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Synthesis of annulated dihydroisoquinoline heterocycles via their nitrogen ylides

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ABSTRACT

3,4-Dihydro-6,7-dimethoxyisoquinoline-1-acetonitrile reacts with some α-bromoketones in dry benzene to give the corresponding isoquinolinium salts, which undergo intramolecular cyclization to give pyrrolo[2,1-*a*]isoquinolines. Cross-coupling of the latter compounds with some aryldiazonium chlorides resulted in the formation of 3-arylhydrazonopyrrolo[2,1-*a*]isoquinolines, 3-arylazopyrrolo[2,1-*a*]isoquinolines and 3-aryl-1,2,3-triazolo[5,1-*a*]isoquinolines, respectively. The structures of the products were established on the basis of their elemental and spectral analyses as well as X-ray single crystal studies.

1. Introduction

Isoquinoline alkaloids have been an interesting structural class of compounds, which have found important medicinal and pharmacological applications.[1,2] On the other hand, substituted tetrahydroisoquinolines have been found to exhibit a broad spectrum of biological activities[3] and furthermore being relevant to pathogenesis of Parkinson's disease.[4] In addition, 1,2,3-triazoles are highly versatile chemicals, which exhibit a wide spectrum of utilities in pharmaceutical and industrial areas.[5] Synthesis of 1,2,3-triazolo[5,1-*a*]isoquinolines was also reported.[6] As part of our research interest towards developing new routes for the synthesis of isoquinoline heterocycles,[7–9] we conduct here a novel route to some new bridgehead-nitrogen heterocycles utilizing some versatile isoquinolinium *N*-ylides.

2. Results and discussion

3,4-Dihydro-6,7-dimethoxyisoquinoline-1-acetonitrile **1** was prepared according to a literature procedure.[10] Treatment of **1** with ethyl bromoacetate in dry benzene at refluxing temperature gave quantitatively the corresponding isoquinolinium bromide salt **2**. Treatment of the bromide salt **2** with triethylamine in refluxing benzene gave a single annulated reaction product identified as 2,3,5,6-tetrahydro-8,9-dimethoxy-2-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile **3** based on elemental and spectral analyses of the reaction product as well as its further chemical transformation. The formation of **3** is assumed to proceed via intramolecular cyclization through elimination of hydrogen bromide and ethanol from the bromide salt **2** (Scheme 1). Coupling of compound **3** with benzenediazonium chloride in pyridine solution afforded the corresponding 3-phenylhydrazono-2-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile derivative **4a** in a good yield, as shown in Scheme 1. Similar results were obtained on coupling of **3** with *p*-tolyl and *p*-chlorophenyldiazonium chlorides to give the corresponding arylhydrazones **4b** and **4c**, respectively. Compounds **4a–c** were found to be regioisomers of 2-arylhydrazono-3-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitriles **5** that were reported earlier by our group.[7a]

The annulation reaction was also extended to salts derived from isoquinoline derivative **1** as shown in Scheme 2. Thus, treatment of isoquinoline-1-acetonitrile **1** with phenacyl bromide **6a** in dry benzene at refluxing temperature gave the corresponding isoquinolinium bromide **7a**. The latter salt when heated at reflux in dry benzene and in the presence of triethylamine furnished a single product as examined by TLC. Elemental analyses and mass spectrum of the reaction product established its molecular formula as $C_{21}H_{18}N_2O_2$. Spectroscopic data (IR, ^1H and ^{13}C NMR) of the reaction product were in complete agreement with the assigned 2-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile structure **9a** and not with structure **8a**, as depicted in Scheme 2. Similar treatment of isoquinoline-1-acetonitrile **1** with other α-bromoketones **6b–e** gave the corresponding isoquinolinium bromide salts **7b–e**, which underwent intramolecular cyclization via elimination of water and hydrogen bromide molecules to give the angularly fused 2-arylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile derivatives **9b–e**. Furthermore, reaction of compound **9a** with aryldiazonium chlorides in cold pyridine afforded, in each case, only one product identified as 3-arylazo-2-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile structures **10a**,**b** (Scheme 2) on the basis of elemental analyses and spectroscopic data

