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A FACILE ROUTE TO PYRROLO[2,1-*a*]- AND 1,2,3-TRIAZOLO[5,1-*a*]-DIHYDROISOQUINOLINES

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Abstract- Treatment of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **1** with α-bromoketones **2a-c** in benzene in presence of triethylamine afforded the corresponding pyrrolo[2,1-*a*]isoquinoline **4**. Also treatment of 3,4-dihydro-6,7-diethoxyisoquinoline-1-carbonitrile **10** with α-bromo ketones **2a,b,d** under the same reaction condition afforded the corresponding pyrroloisoquinoline **12**. While treatment of isoquinolinium salt **11** with *p*-tolyldiazonium chloride in ethanol afforded triazoloisoquinoline derivative **16**.

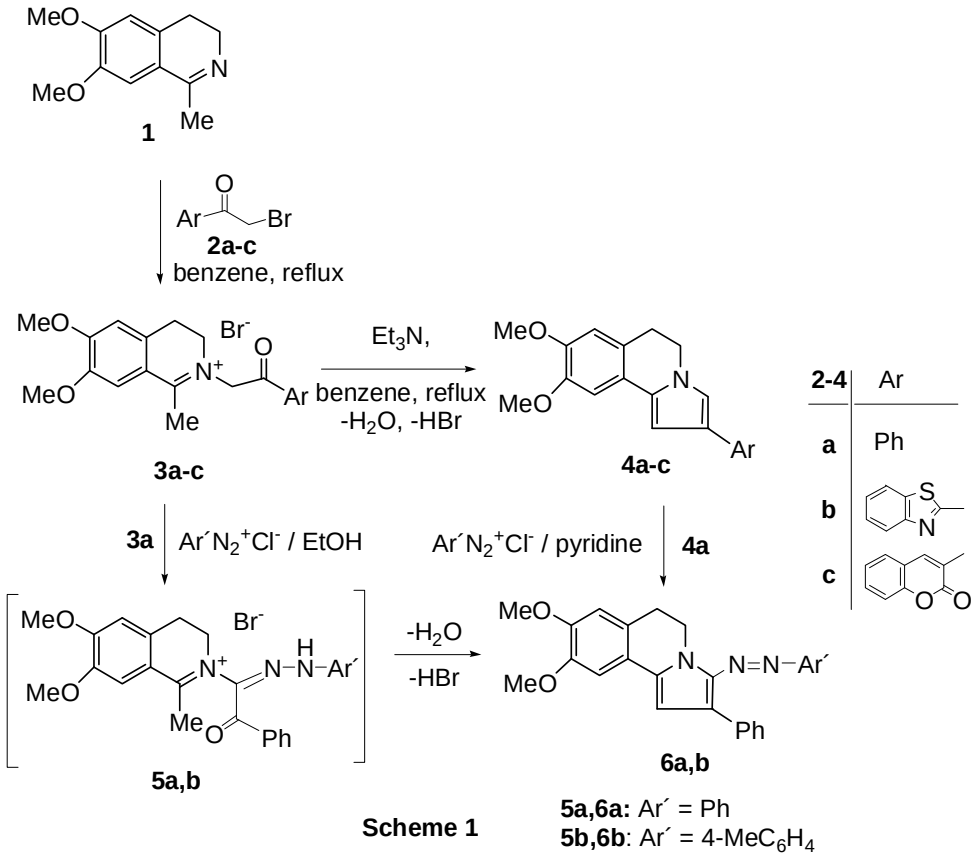
INTRODUCTION

The chemistry of tetrahydroisoquinoline alkaloids has recently attracted great interest due to their fascinating range of biological activities.[1-3] Tetrahydroisoquinoline moiety was found in many marine natural products and has been demonstrated to be potent antitumor agents.[4] In addition, 1,2,3-triazoles are highly versatile chemicals which exhibit a wide spectrum of utilities in pharmaceutical and industrial areas.[5] As a continuation of our previous studies on the chemistry of 1-substituted tetrahydro-isoquinoline in construction of tetrahydroisoquinoline-based heterocycles,[6-13] our present aim is to synthesis pyrrolo and 1,2,3-triazolo-tetrahydroisoquinoline heterocycles.

