Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2006, **16(1)**, 29–30
Mendeleev Communications

Synthesis of dibenzo[*b*,*g*][1,5]diazoninedione and isoindolo[2,1-*a*]quinazoline derivatives

Mehdi Bakavoli,*[a,b] Abolghasem Davoodnia,[b] Mohammad Rahimizadeh[a] and Majid M. Heravi[a,c]

[a] *Department of Chemistry, School of Sciences, Ferdowsi University, 91779 Mashhad, Iran. Fax: +98 511 843 8032; e-mail: mbakavoli@yahoo.com*
[b] *Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad, Iran*
[c] *Department of Chemistry, School of Sciences, Azzahra University, Tehran, Iran*

DOI: 10.1070/MC2006v016n01ABEH002177

Starting from 2-aminobenzonitrile 1 and 2-chloromethylbenzoyl chloride 2, a new synthetic pathway to tetracyclic compound 6 is described. Reaction of 2-aminobenzamide 7 with compound 2 leads to the tricyclic ring system 9 which was easily converted to compound 6 in the presence of KOH in refluxing H_2O–EtOH.

Our interest in polycyclic N-heterocyclic compounds[1,2] led us to the synthesis of isoindolo[2,1-*a*]quinazoline **6** and dibenzo[*b*,*g*][1,5]diazoninedione **9**. Isoindoloquinazolines are usually prepared by the cyclocondensation of anthranyl amide with either phthalic anhydride[3–5] or 2-ketobenzoic acid.[6] Other procedures involve the heterocyclisation of 2-aminobenzylamine with phthalaldehyde[7,8] or anthranilic acid with 2-chloromethylbenzonitrile.[9]

The synthesis of tricyclic compound **9** was described previously.[10] Inspired by this fact and due to few reports on the biological activities of these polycyclic N-heterocycles,[11,12] we deemed it interesting to look for specific routes to new derivatives of dibenzodiazoninediones and isoindoloquinazolinones.

Our approach is based on the use of 2-chloromethylbenzoyl chloride **2** as a starting material. Reaction of this compound with benzonitriles **1** in boiling dichloromethane involves a nucleophilic attack of the NH_2 group on the acyl carbonyl group[13–15] to give corresponding 2-(chloromethyl)-*N*-(2-cyanophenyl)benzamides **3** (Scheme 1).† These products were cyclised to the corresponding tetracyclic compounds, isoindolo[2,1-*a*]-quinazolinones **6**, by two methods.‡

Method A involves transformation of compounds **3** into isoindolylbenzonitriles **4**§ and cyclisation of these latter compounds through a cyclocondensation reaction. The process was carried out by refluxing compounds **3** in the presence of potassium *tert*-butoxide in *tert*-butanol with subsequent treatment of products **4** in a boiling aqueous ethanolic potassium hydroxide solution.

Method B consists of a direct intramolecular heterocyclisation of compounds **3** by ethanolic potassium hydroxide. The reaction was carried out by refluxing a mixture of potassium

† The melting points were measured on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC l00 spectrometer. The mass spetra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermofinnigan Flash EA microanalyzer.

Typical procedure for the preparation of **3a**. 2-Chloromethylbenzoyl chloride **2** (4.54 g, 24 mmol) was gradually added to a boiling solution of 2-aminobenzonitrile **1a** (2.36 g, 20 mmol) in dichloromethane (25 ml). Heating was continued for 3 h. After completion of the reaction, as monitored by TLC, the mixture was filtered. The solvent was evaporated to dryness, and the residue was crystallised from ethanol to yield 4.33 g of **3a** as a white solid (80%).