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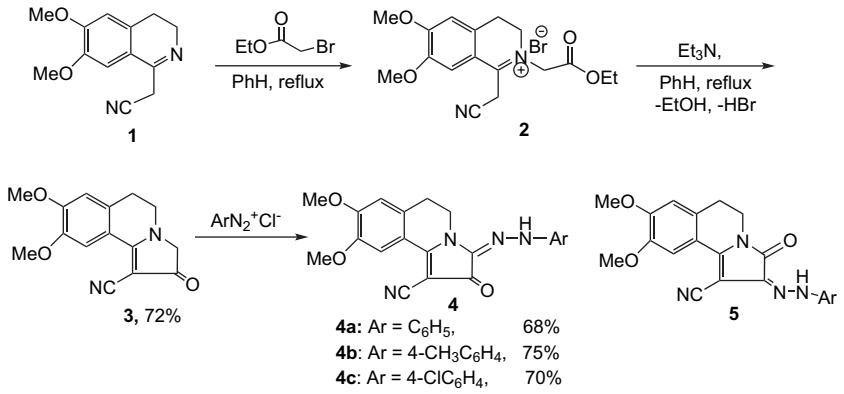
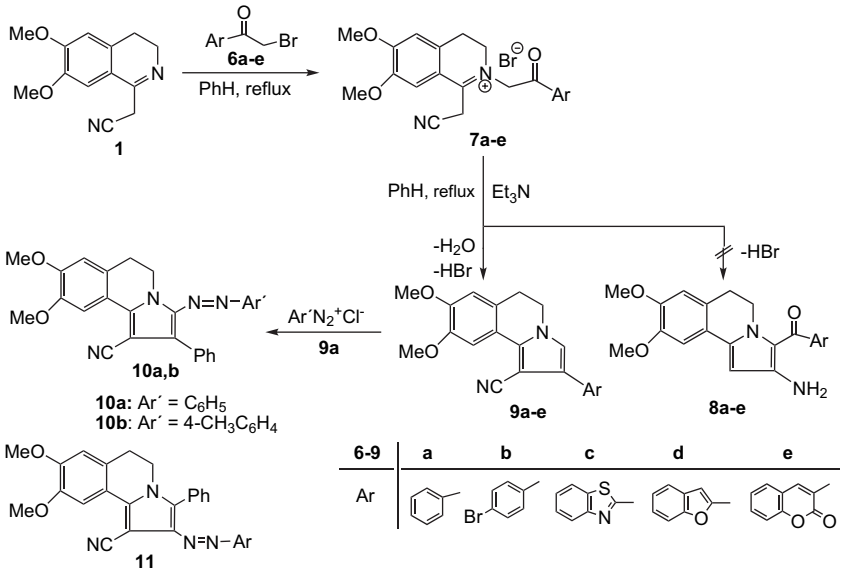


Scheme 1.



Scheme 2.

(MS, IR, ^{1}H and ^{13}C NMR) of the reaction products. Compounds **10a**,**b** were proved to be regioisomers of our early published[7b] 2-arylazo-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile structures **11** (Scheme 2).

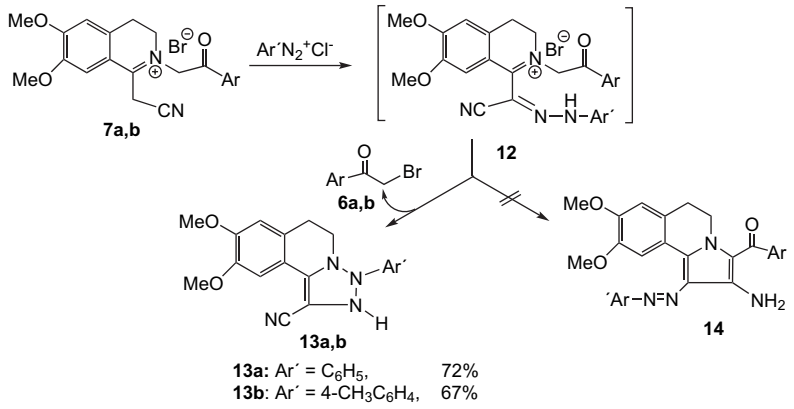
Reaction of isoquinolinium bromide salt **7a** with benzenediazonium chloride in ethanol under neutral conditions afforded a single product as tested by TLC. The product should be the hydrazone structure **12** as shown in Scheme 3. However, mass spectrum of the reaction product gave a molecular ion peak at *m*/*z* 334, which is consistent with the elemental analyses of the molecular formula $C_{19}H_{18}N_4O_2$. These data indicate that the bromide salt **12** is not isolable and support the formation of the triazole structure **13a**, which is obtained from intramolecular cyclization of the salt **12** via phenacyl bromide elimination under the base-free coupling condition. Spectroscopic data (IR, ^{1}H and ^{13}C NMR) of the reaction product provided a further evidence for the formation of the triazole structure **13a**. In addition, single crystal X-ray analysis of the reaction product (Fig. 1) provided an unequivocal evidence for the formation of 3-phenyl-1,2,3-triazolo[5,1-*a*]isoquinoline-1-carbonitrile **13a** and ruled out the other possible structure **14** as outlined in Scheme 3. Interestingly, compound **13a** was alternatively obtained from the reaction of the bromide salt **7b** (Ar=*p*-BrC_6H_4) with benzenediazonium chloride, which rationales the elimination of *p*-bromophenacyl bromide from the intermediate **12** followed by an intramolecular N–N bond formation to give **13a**.