RESULTS AND DISCUSSION

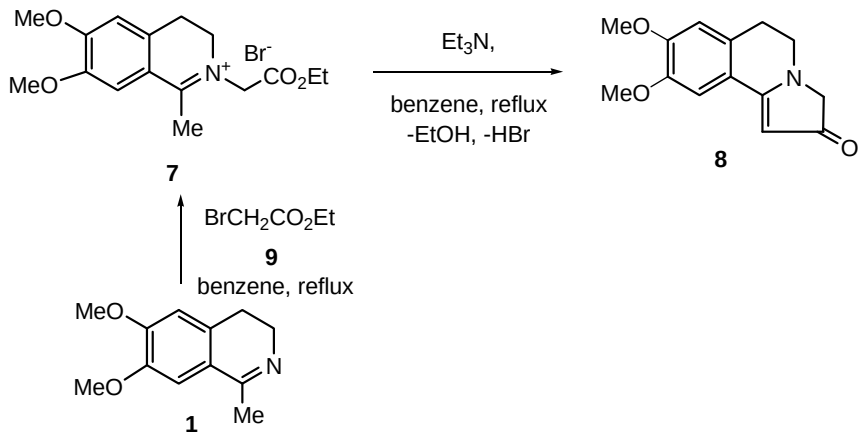
3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline **1** was prepared following literature procedure.[14] When compound **1** was treated with phenacyl bromide **2a** in dry benzene at refluxing temperature it gave the corresponding isoquinolinium bromide **3a**. Heating the latter salt in presence of triethylamine in dry benzene resulted in the formation of a single product as examined by TLC. The molecular formula of the reaction product was established as $C_{20}H_{19}NO_2$ on the basis of its elemental analyses and mass spectrum. Spectral data (IR, ^{1}H NMR) of the reaction product were in consistent with structure **4a**, named as

5,6-dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-*a*]isoquinoline, as shown in Scheme 1. Similarly, treatment of 1-methylisoquinoline **1** with the α-bromoketones **2b,c** furnished the corresponding isoquinolinium bromide salts **3b,c** which on treatment with triethylamine in refluxing benzene underwent intramolecular cyclization *via* elimination of water and hydrogen bromide to give 2-arylpyrrolo[2,1-*a*]isoquinoline derivatives **4b,c**. In addition, reaction of compound **4a** with aryldiazonium chlorides in cold pyridine afforded 3-arylazo-2-phenylpyrrolo[2,1-*a*]isoquinoline derivatives **6a,b** (Scheme 1). The latter structures were substantiated from their elemental analyses and spectral data (MS, IR, ^{1}H and ^{13}C NMR) of the reaction products as well as their alternative synthesis from reaction of **3a** with aryldiazonium chlorides. Thus, treatment of the isoquinolinium bromide salt **3a** in cold ethanol with aryldiazonium chlorides resulted in the formation of compounds identical in all aspects with compounds **6a,b** that obtained above. Compounds **6a,b** could be directly obtained during the arylazo coupling of **3a** without separation of the hydrazones **5a,b** as outlined in Scheme 1.