2-(Chloromethyl)-N-*(2-cyanophenyl)benzamide* **3a**: mp 169–171 °C. ^{1}H NMR ($CDCl_3$, TMS) δ: 8.47 (d, 1H, aromatic ring), 8.13 (br. s, 1H, NH), 7.25–7.75 (m, 7H, aromatic rings), 4.91 (s, 2H, CH_2Cl). FT-IR (KBr, ν/cm^{-1}): 3209 (NH), 2230 (CN), 1651 (CO). MS, *m*/*z*: 270 [M]$^+$. Found (%): C, 66.59; H, 4.07; N, 10.31. Calc. for $C_{15}H_{11}ClN_2O$ (270.5) (%): C, 66.55; H, 4.10; N, 10.35.

N-*(4-Chloro-2-cyanophenyl)-2-(chloromethyl)benzamide* **3b**: white solid (4.6 g, 75%), mp 131–133 °C. ^{1}H NMR ($CDCl_3$, TMS) δ: 8.47 (d, 1H, aromatic ring), 8.11 (br. s, 1H, NH), 7.3–7.8 (m, 6H, aromatic rings), 4.89 (s, 2H, CH_2Cl). FT-IR (KBr, ν/cm^{-1}): 3239 (NH), 2230 (CN), 1646 (CO). MS, *m*/*z*: 304 [M]$^+$. Found (%): C, 59.01; H, 3.25; N, 9.22. Calc. for $C_{15}H_{10}Cl_2N_2O$ (305) (%): C, 59.04; H, 3.30; N, 9.18.

‡ *Typical procedure for the preparation of* **6a**.

Method A. Compound **3a** (1.17 g, 5 mmol) in a mixture of ethanol (20 ml), water (10 ml) and potassium hydroxide (0.34 g, 6 mmol) was heated under reflux for 5 h. After cooling the reaction mixture, the precipitate was filtered off, washed with chloroform and recrystallised from ethanol to yield 0.79 g of **6a** as a white powder (68%).

*11*H-*Isoindolo[2,1-*a*]quinazolin-5-one* **6a**: mp 280–282 °C (lit.,[16] mp 274–277 °C). ^{1}H NMR ($CDCl_3$, TMS) δ: 7.4–8.2 (m, 8H, aromatic rings), 5.43 (s, 2H, CH_2). FT-IR (KBr, ν/cm^{-1}): 1651 (CO). MS, *m*/*z*: 234 [M]$^+$. Found (%): C, 76.95; H, 4.35; N, 11.90. Calc. for $C_{15}H_{10}N_2O$ (234) (%): C, 76.91; H, 4.30; N, 11.96.

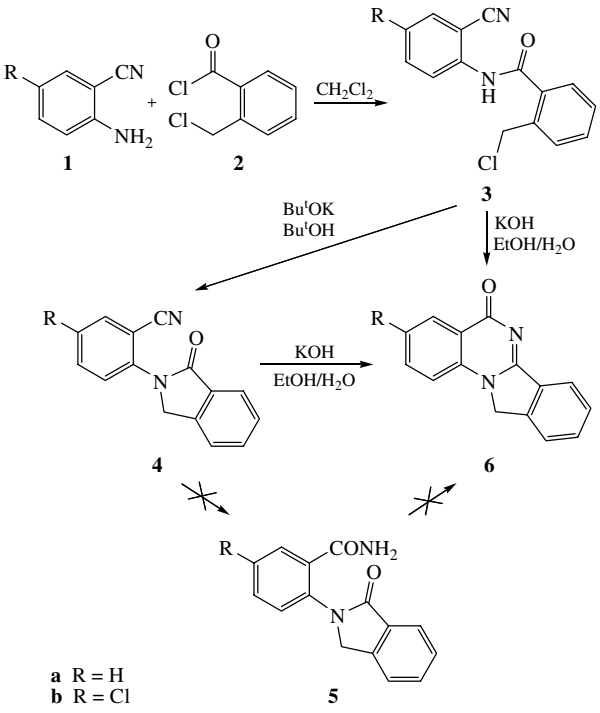
*3-Chloro-11*H-*isoindolo[2,1-*a*]quinazolin-5-one* **6b**: white solid (0.88 g, 66%), mp 272–274 °C. ^{1}H NMR ([$^2H_6$]DMSO, TMS) δ: 7.45–8.15 (m, 7H, aromatic rings), 5.426 (s, 2H, CH_2). FT-IR (KBr, n/cm^{-1}): 1645 (CO). MS, *m*/*z*: 268 [M]$^+$. Found (%): C, 67.10; H, 3.32; N, 10.40. Calc. for $C_{15}H_9ClN_2O$ (268.5) (%): C, 67.05; H, 3.38; N, 10.43.