Furthermore, treatment of either compound **7a** or **7b** with *p*-tolyldiazonium chloride under similar reaction conditions gave only one and the same product identified as 2,3,5,6-tetrahydro-8,9-dimethoxy-3-*p*-tolyl-[1,2,3]triazolo[5,1-*a*]isoquinoline-1-carbonitrile **13b** (Scheme 3).

3. Experimental

3.1. General

Melting points were measured on a Gallenkamp apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. NMR spectra were determined in $CDCl_3$ or DMSO-d_6 at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR) on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX



Scheme 3.

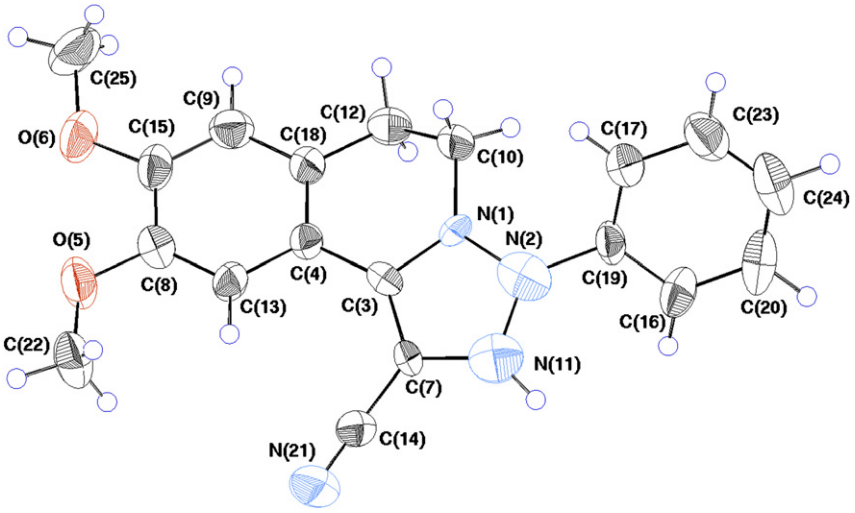


Figure 1. X-ray structure of compound **13a**.

spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University. Isoquinoline-1-acetonitrile **1**,[10] α-haloketones **6a**,**b**,[11] **6c**,[12] **6d**[13] and **6e**[14] were prepared according to the procedures reported in the literature.

3.2. Synthesis of the isoquinolinium salt 2

To a solution of isoquinoline-1-acetonitrile derivative **1** (0.92 g, 4 mmol) in dry benzene (20 mL), ethyl α-bromoacetate (0.67 g, 4 mmol) was added. The mixture was refluxed for 2 h, then left to cool. The solid product was filtered off, washed with ether and dried to afford the isoquinolinium bromide **2** as green powder (1.24 g, 78%), mp 258–260 °C; IR (KBr) ν 1726 (C=O), 2194 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 2H), 2.74 (t, 3H, J=7.2 Hz), 2.94 (t, 2H, J=6.3 Hz), 3.77 (q, 2H, J=7.2 Hz), 3.55 (s, 2H), 3.78 (t, 2H, J=6.3 Hz), 3.78 (s, 3H), 3.84 (s, 3H), 7.0 (s, 1H), 7.6 (s, 1H). Anal. Calcd for $C_{17}H_{21}BrN_2O_4$: C, 51.40; H, 5.33; N, 7.05. Found: C, 51.35; H, 5.19; N, 7.28%.

3.3. Synthesis of 2-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile 3

To a solution of isoquinolinium bromide salt **2** (0.794 g, 2 mmol) in dry benzene (30 mL), triethylamine (0.4 mL) was added and the reaction mixture was refluxed 3–5 h, then left to cool to room temperature. The triethylamine–hydrobromide salt was removed by filtration and the filtrate was evaporated under vacuum. The residue was triturated with methanol where a black-coloured precipitate was formed that was filtered off, washed with methanol and dried. Recrystallization from DMF afforded 2,3,5,6-tetrahydro-8,9-dimethoxy-2-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile **3** as grey powder (0.39 g, 72%), mp >300 °C; IR (KBr) ν 1693 (C=O), 2205 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.94 (t, 2H, J=6.9 Hz), 3.55 (s, 2H), 3.6 (t, 2H, J=6.9 Hz), 3.78 (s, 3H), 3.8 (s, 3H), 7.0 (s, 1H), 7.69 (s, 1H); MS (m/z) (%), 270 (M^+, 79), 241 (52), 225 (91), 182 (40), 166 (19), 127 (30.7), 76 (21.7), 51 (30.7). Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.72; H, 5.49; N, 10.61%.