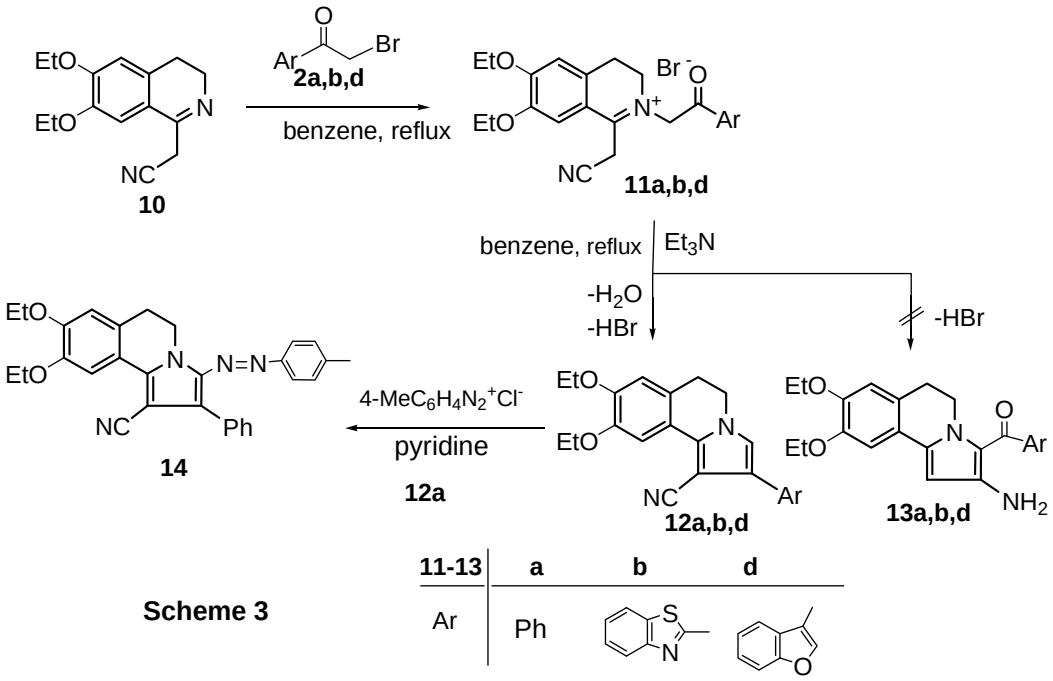
Scheme 1

Prompted by the foregoing results, compound **1** was treated with ethyl bromoacetate in dry benzene at refluxing temperature to give quantitatively the corresponding isoquinolinium bromide salt **7**. Treatment of the latter salt with triethylamine in refluxing benzene gave a single reaction product identified as 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2(3*H*)-one **8** based on elemental and spectral analyses of the reaction product (Scheme 2).



Scheme 2

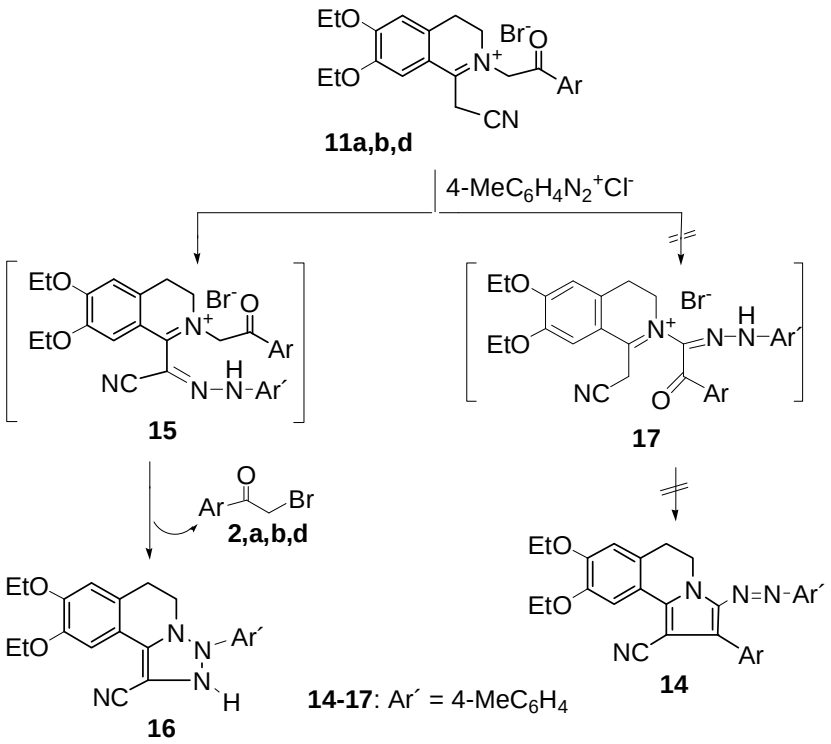
Next, reaction of 6,7-diethoxy-3,4-dihydroisoquinolin-1-acetonitrile **10** with α-bromoketones **2a,b,d** gave the corresponding isoquinolinium bromide salts **11a,b,d** in almost quantitative yields (Scheme 3). Compounds **11a,b,d** underwent intramolecular cyclization when treated with triethylamine in refluxing benzene to afford the corresponding 2-arylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile derivatives **12a,b,d** and not the other structures **13a,b,d** that are depicted in Scheme 3. Compound **12a** smoothly coupled with *p*-tolyldiazonium chloride in cold pyridine to afford a product identified as 3-(*p*-tolylazo)-5,6-dihydro-8,9-diethoxy-2-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile **14** (Scheme 3) on the basis of its elemental analyses and spectral data (MS, IR, ^{1}H and ^{13}C NMR).



