporated under reduced pressure. The solid was dissolved in aqueous ethanolic (water/EtOH: 1/1) 10% KOH (250 mL), added with $K_3Fe(CN)_6$ (17.5 g, 53.2 mmol) and refluxed for 4 hours. After cooling, the mixture was diluted with water (450 mL), extracted with toluene (5 x 200 mL), and the organic phase was evaporated under reduced pressure. The residue was dissolved in the minimum amount of butan-2-one (50 mL), filtering off the insoluble residue. The solution was evaporated under reduced pressure to give **7b** in traces.

Compound **8**: 1H -NMR ($CDCl_3$): δ 10.25 (s, 1 H, CHO), 9.40 (dd, $J=8.3$ and 1.1, 1 H, 8-H), 8.29 (d, $J=8.1$, 1 H, 2-H or 3-H), 7.98 (d, $J=8.1$, 1 H, 2-H or 3-H), 7.90 (dd, $J=8.3$ and 1.1, 1 H, 5-H), 7.72 (td, $J=8.3$, $J=1.1$, 1 H, 6-H or 7-H), 7.63 (td, $J=8.3$ and 1.1, 1 H, 6-H or 7-H), 7.45 (br s, 1 H, NH), 4.34 (q, $J=7.1$, 2 H, $\underline{CH_2CH_3}$), 1.39 (t, $J=7.1$, 3 H, $\underline{CH_2CH_3}$); anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H 5.39; N, 5.76; found: C, 69.22; H, 5.38; N, 5.72.

Compound **7b**: 1H -NMR ($CDCl_3$): δ 9.42 (s, 1 H, 4-H), 9.28 (s, 1 H, 2-H), 9.21 (d, $J=8.4$, 1 H, 10-H), 7.89 (d, $J=8.4$, 1 H, 7-H), 7.82 (d, $J=8.9$, 1 H, 5-H or 6-H), 7.77-7.73 (m, 2 H, 8-H and 9-H), 7.64 (d, $J=8.9$, 1 H, 5-H or 6-H); HRMS (ESI-TOF) for $C_{12}H_9N_2$ (M^++1): calcd.: 181.0760, found: 181.0784; anal. calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.55; found: C, 79.88; H, 4.53; N, 15.59.

References

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