3.4. Synthesis of 3-arylhydrazono-2-oxopyrrolo[2,1-*a*]-isoquinoline-1-carbonitrile 4

To a cold solution of 2-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile **3** (0.54 g, 2 mmol) in pyridine (20 mL), the appropriate aryldiazonium salt (2 mmol) was added portionwise over 1 h at 0–5 °C. After the addition was completed, the reaction mixture was left to stir at room temperature for further 3 h, then diluted with 10 mL water and the precipitate was filtered, washed with ethanol and dried. Recrystallization from DMF afforded the corresponding 3-arylhydrazono-2-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile derivatives **4a**–**c**.

*3.4.1. 3-(Phenylhydrazono)-2,3,5,6-tetrahydro-8,9-dimethoxy-2-oxopyrrolo[2,1-a]-isoquinoline-1-carbonitrile (**4a**)*

Brownish red crystals (0.51 g, 68%); mp 294–296 °C; IR (KBr) ν 1727 (C=O), 2197 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.03 (t, 2H, J=6.9 Hz), 3.82 (s, 3H), 3.84 (s, 3H), 3.7 (t, 2H, J=6.9 Hz), 7.0 (s, 1H), 7.4 (s, 1H), 7.6–7.7 (m, 5H), 12.5 (s, 1H, NH); MS (*m*/*z*) (%), 374 (M^+, 100), 269 (2.3), 241 (48.5), 227 (25.2), 211 (45.8), 197 (9.3), 167 (8.6), 128 (8.3), 77 (9.7), 51 (12.5). Anal. Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.60; H, 4.63; N, 14.77%.

*3.4.2. 3-(p-Tolylhydrazono)-2,3,5,6-tetrahydro-8,9-dimethoxy-2-oxopyrrolo[2,1-a]-isoquinoline-1-carbonitrile (**4b**)*

Intense red powder (0.58 g, 75%); mp 261–263 °C; IR (KBr) ν 1724 (C=O), 2203 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 3.03 (t, 2H, J=6.3 Hz), 3.78 (t, 2H, J=6.3 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 7.0 (s, 1H), 7.15 (d, 2H, J=8.4 Hz), 7.29 (d, 2H, J=8.4 Hz), 7.6 (s, 1H), 12.51 (s, 1H, NH); MS (*m*/*z*) (%), 388 (M^+, 100), 373 (3.5), 268 (2.4), 255 (6), 223 (2.9), 194 (5), 106 (9.3). Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 68.28; H, 5.47; N, 14.25%.

*3.4.3. 3-(p-Chlorophenylhydrazono)-2,3,5,6-tetrahydro-8,9-dimethoxy-2-oxopyrrolo[2,1-a]-isoquinoline-1-carbonitrile (**4c**)*

Orange red powder (0.57 g, 70%); mp 278–280 °C; IR (KBr) ν 1679 (C=O), 2204 (C≡N) cm^{-1}; MS (*m*/*z*) (%), 408 (M^+, 100), 225 (9.2), 127 (15.1), 101 (6), 90 (16.1), 63 (10.2). Anal. Calcd for $C_{21}H_{17}ClN_4O_3$: C, 61.69; H, 4.19; N, 13.70. Found: C, 61.78; H, 4.33; N, 13.49%.

3.5. Synthesis of the isoquinolinium salts 7a–e

To a solution of the appropriate α-bromoketone derivatives **6a**–**e** (2 mmol) in dry benzene (20 mL), isoquinoline-1-acetonitrile **1** (0.46 g, 2 mmol) was added. The mixture was refluxed for 2 h, then left to cool. The solid product was filtered off, washed with ether and dried to afford the isoquinolinium bromides **7a**–**e**, respectively.

*3.5.1. Isoquinolinium salt **7a***

Yellowish-brown crystals (0.59 g, 69%); mp 184–186 °C (methanol); IR (KBr) ν 1644 (C=O), 2253 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50 (s, 2H), 2.75 (t, 2H, J=6.3 Hz), 3.24 (t, 2H, J=6.3 Hz), 3.77 (s, 3H), 3.79 (s, 2H), 3.82 (s, 3H), 6.98 (s, 1H), 7.16–7.49 (m, 5H), 7.62 (s, 1H). Anal. Calcd for $C_{21}H_{21}BrN_2O_3$: C, 58.75; H, 4.93; N, 6.53. Found: C, 58.94; H, 5.03; N, 6.77%.

*3.5.2. Isoquinolinium salt **7b***

Brown crystals (0.72 g, 71%); mp 152–154 °C (methanol); IR (KBr) ν 1649 (C=O), 2253 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.83 (t, 2H, J=6.3 Hz), 3.44 (t, 2H, J=6.3 Hz), 3.88 (s, 3H), 3.91 (s, 3H), 4.24 (s, 2H), 4.40 (s, 2H), 6.67 (s, 1H), 6.98 (s, 1H), 7.65 (d, 2H, J=6.9 Hz), 7.86 (d, 2H, J=6.9 Hz). Anal. Calcd for $C_{21}H_{20}Br_2N_2O_3$: C, 49.63; H, 3.97; N, 5.51. Found: C, 49.46; H, 3.68; N, 5.22%.