Method B. Compounds **4a** and **4b** were treated as in *Method A* to yield desired **6a** and **6b**, respectively.

§ *Typical procedure for the preparation of* **4a**. Compounds **3a** (1.35 g, 5 mmol) in *tert*-butanol (30 ml) and potassium *tert*-butoxide (0.56 g, 5 mmol) were heated under reflux for 4 h. After the reaction was ceased, water was added, the precipitate was filtered off and recrystallised from benzene–petroleum ether to yield 0.84 g of **4a** as a white solid (72%).

*2-(1-Oxo-1,3-dihydro-2*H-*isoindol-2-yl)benzonitrile* **4a**: mp 177–179 °C. ^{1}H NMR ($CDCl_3$, TMS) δ: 7.2–8.05 (m, 8H, aromatic rings), 5.0 (s, 2H, CH_2). FT-IR (KBr, ν/cm^{-1}): 2235 (CN), 1690 (CO). MS, *m*/*z*: 234 [M]$^+$. Found (%): C, 76.97; H, 4.28; N, 11.91. Calc. for $C_{15}H_{10}N_2O$ (234) (%): C, 76.91; H, 4.30; N, 11.96.

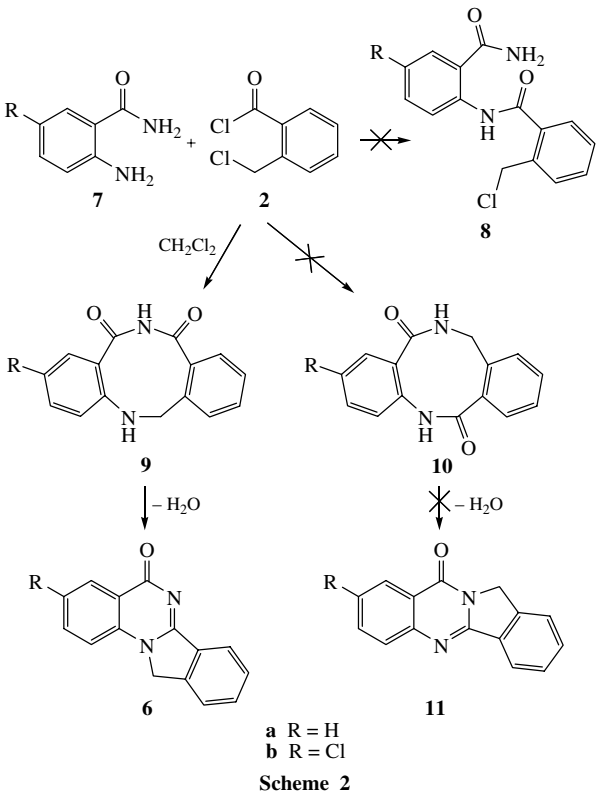
*5-Chloro-2-(1-oxo-1,3-dihydro-2*H-*isoindol-2-yl)benzonitrile* **4b**: white solid (0.85 g, 63%), mp 252–254 °C. ^{1}H NMR ([$^2H_6$]DMSO, TMS) δ: 7.5–8.2 (m, 7H, aromatic rings), 5.06 (s, 2H, CH_2). FT-IR (KBr, ν/cm^{-1}): 2236 (CN), 1691 (CO). MS, *m*/*z*: 268 [M]$^+$. Found (%): C, 67.01; H, 3.35; N, 10.48. Calc. for $C_{15}H_9ClN_2O$ (268.5) (%): C, 67.05; H, 3.38; N, 10.43.



