Synthesis of novel benzimidazo[1,2-*c*][1,2,4]triazolo[4,3-*a*]quinazoline derivatives

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Cyclocondensation of 2-(1*H*-benzimidazol-2-yl)anilines **1a,b** with carbon disulfide in the presence of potassium *t*-butoxide in boiling DMF afforded the corresponding benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thiones **2a,b**. Treatment of these compounds with hydrazine hydrate at reflux in ethanol gave the hydrazine derivatives **3a,b** which were subsequently cyclised to the title compounds **4a–f** on heating with orthoesters in ethanol.

Keywords: fused benzimidazoles, 1,2,4-triazoles, quinazolines

Benzimidazole derivatives show a variety of biological activities such as antibacterial, antitumor, antiviral and antitubercular activity.[1-4] These compounds are an important class of nitrogen heterocycles and they constitute useful intermediates in organic synthesis.[5] In connection with our interest in the synthesis of nitrogen and sulfur heterocycles of biological significance,[6] we recently reported the synthesis of some new polyheterocyclic compounds.[7] Arising from these studies, we now report the synthesis of some novel pentacyclic fused benzimidazole derivatives from benzimidazole intermediates.

Results and discussion

Our approach is based on the use of 2-(1*H*-benzimidazol-2-yl)anilines (**1a,b**) as starting materials. Reaction of these compounds with carbon disulfide in the presence of potassium *t*-butoxide in boiling DMF gave the corresponding benzimidazo[1,2-*c*]quinazolin-6(5*H*)-thiones (**2a,b**) in high yield. The synthesis of this heterocyclic ring system from cyclocondensation of **1a,b** with several electrophilic reagents such as acetic acid, acetone and isocyanates has been reported earlier.[8]

The thione derivatives **2a,b** were then refluxed with hydrazine hydrate in ethanol to give the hydrazine derivatives **3a,b**. These compounds were subsequently cyclised to new pentacyclic fused benzimidazoles **4a–f** when heated with orthoesters in ethanol (Scheme 1). The structural assignments of compounds **4a–f** was based upon the spectral and microanalytical data (see Experimental section). For example, the ^{1}H NMR spectrum of **4a** did not show the NH_2 and NH signals of the precursor **3a** but showed a sharp 1H signal at δ = 9.8 ppm from the triazole ring, indicating the formation of the pentacyclic compound **4a**.

In conclusion, we describe the synthesis of a novel heterocyclic ring system through heterocyclisation of the hydrazines **3a,b** with orthoesters in boiling ethanol.

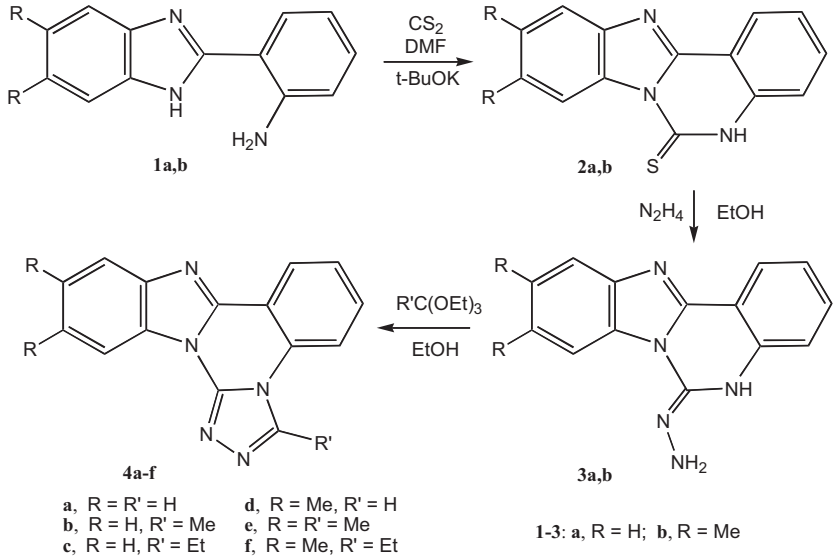
Experimental

The melting points were measured on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance DRX -500 spectrometer. The mass spectra were obtained on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a ThermoFinnigan Flash EA microanalyser.