Scheme 3

Treatment of compounds **11a** with *p*-tolyldiazonium chloride in ethanol under neutral conditions afforded a single product as tested by TLC. The product was analyzed correctly for $C_{22}H_{24}N_4O_2$ with mass spectrum having a molecular ion peak at m/e 376. In addition, the spectral data (IR, ^{1}H and ^{13}C NMR) of

the reaction product provided a firm support for the formation of the triazole structure **16**; named as 2,3,5,6-tetrahydro-8,9-diethoxy-3-*p*-tolyl[1,2,3]triazolo[5,1-*a*]isoquinoline-1-carbonitrile as shown in Scheme 4. This finding shows that the hydrazones **15** or **17** are not isolable. Formation of the triazole structure **16** can be discussed *via* intramolecular cyclization of the salt **15** *via* phenacyl bromide elimination under the base-free coupling condition. Interestingly, coupling of either bromide salts **11b** or **11d** with *p*-tolyldiazonium chloride under similar reaction conditions furnished one and the same product that was found to be identical with compound **16**. This finding excludes the formation of the hydrazone **17** and consequently the pyrrolo[2,1-*a*]isoquinoline structure **14** and rationales the elimination of the α-bromoketones **2b** or **2d** from the intermediate hydrazone **15** followed by an intramolecular N-N bond formation to give **16**.



Scheme 4

EXPERIMENTAL

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 spectrometers at 70 e.V. Elemental analyses were carried out at the Microanalytical center of Cairo University. 1-Methylisoquinoline **1**,[14] isoquinoline-1-acetonitrile **10**,[15] α-bromoketones **2a**,[16] **2b**,[17] **2c**[18] and **2d**[19] were prepared according to the procedures reported in literature.

Synthesis of the Isoquinolinium Salts 3a-c

To a solution of the appropriate α-bromoketone derivatives **2a-c** (2 mmol) in dry benzene (20 mL), 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **1** (0.41g, 2 mmol) was added. The mixture was refluxed for 3 h, then left to cool. The solid product was filtered off, washed with Et_2O, and dried to afford the isoquinolinium bromides **3a-c**, respectively.

Isoquinolinium salt 3a: Yield (67%); mp138-140 °C (MeOH); IR (KBr) υ 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50 (s, 3H, Isoquinoline-CH_3), 3.24 (s, 2H, CH_2CO), 3.45 (m, 2H, Isoquinoline-CH_2), 3.56 (s, 3H, OCH_3), 3.61(s, 3H, OCH_3), 4.49 (m, 2H, Isoquinoline-CH_2), 7.62 (s, 1H, Isoquinoline-CH), 7.74 (s, 1H, Isoquinoline-CH),7.71 (m, 2H, Ar H), 7.80 (d, 1H, *J* = 9 Hz, Ar H), 8.18 (d, 1H, *J* = 9 Hz, Ar H), 8.36 (s, 1H, Ar H). Anal. Calcd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.48; N, 3.46. Found: C, 59.34; H, 5.25; N, 3.63 %.

Isoquinolinium salt 3b: Yield (70%); mp 217-219 °C (AcOH); IR (KBr) υ 1649 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.48 (s, 3H, Isoquinoline-CH_3), 3.07 (m, 2H, Isoquinoline-CH_2), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2CO), 4.13 (m, 2H, Isoquinoline-CH_2), 6.92 (s, 1H, Isoquinoline-CH), 7.35 (s, 1H, Isoquinoline-CH), 7.42-8.10 (m, Ar H). Anal. Calcd for $C_{21}H_{21}BrN_2O_3S$: C, 54.67; H, 4.59; N, 6.07; S, 6.95. Found: C, 54.59; H, 4.67; N, 6.32; S, 6.75 %.