Scheme 1

hydroxide and 2-(chloromethyl)-*N*-(2-cyanophenyl)benzamides **3** in aqueous ethanol (Scheme 1). In both methods, the tetracyclic compounds (isoindoloquinazolinones) were obtained in good yields and their structures were confirmed by spectral and microanalytical data.

Note that, in this multi-step synthesis, likely key intermediate **5** was not isolated. It seems likely that hydrolysis of the nitrile group into amide and ring closure occur simultaneously. A study to isolate this intermediate was carried out to monitor the formation of tetracyclic compounds **6**. As shown in Scheme 2, 2-aminobenzamides **7** were used as starting materials. The reaction of 2-chloromethylbenzoyl chloride **2** with **7** in dichloromethane at room temperature did not give intermediate **5** or **8** but instead gave a product which may have had structure **9**¶ or **10**.



Scheme 2

An unequivocal decision between structures **9** and **10** was possible with the help of spectroscopic analysis and their ring transformation to tetracyclic compounds **6** and **11**, respectively. The ^{1}H NMR spectrum of the products exhibit two broad peaks at δ 8.33 to 8.38 ppm and 12.20 to 12.38 ppm, which are consistent with structure **9a**,**b**. In addition, the ^{13}C NMR spectrum of these compounds shows two characteristic signals due to two different carbonyl groups. For example, in case of **9a**, these signals appear at δ 166.2 and 170.8 ppm, which indicates the formation of this product. Furthermore, when these compounds were heated under reflux in the presence of potassium hydroxide in aqueous ethanol the products isolated had identical physical and spectral characteristics as compounds **6a**,**b**,†† which were prepared by another procedure shown in Scheme 1.

In conclusion, we developed a method for preparing new tricyclic dibenzo[*b*,*g*][1,5]diazoninediones and tetracyclic isoindolo[2,1-*a*]quinazoline derivatives in good yields.

References

1 M. Bakavoli, A. Davoodnia, M. Rahimizadeh, M. M. Heravi and M. Ghassemzadeh, *J. Chem. Res. (S)*, 2002, 178.
2 M. Bakavoli, A. Davoodnia, M. Rahimizadeh and M. M. Heravi, *Phosphorus Sulfur Silicon Relat. Elem.*, 2002, **177**, 2303.
3 G. Rabilloud, B. Sillion and G. de Gaudemaris, *Makromol. Chem.*, 1967, **108**, 18 (*Chem. Abstr.*, 1967, **67**, 117374z).
4 M. Kurihara, *J. Org. Chem.*, 1969, **34**, 2123.
5 Suh Myung Eun, *Yakhak Hoechi*, 1990, **34**, 133 (*Chem. Abstr.*, 1990, **114**, 81755x).
6 P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, 1968, **33**, 2402.
7 E. F. M. Stephenson, *J. Chem. Soc.*, 1954, 2354.
8 J. Troschuetz, A. Kirfel and G. Will, *Arch. Pharm. (Weinheim, Ger.)*, 1985, **318**, 690 (*Chem. Abstr.*, 1985, **103**, 178227n).
9 F. S. Babichev, F. P. Trinus, L. A. Gromov, V. A. Kovtunenko, V. A. Portnyagina, T. F. Troyan and A. K. Tyltin, *Otkrytiya, Izobreteniya, Prom. Obraztsy, Tovarnye Znaki*, 1976, **53** (3), 72 (*Chem. Abstr.*, 1977, **86**, P5491w).
10 P. Aeberli and W. J. Houlihan, *J. Heterocycl. Chem.*, 1978, **15**, 1141.
11 W. J. Houlihan, *US Patent*, 3,509,147 (Cl. 260–251; C07d) (*Chem. Abstr.*, 1970, **73**, P25510m).
12 W. J. Houlihan, *US Patent*, 3,609,139 (Cl. 260/239 DD; A61k) (*Chem. Abstr.*, 1971, **75**, P151851c).
13 J. A. Tyrell and W. E. McEwen, *J. Org. Chem.*, 1981, **46**, 2476.
14 J. Kant, F. D. Popp and B. C. Uff, *J. Heterocycl. Chem.*, 1985, **22**, 1313.
15 W. Lertwanawatana, S. Thianpatanagul, J. L. Cashaw and V. E. Davis, *Tetrahedron Lett.*, 1984, **25**, 3485.
16 F. S. Babichev and A. K. Tyltin, *Ukr. Khim. Zh.*, 1970, **36** (2), 175 (in Russian).