*3.5.3. Isoquinolinium salt **7c***

Brown powder (0.71 g, 74%); mp 233–235 °C (DMF); IR (KBr) ν 1649 (C=O), 2214 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (t, 2H, J=6.9 Hz), 3.86 (s, 3H), 3.92 (s, 3H), 3.94 (s, 2H), 4.83 (t, 2H, J=6.9 Hz), 4.89 (s, 2H), 6.72 (s, 1H), 7.27–7.40 (m, 2H), 7.77 (s, 1H), 7.79 (d, 1H, J=7.8 Hz), 7.93 (d, 1H, J=7.8 Hz). Anal. Calcd for $C_{22}H_{20}BrN_3O_3S$: C, 54.32; H, 4.14; N, 8.62; S, 6.58. Found: C, 54.15; H, 3.95; N, 8.74; S, 6.46%.

*3.5.4. Isoquinolinium salt **7d***

Yellow crystals (0.62 g, 67%); mp 201–203 °C (ethanol); IR (KBr) ν 1651 (C=O), 2217 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.01 (t, 2H, J=6.9 Hz), 3.94 (s, 3H), 3.96 (s, 3H), 3.99 (s, 2H), 4.05 (s, 2H), 4.38 (t, 2H, J=6.9 Hz), 6.79 (s, 1H), 6.89 (s, 1H), 7.29–7.59 (m, 4H), 7.80 (s, 1H). Anal. Calcd for $C_{23}H_{21}BrN_2O_4$: C, 58.86; H, 4.51; N, 5.97. Found: C, 58.64; H, 4.59; N, 5.81%.

*3.5.5. Isoquinolinium salt **7e***

Yellowish-white crystals (0.75 g, 76%); mp>300 °C (dioxane); IR (KBr) ν 1715 (C=O), 2212 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (t, 2H, J=6.3 Hz), 3.93 (s, 3H), 3.98 (s, 3H), 4.05 (t, 2H, J=6.3 Hz), 4.76 (s, 4H), 6.64 (s, 1H), 6.76 (s, 1H), 7.38–7.43 (m, 2H), 7.69–7.82 (m, 2H), 8.64 (s, 1H). Anal. Calcd for $C_{24}H_{21}BrN_2O_5$: C, 57.96; H, 4.26; N, 5.63. Found: C, 57.80; H, 4.34; N, 5.42%.

3.6. Synthesis of 2-arylpyrrolo[2,1-*a*]isoquinoline-1-carbonitriles 9a–e

To a solution of the appropriate isoquinolinium bromides **7a**–**e** (2 mmol) in dry benzene (30 mL), triethylamine (0.4 mL) was added and the reaction mixture was refluxed 2–4 h, then left to cool to room temperature. The triethylamine–hydrobromide salt was removed by filtration and the filtrate was evaporated under vacuum. The residue was triturated with methanol and the solid formed was filtered off, washed with methanol and dried. Recrystallization from proper solvent afforded the corresponding pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile derivatives **9a**–**e**.

*3.6.1. 5,6-Dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-a]-isoquinoline-1-carbonitrile (**9a**)*

Yellow crystals (0.45 g, 69%); mp 208–210 °C (ethanol); IR (KBr) ν 2212 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.0 (t, 2H, J=6.6 Hz), 3.91 (s, 3H), 3.96 (s, 3H), 4.09 (t, 2H, J=6.6 Hz), 6.48 (s, 1H), 6.75 (s, 1H), 7.34–7.44 (m, 5H), 7.75 (s, 1H); ^{13}C NMR δ 28.8, 42.3, 55.9, 56.1, 86.9, 107.0, 110.9, 111.7, 118.3, 119.9, 124.7, 128.1, 128.7, 128.8, 130.8, 134.1, 136.3, 148.4, 148.9; MS (*m*/*z*) (%), 330 (M^+, 100), 243 (17.6), 230 (27.8), 165 (12.1), 86 (8.5). Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.36; H, 5.46; N, 8.48. Found: C, 76.15; H, 5.32; N, 8.71%.