The benzimidazol-2-ylanilines **1a**,**b** were prepared as described by Zaikia and Joullié.[9]

Typical procedure for the preparation of **2**

A mixture of 2-(1*H*-benzimidazol-2-yl)aniline **1a** (2.09 g, 10 mmol) and carbon disulfide (1.2 ml, 20 mmol) in DMF (10 ml) containing potassium *t*-butoxide (1.12 g, 10 mmol) was heated under reflux for 8 hours. After cooling the reaction mixture, water was added, the precipitate was filtered and recrystallised from ethanol to give 1.88 g



Scheme 1

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of **2a** as white crystals (75%). The thione **2b** was similarly prepared from **1b**.

Benzimidazo[1,2-c]quinazoline-6(5H)-thione (**2a**): M.p. 305–307°C (Lit.[10] 308–310°C). FT IR (KBr, ν_{max}/cm^{-1}) 3190 (NH). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 7.5–8.5 (m, 8H, aromatic rings), 9.4 (broad, 1H, NH). MS: *m/z* 251 (M^+, 4), 250 (10), 249 (19), 248 (53), 247 (100), 246 (96), 215 (12), 188 (13), 157 (15), 123 (32), 100 (15), 89 (28), 62 (18).

9,10-Dimethylbenzimidazo[1,2-c]quinazoline-6(5H)-thione (**2b**): White crystals (2.18 g, 78%), m.p. 294–296°C. FT IR (KBr, ν_{max}/cm^{-1}): 3200 (NH). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 7.4–8.5 (m, 6H, aromatic rings), 9.1 (broad, 1H, NH). MS: *m/z* 279 (M^+, 8), 278 (15), 276 (83), 275 (100), 215 (10), 245 (31), 187 (14), 121 (17), 100 (12), 89 (37), 64 (19). Found: C, 68.32; H, 4.88; N, 14.81. Calc. for $C_{16}H_{13}N_3S$ (279): C, 68.79; H, 4.69; N, 15.04%.

Typical procedure for the preparation of **3**

A mixture of benzimidazo[1,2-*c*]quinazolin-6(5*H*)-thione **2a** (2.51 g, 10 mmol) and hydrazine hydrate (2.0 ml) in ethanol (15 ml) was heated under reflux for 10 hours. The reaction mixture was cooled to room temperature and the precipitate was filtered and recrystallised from ethanol to give **3a** (1.99 g, 80%) as white crystals.

6-Hydrazinobenzimidazo[1,2-c]quinazoline (**3a**): M.p. 206–208°C. FT IR (KBr, ν_{max}/cm^{-1}): 3150–3300 (NH and NH_2). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 7.1–8.7 (m, 10H, aromatic rings and NH_2), 10.8 (br. s, 1H, NH). MS: *m/z* 249 (M^+, 4), 248 (16), 247 (13), 246 (72), 245 (100), 244 (96), 228 (39), 216 (93), 215 (91), 188 (14), 140 (12), 100 (24), 89 (42), 76 (16), 64 (27). Found: C, 67.74; H, 4.62; N, 28.02. Calc. for $C_{14}H_{11}N_5$ (249): C, 67.46 H, 4.45; N, 28.10%.

6-Hydrazino-9,10-dimethylbenzimidazo[1,2-c]quinazoline (**3b**): White crystals (2.16 g, 78%), m.p. 199–201°C. FT IR (KBr, ν_{max}/cm^{-1}): 3100–3300 (NH and NH_2). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.1–8.7 (m, 8H, aromatic rings and NH_2), 10.7 (br s, 1H, NH). MS: *m/z* 277 (M^+, 4), 276 (6), 275 (14), 274 (23), 273 (100), 272 (49), 245 (56), 228 (10), 116 (12), 101 (25), 89 (15), 75 (26). Found: C, 69.07; H, 5.74; N, 25.11. Calc. for $C_{16}H_{15}N_5$ (277): C, 69.29; H, 5.45; N, 25.25%.

Typical procedure for the preparation of **4**

A mixture of 6-hydrazinobenzimidazo[1,2-*c*]quinazoline **3a** (1.0 g, 4 mmol) and triethyl orthoformate (1.6 ml, 10 mmol) in ethanol (15 ml) was heated under reflux for 1 hours. After completion of the reaction, which was monitored by TLC**,** the mixture was cooled and the precipitate was filtered off and recrystallised from ethanol to give **4a** (0.73 g, 70%) as white crystals.

Benzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazoline(**4a**):M.p.360–362°C. NMR ([$^2H_6$]DMSO, TMS): δ_H 7.5–8.7 (m, 8H, aromatic ring H), 9.8 (s, 1H, triazole CH). δ_C 112.0, 118.8, 119.3, 122.9, 123.7, 125.7, 128.1, 128.3, 128.4, 128.5, 131.8, 138.5, 142.3, 143.4, 145.5. MS: *m/z* 259 (M^+, 3), 257 (4), 256 (7), 255 (40), 254 (100), 253 (98), 226 (15), 199 (8), 125 (7), 100 (10), 88 (11), 79 (13), 56 (10). Found: C, 69.37; H, 3.66; N, 26.88. Calc. for $C_{15}H_9N_5$ (259): C, 69.49; H, 3.50; N, 27.01%.

3-Methylbenzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazoline (**4b**): White crystals (0.82 g, 75%), m.p. 346–348°C. NMR ([$^2H_6$]DMSO, TMS): δ_H 3.1 (s, 3H, CH_3), 7.6–8.8 (m, 8H, aromatic rings). δ_C 23.6, 115.1, 117.6, 119.4, 122.8, 123.6, 125.2, 127.1, 127.3, 127.4, 129.3, 131.7, 141.9, 143.8, 146.9, 148.6. MS: *m/z* 273 (M^+, 5), 271 (7), 270 (28), 269 (100), 268 (69), 227 (29), 125 (8), 100 (15), 88 (16), 75 (13). Found: C, 70.21; H, 4.18; N, 25.49. Calc. for $C_{16}H_{11}N_5$ (273): C, 70.32; H, 4.06; N, 25.63%.

3-Ethylbenzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazoline (**4c**): White crystals (0.8 g, 70%), m.p. 319–321°C. NMR ([$^2H_6$]DMSO, TMS): δ_H 1.55 (t, *J* = 6 Hz, 3H, CH_3), 3.3 (q, *J* = 6 Hz, 2H, CH_2), 7.6–8.7 (m, 8H, aromatic ring H). δ_C: 9.8, 28.4, 115.4, 117.6, 119.4, 122.9, 123.6, 125.1, 127.2, 127.3, 127.5, 128.8, 131.7, 141.7, 143.8, 146.9, 152.1. MS: *m/z* 287 (M^+, 5), 286 (8), 285 (18), 284 (71), 283 (100), 282 (66), 281(20), 268 (14), 227 (13), 140 (13), 125 (10), 100 (14), 88 (15), 75 (14), 56 (19). Found: C, 71.13; H, 4.43; N, 24.28. Calc. for $C_{17}H_{13}N_5$ (287): C, 71.06; H, 4.56; N, 24.37%.

11,12-Dimethylbenzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazoline (**4d**): White crystals (0.93 g, 81%), m.p. 352–354°C. ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 7.6–8.6 (m, 6H, aromatic ring H), 9.8 (s, 1H, CH of triazole ring). MS: *m/z* 287 (M^+, 4), 286 (6), 285 (25), 284 (96), 283 (100), 282 (68), 268 (29), 254 (21), 140 (19), 125 (12), 113 (13), 83 (15), 69 (19), 55 (35), 42 (37). Found: C, 70.91; H, 4.64; N, 24.25. Calc. for $C_{17}H_{13}N_5$ (287): C, 71.06; H, 4.56; N, 24.37%.

3,11,12-Trimethylbenzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazoline (**4e**): White crystals (0.94 g, 78%), m.p. 339–341°C. ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.4 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 7.6–8.7 (m, 6H, aromatic ring H). MS: *m/z* 301 (M^+, 5), 299 (38), 298 (100), 297 (98), 296 (36), 282 (15), 254 (20), 240 (15), 147 (8), 114 (10), 89 (8), 56 (20), 42 (26). Found: C, 71.53; H, 5.21; N, 23.05. Calc. for $C_{18}H_{15}N_5$ (301): C, 71.74; H, 5.02; N, 23.24%.

3-Ethyl-11,12-dimethylbenzimidazo[1,2-c][1,2,4]triazolo[4,3-a]quinazoline (**4f**): White crystals (0.92 g, 73%), m.p. 308–310°C. ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 1.48 (t, *J* = 7 Hz, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 2.7 (q, *J* = 7 Hz, 2H, CH_2), 7.6-8.7 (m, 6H, aromatic ring H). MS: *m/z* 315 (M^+, 8), 314 (37), 313 (97), 312 (100), 311 (98), 297 (25), 254 (36), 240 (26), 154 (21), 114 (24), 100 (20), 82 (31), 56 (32), 42 (22). Found: C, 72.22; H, 5.51; N, 22.13. Calc. for $C_{19}H_{17}N_5$ (315): C, 72.36; H, 5.43; N, 22.21%.

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