Received: 27th April 2005; Com. 05/2502

¶ *Typical procedure for the preparation of* **9a**. To a magnetically stirred mixture of 2-aminobenzamide **7** (1.36 g, 10 mmol) in dichloromethane (30 ml), 2-chloromethylbenzoyl chloride (2.27 g, 12 mmol) was slowly added. Stirring was continued for 30 min at room temperature. The precipitate was filtered off and recrystallised from ethanol to yield 1.92 g of **9a** as a white powder (76%).

*5*H*-Dibenzo[*b,g*][1,5]diazonine-11,13(6*H*,12*H*)-dione* **9a**: white solid (1.92 g, 76%), mp 203–205 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, TMS) δ: 12.38 (br. s, 1H, NH), 8.62 (d, 1H, aromatic rings), 8.35 (br. s, 1H, NH), 7.1–8.1 (m, 7H, aromatic rings), 5.04 (s, 2H, CH$_2$). ^{13}C NMR (DMSO) δ: 43.4, 119.8, 120.3, 122.9, 127.3, 128.7, 129.0, 130.8, 131.1, 132.4, 136.0, 136.3, 139.7, 166.2, 170.8. FT-IR (KBr, ν/cm^{-1}): 3349, 3167 (NH), 1662 (CO). MS, *m*/*z*: 252 [M]$^+$. Found (%): C, 71.37; H, 4.83; N, 11.08. Calc. for C$_{15}$H$_{12}$N$_2$O$_2$ (252) (%): C, 71.42; H, 4.79; N, 11.10.

*2-Chloro-5*H*-dibenzo[*b,g*][1,5]diazonine-11,13(6*H*,12*H*)-dione* **9b**: white solid (2.04 g, 71%), mp 235–237 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, TMS) δ: 12.20 (br. s, 1H, NH), 8.62 (d, 1H, aromatic rings), 8.35 (br. s, 1H, NH), 7.4–8.1 (m, 6H, aromatic rings), 5.02 (s, 2H, CH$_2$). ^{13}C NMR (DMSO) δ: 43.3, 122.0, 126.8, 127.3, 127.9, 128.3, 129.0, 131.0, 131.1, 132.0, 135.7, 136.3, 138.4, 166.2, 169.4. FT-IR (KBr, ν/cm^{-1}): 3362, 3176 (NH), 1662 (CO). MS, *m*/*z*: 286 [M]$^+$. Found (%): C, 62.90; H, 3.85; N, 9.72. Calc. for C$_{15}$H$_{11}$ClN$_2$O$_2$ (286.5) (%): C, 62.84; H, 3.87; N, 9.77.

†† *Typical procedure for the conversion of* **9a** *to* **6a**. Compound **9a** (1.26 g, 5 mmol) in a mixture of ethanol (20 ml), water (10 ml) and potassium hydroxide (0.34 g, 6 mmol) was heated under reflux for 2 h. After cooling the reaction mixture, the precipitate was filtered off, washed with chloroform and recrystallised from ethanol to yield 0.8 g of **6a** as a white powder (68%).