*3.6.2. 2-(4-Bromophenyl)-5,6-dihydro-8,9-dimethoxypyrrolo-[2,1-a]isoquinoline-1-carbonitrile (**9b**)*

Yellowish-brown powder (0.59 g, 73%); mp 174–176 °C (methanol); IR (KBr) ν 2177 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (t, 2H, J=6.3 Hz), 3.43 (t, 2H, J=6.3 Hz), 3.90 (s, 3H), 3.92 (s, 3H), 5.57 (s, 1H), 6.67 (s, 1H), 6.99 (s, 1H), 7.61 (d, 2H, J=6.9 Hz), 7.78 (d, 2H, J=6.9 Hz); MS (*m*/*z*) (%), 409 (M^+, 13.6), 230 (6.8), 101 (19.9), 86 (100), 79 (12.7), 58 (37.2). Anal. Calcd for $C_{21}H_{17}BrN_2O_2$: C, 61.63; H, 4.16; N, 6.84. Found: C, 61.38; H, 3.92; N, 6.95%.

*3.6.3. 2-(Benzothiazol-2-yl)-5,6-dihydro-8,9-dimethoxy-pyrrolo[2,1-a]isoquinoline-1-carbonitrile (**9c**)*

Pale brown crystals (0.55 g, 72%); mp 264–266 °C (acetic acid); IR (KBr) ν 2215 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (t, 2H, J=6.9 Hz), 3.87 (s, 3H), 3.91 (s, 3H), 4.84 (t, 2H, J=6.9 Hz), 6.72 (s, 1H), 7.01 (s, 1H), 7.30–7.41 (m, 2H), 7.74 (s, 1H), 7.79 (d, 1H, J=7.2 Hz), 7.92 (d, 1H, J=7.2 Hz); MS (*m*/*z*) (%), 387 (M^+, 100), 345 (6.7), 328 (8.1), 300 (7.3), 156 (12), 69 (8.1). Anal. Calcd for $C_{22}H_{17}N_3O_2S$: C, 68.22; H, 4.42; N, 10.85; S, 8.28. Found: C, 68.05; H, 4.37; N, 10.72; S, 8.43%.

*3.6.4. 2-(2-Benzofuryl)-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-a]-isoquinoline-1-carbonitrile (**9d**)*

Pale yellow crystals (0.49 g, 67%); mp 218–220 °C (DMF); IR (KBr) ν 2214 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (t, 2H, J=6.9 Hz), 3.95 (s, 3H), 3.99 (s, 3H), 4.42 (t, 2H, J=6.9 Hz), 6.79 (s, 1H), 6.81 (s, 1H), 6.89 (s, 1H), 7.28–7.35 (m, 2H), 7.79 (d, 1H, J=8.4 Hz), 7.92 (d, 1H, J=8.4 Hz), 7.80 (s, 1H); ^{13}C NMR δ 28.5, 42.7, 56.0, 56.1, 87.7, 104.0, 107.2, 110.8, 111.0, 113.6, 117.7, 119.3, 120.8, 123.2, 124.0, 124.5, 124.6, 128.3, 137.4, 147.2, 148.5, 149.4, 154.5; MS (*m*/*z*) (%), 370 (M^+, 100), 355 (23.3), 327 (22.5), 185 (12.8), 89 (2.4). Anal.

Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.49; H, 4.75; N, 7.25%.

*3.6.5. 5,6-Dihydro-8,9-dimethoxy-2-(2-oxo-2H-chromen-3-yl)pyrrolo[2,1-a]-isoquinoline-1-carbonitrile (**9e**)*

Pale yellow crystals (0.61 g, 77%); mp 296–297 °C (DMF); IR (KBr) ν 1715 (C=O), 2212 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (t, 2H, J=6.9 Hz), 3.92 (s, 3H), 3.98 (s, 3H), 4.06 (t, 2H, J=6.9 Hz), 6.64 (s, 1H), 6.76 (s, 1H), 7.35–7.42 (m, 2H), 7.56–7.60 (m, 2H), 7.78 (s, 1H), 7.82 (s, 1H); MS (*m*/*z*) (%), 398 (M^+, 100), 384 (18.8), 355 (23.9), 312 (12.5), 299 (32.9), 199 (12.7), 156 (10.1), 127 (15.1), 87 (10.1). Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.57; H, 4.71; N, 6.95%.

3.7. Synthesis of 3-arylazo-2-phenylpyrrolo[2,1-*a*]-isoquinoline-1-carbonitriles 10a,b

To a cold solution of 2-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile **9a** (2 mmol) in pyridine (20 mL), the appropriate aryldiazonium salt (2 mmol) was added portionwise over 1 h at 0–5 °C. After the addition was completed, the reaction mixture was left to stir at room temperature overnight, then diluted with 10 mL water. The precipitate was filtered off, washed with ethanol and dried. Recrystallization from proper solvent afforded the corresponding 3-arylazo-2-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile derivatives **10a**,**b**.