Isoquinolinium salt 3c: Yield (72%); mp 227-229 °C (AcOH); IR (KBr) υ 1720 (C=O), 1689 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H, Isoquinoline-CH_3), 2.98 (t, 2H, *J* = 6 Hz, Isoquinoline-CH_2), 3.8 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.1 (t, 2H, *J*= 6 Hz, Isoquinoline-CH_2), 4.70 (s, 2H, CH_2CO), 6.89 (s, 1H, Isoquinoline-CH), 7.17 (s, 1H, Isoquinoline-CH), 7.32-8.22 (m, Ar H). Anal. Calcd for $C_{23}H_{22}BrNO_5$: C, 58.49; H, 4.69; N, 2.97. Found: C, 58.36; H, 4.51; N, 2.75 %.

Synthesis of 5,6-dihydro-8,9-dimethoxy-2-arylpyrrolo[2,1-a]isoquinoline 4

To a solution of isoquinolinium bromide salt **3a-c** (2 mmol) in dry benzene (30 mL), triethylamine (0.4 mL) was added and the reaction mixture was refluxed for 3~5 h, then left to cool to rt. The triethylamine hydrobromide was removed by filtration and the filtrate was evaporated under vacuum. The residue was triturated with MeOH where a brown precipitate was formed that was filtered off, washed with MeOH and dried. Recrystallization from the proper solvent afforded the corresponding 5,6-dihydro-8,9-dimethoxy-2-arylpyrrolo[2,1-*a*]isoquinoline **4**.

5,6-Dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-a]isoquinoline 4a

Yield (65%); mp 242-244 °C (EtOH); IR (KBr) υ 1604 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.95 (t, 2H,

J = 9Hz, Isoquinoline-CH_2), 3.76 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.03 (t, 2H, *J* = 9 Hz, Isoquinoline-CH_2), 6.87-7.56 (m, Ar H); MS *m/z* (%) 305 (M^+, 40), 290 (30.9), 205 (90.3), 190 (80.9). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.69; H, 6.15; N, 4.35 %.

5,6-Dihydro-8,9-dimethoxy-2-(benzothiazol-2-yl)pyrrolo[2,1-a]isoquinoline 4b

Yield (69%); mp 207-208 °C (MeOH); IR (KBr) υ 1658 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (t, 2H, *J* = 6.6 Hz, Isoquinoline-CH_2), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.07 (t, 2H, *J* = 6.6 Hz, Isoquinoline-CH_2), 6.65 (s, 1H, Isoquinoline-CH), 6.87 (s, 1H, Isoquinoline-CH), 7.21-7.35 (m, 4H, Ar H), 7.73 (d, 1H, *J* = 8.1Hz, Ar H), 7.86 (d, 1H, *J* = 8.1Hz, Ar H); ^{13}C NMR ($CDCl_3$) δ 28.46, 44.35, 46.0, 55.85, 101.34, 105.88, 111.18, 118.98, 121.06, 121.15, 122.89, 123.83, 125.66, 128.03, 131.24, 133.83, 147.78, 148.23, 153.84, 163.66; MS *m/z* (%) 362 (M^+,100), 347 (42.6), 275 (12.0), 181 (14.9). Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73; S, 8.85. Found: C, 69.65; H, 5.27; N, 7.72; S, 8.96 %.

5,6-Dihydro-8,9-dimethoxy-2-(2-oxo-2H-chromen-3-yl)pyrrolo[2,1-a]isoquinoline 4c

Yield (68%); mp 245-247 °C (MeOH); IR (KBr) υ 1719 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (t, 2H, *J* = 6.6 Hz, Isoquinoline-CH_2), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.13 (t, 2H, *J* = 6.6 Hz, Isoquinoline-CH_2), 6.69 (s, 1H, Isoquinoline-CH), 6.73 (s, 1H, Isoquinoline-CH), 6.81 (s, 1H, Pyrrole-CH), 7.26-7.52 (m, 5H, Ar H), 7.85 (s, 1H, Oxochromon-CH); ^{13}C NMR ($CDCl_3$) δ 28.83, 44.28, 56.02, 56.07, 99.87, 106.08, 111.40, 116.09, 117.31, 120.19, 121.61, 122.69, 122.89, 123.25, 124.20, 126.87, 129.56, 130.59, 132.17, 147.77, 148.36, 152.04, 160.31; MS *m/z* (%) 373 (M^+,100), 358 (39.4), 330 (17.4), 187 (12.3). Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.76; H, 5.36; N, 3.58 %.