*3.7.1. 3-Phenylazo-5,6-dihydro-8,9-dimethoxy-2-phenyl-pyrrolo[2,1-a]isoquinoline-1-carbonitrile (**10a**)*

Yellowish-orange crystals (0.60 g, 70%); mp 286–288 °C (DMF); IR (KBr) ν 2206 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (t, 2H, J=6.6 Hz), 3.94 (s, 3H), 4.0 (s, 3H), 4.17 (t, 2H, J=6.6 Hz), 6.76 (s, 1H), 7.37–7.58 (m, 8H), 7.82 (m, 2H), 8.0 (s, 1H); MS (*m*/*z*) (%), 434 (M^+, 100), 329 (61.9), 313 (19.8), 298 (60.3), 255 (27.7), 210 (13.3), 77 (99.5). Anal. Calcd for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.56; H, 5.34; N, 12.67%.

*3.7.2. 3-(p-Tolylazo)-5,6-dihydro-8,9-dimethoxy-2-phenyl-pyrrolo[2,1-a]isoquinoline-1-carbonitrile (**10b**)*

Yellowish-white crystal (0.67 g, 75%); mp 176–178 °C (ethanol); IR (KBr) ν 2212 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.58 (t, 2H, J=6.9 Hz), 3.96 (s, 3H), 3.97 (s, 3H), 3.98 (t, 2H, J=6.9 Hz), 6.75 (s, 1H), 7.19 (d, 2H, J=8.1 Hz), 7.38–7.43 (m, 5H), 7.55 (d, 2H, J=8.1 Hz), 8.06 (s, 1H); ^{13}C NMR δ 21.2, 28.6, 42.4, 56.1, 56.3, 107.1, 110.7, 110.9, 111.8, 118.2, 118.3, 121.1, 124.6, 128.0, 128.7, 128.8, 129.5, 131.9, 138.3, 147.6, 152.2; MS (*m*/*z*) (%), 448 (M^+, 70), 330 (55.2), 316 (4.4), 287 (28.1), 199 (10.8), 91 (100), 64 (4). Anal. Calcd for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.36; N, 12.49. Found: C, 75.26; H, 5.19; N, 12.57%.

3.8. 3-Aryl-[1,2,3]triazolo[5,1-*a*]isoquinoline-1-carbonitriles 13a,b

To a cold solution of the appropriate isoquinolinium bromide salts **7a**,**b** (2 mmol) in base-free absolute ethanol (20 mL), the appropriate phenyl or *p*-tolyldiazonium salts (2 mmol) was added portionwise over 1 h at 0–5 °C. After the addition was completed, the reaction mixture was left to stir at room temperature overnight, then diluted with 10 mL water. The precipitate so formed was filtered off, washed with methanol and dried. Recrystallization from proper solvent afforded the corresponding 1,2,3-triazolo[5,1-*a*]-isoquinoline-1-carbonitrile derivatives **13a**,**b**.

*3.8.1. 2,3,5,6-Tetrahydro-8,9-dimethoxy-3-phenyl-[1,2,3]-triazolo[5,1-a]isoquinoline-1-carbonitrile (**13a**)*

Yellow crystal (0.48 g, 72%); mp 225–227 °C (acetonitrile); IR (KBr) ν 2211 (C≡N), 3327 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.99 (t, 2H, J=6.6 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 4.10 (t, 2H, J=6.9 Hz), 6.67 (s, 1H), 7.02 (s, 1H), 7.41–7.50 (m, 5H), 7.61 (s, 1H); ^{13}C NMR δ 27.7, 41.9, 55.6, 85.6, 106.8, 111.9, 117.7, 118.9, 121.2, 125.7, 127.7, 130.2, 133.8, 135.6, 147.8, 148.9; MS (*m*/*z*) (%), 334 (M^+, 3.7), 315 (42.4), 287 (43.2), 243 (20.5), 165 (9.6), 51 (6.8). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.36; H, 5.47; N, 16.82%.

*3.8.2. 2,3,5,6-Tetrahydro-8,9-dimethoxy-3-p-tolyl-[1,2,3]-triazolo[5,1-a]isoquinoline-1-carbonitrile (**13b**)*

Orange-yellow crystals (0.46 g, 67%); mp 207–209 °C (methanol); IR (KBr) ν 2207 (C≡N), 3358 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 3.15 (t, 2H, J=6.9 Hz), 3.91 (s, 3H), 4.02 (s, 3H), 4.08 (t, 2H, J=6.9 Hz), 6.85 (s, 1H), 7.07 (d, 2H, J=7.8 Hz), 7.62 (s, 1H), 7.95 (d, 2H, J=7.8 Hz), 9.55 (s, 1H); MS (*m*/*z*) (%), 348 (M^+, 77.6), 230 (10.7), 187 (4.2), 157 (4.6), 91 (100), 51 (18.5). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.76; N, 16.08. Found: C, 68.91; H, 5.63; N, 16.24%.

3.9. X-ray structure determination of compound 13a

The X-ray diffraction measurement was made on using maXus (Bruker Nonius, Delft & MacScience, Japan) at temperature 300(2) K and wavelength 0.71073 Å; radiation: Mo Kα. Crystal data for compound **13a**: $C_{19}H_{18}N_4O_2$, M=334.37, crystal system, space group: triclinic, $P21/n$; unit cell dimensions: a=7.1322(6) Å, b=9.1238(6) Å, c=13.3906(13) Å, α=102.942(3)°, β=90.099(3)°, γ=91.293(7)°; volume: 848.99(12) $Å^3$; Z=2; calculated density: 1.435 Mg/m^3; absorption coefficient: μ=0.25 mm^{-1}; reflection 3562 measured, θ_{max}=22.37°; ωR factor=0.135.

Crystallographic data for the structural analysis of compound **13a** has been deposited with the Cambridge Crystallographic Data Centre (CCDC) under the number 684888. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.043.

References and notes

1. (a) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison Wesley Longman: Essex, UK, 1997; (b) Harris, J.; Pope, W. J. *J. Chem. Soc.* **1992**, *121*, 1029; (c) *Comprehensive Heterocyclic Chemistry II*; Katritsky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 7, p 431; (d) Katritsky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Elsevier: Oxford, UK, 2000.
2. (a) Shamma, M. *The Isoquinoline Alkaloids*; Academic: London, 1972; pp 194–228; (b) Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1988**, *51*, 389; (c) Guinaudeau, H. *J. Nat. Prod.* **1994**, *57*, 1033.
3. Monsees, A.; Laschat, S.; Kotila, S.; Fox, T.; Würthwein, E. U. *Liebigs Ann.* **1997**, 533.
4. (a) Yamakawa, T.; Ohta, S. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 676; (b) Okuda, K.; Kotake, Y.; Ohta, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2853; (c) Shinohara, T.; Takeda, A.; Toda, J.; Terasawa, N.; Sano, T. *Heterocycles* **1997**, *46*, 555.
5. For reviews on 1,2,3-triazoles, see: (a) Dehne, H. *Methoden der Organischen Chemie (Houben-Weyl)*; Schumann, E., Ed.; Thieme: Stuttgart, 1994; Vol. E8d, pp 305–405; (b) Wamhoff, H. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 669–732; (c) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Ali, A. A.-S. *J. Heterocycl. Chem.* **1989**, *26*, 1461.
6. (a) Abarca, B.; Ballesteros, R.; Elmasnouy, M. *Tetrahedron* **1999**, *55*, 12881; (b) Abarca, B.; Ballesteros, R.; Houari, N.; Samadi, A. *Tetrahedron* **1998**, *54*, 3913; (c) Abarca, B.; Ballesteros, R.; Houari, N. *Tetrahedron* **1997**, *53*, 12765.
7. (a) Abdelhadi, H. A.; Elwan, N. M.; Abdallah, T. A.; Hassaneen, H. M. *J. Chem. Res., Synop.* **1996**, 292; (b) Elwan, N. M.; Abdelhadi, H. A.; Abdallah, T. A.; Hassaneen, H. M. *Tetrahedron* **1996**, *52*, 3451; (c) Abdallah, T. A.; Abdelhadi, H. A.; Hassaneen, H. M. *Phosphorus, Sulfur Silicon* **2002**, *177*, 59; (d) Abdallah, T. A. *Synth. Commun.* **2002**, *32*, 2459.
8. (a) Awad, E. M.; Elwan, N. M.; Hassaneen, H. M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2001**, *84*, 1172; (b) Awad, E. M.; Elwan, N. M.; Hassaneen, H. M. *Helv. Chim. Acta* **2002**, *85*, 320; (c) Abdallah, T. A.; Abdelhadi, H. A.; Ibrahim, A.

A.; Hassaneen, H. M. *Synth. Commun.* **2002**, *32*, 581; (d) Abdallah, T. A.; Abdelhadi, H. A.; Hassaneen, H. M.; Hassaneen, H. M. *Molecules* **2002**, *7*, 540.
9. (a) Farag, A. M.; Shawali, A. S.; Abed, N. M.; Dawood, K. M. *Gazz. Chim. Ital.* **1993**, *123*, 467; (b) Dawood, K. M.; Kirschning, A. *Tetrahedron* **2005**, *61*, 12121; (c) Dawood, K. M.; Solodenko, V.; Kirschning, A. *ARKIVOC* **2007**, 104.
10. Osbond, J. *J. Chem. Soc.* **1951**, 3464.
11. Cowper, R. M.; Davidson, L. H. *Org. Synth. Coll.* **1943**, *II*, 840.
12. Sawhney, S. N.; Singh, J. *Indian J. Chem.* **1970**, *8*, 882.
13. Elliott, E. D. *J. Am. Chem. Soc.* **1951**, *73*, 754.
14. Czerney, P.; Hartmann, H. *J. Prakt. Chem.* **1983**, *325*, 551.