Synthesis of 3-arylazo-5,6-dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-a]isoquinoline 6

To a cold solution of 2-phenylpyrrolo[2,1-*a*]isoquinoline **4a** (0.61g, 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 rt overnight then diluted with water (10 mL). The precipitate was filtered off, washed with EtOH and dried. Recrystallization from the proper solvent afforded the corresponding 3-arylazo-2-phenylpyrrolo[2,1-*a*]isoquinoline derivatives **6a,b**.

3-Phenylazo-5,6-dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-a]isoquinoline 6a

Yield (67%); mp 159-161 °C (dioxane-EtOH); IR (KBr) υ 1604 (C=C), 1375 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (t, 2H, *J* = 6.9 Hz, Isoquinoline-CH_2), 3.93 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.80 (t, 2H, *J* = 6.9 Hz, Isoquinoline-CH_2), 6.75 (s, 1H, Isoquinoline-CH), 6.86 (s, 1H, Isoquinoline-CH), 7.35-7.51(m,

7H, Ar H), 7.82 (d, 2H, *J* = 8.0 Hz, Ar H), 7.92 (d, 2H, *J* = 8.0 Hz, Ar H); ^{13}C NMR ($CDCl_3$) δ 28.56, 43.57, 56.01, 56.15, 105.14, 107.16, 111.03, 120.31, 121.82, 125.69, 126.87, 128.06, 128.33, 128.51, 128.95, 129.54, 132.08, 134.95, 138.92, 148.42, 149.37, 154.10; MS *m/z* (%) 409 (M^+, 100), 317 (56.1), 301 (19.0). Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.53; H, 5.46; N, 10.32 %.

3-(p-Tolylazo)-5,6-dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-a]isoquinoline 6b

Yield (68%); mp 195-196 °C (AcOH); IR (KBr) υ 1602 (C=C), 1356 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3H, CH_3), 3.45 (m, 2H, Isoquinoline-CH_2), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.70 (m, 2H, Isoquinoline-CH_2), 6.95 (s, 1H, Isoquinoline-CH), 7.05 (s, 1H, Isoquinoline-CH), 7.23-7.43 (m, Ar H),7.60 (d, 2H, *J* = 8.1 Hz, Ar H), 7.86 (d, 2H, *J* = 8.1 Hz, Ar H), 8.0 (s, 1H, Pyrrole-CH); ^{13}C NMR (DMSO-d_6) δ 20.88, 27.62, 43.36, 55.63, 55.89, 105.94, 107.96, 111.90, 119.38, 121.44, 125.60, 126.83, 127.49, 128.09, 129.00, 129.74, 130.88, 134.52, 135.12, 138.47, 148.14, 149.31, 151.50; MS *m/z* (%) 423 (M^+, 100), 317 (31.2), 218 (12.2). Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.43; H, 5.68; N, 9.85 %.

Synthesis of the Isoquinolinium Salt 7

To a solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **1** (0.82 g, 4 mmol) in dry benzene (20 mL), ethyl α-bromoacetate **9** (0.67 g, 4 mmol) was added. The mixture was refluxed for 6h, then left to cool. The solid product was filtered off, washed with ether, and dried to afford the isoquinolinium bromide **7** as brown powder (0.98 g), Yield (76%); mp 200-202 °C (MeOH); IR (KBr) υ 1745 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 3H, Isoquinoline-CH_3), 3.0 (t, 3H, *J* = 7.5 Hz, Ester-CH_3), 3.07 (m, 2H, Isoquinoline-CH_2), 3.86 (q, 2H, *J* = 7.5 Hz, Ester-CH_2), 3.9 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 4.1(m, 2H, Isoquinoline-CH_2), 4.68 (s, 2H, CH_2COO), 6.8 (s, 1H, Isoquinoline-CH), 7.17 (s, 1H, Isoquinoline-CH). Anal. Calcd for $C_{16}H_{22}BrNO_4$: C, 51.62; H, 5.96; N, 3.76. Found: C, 51.35; H, 5.74; N, 3.62 %.

Synthesis of 5,6- dihydro-8,9-dimethoxy- 2-oxopyrrolo[2,1-a]isoquinoline 8

To a solution of isoquinolinium bromide salt **7** (0.74 g, 2 mmol) in dry benzene (30 mL), triethylamine (0.4 mL) was added and the reaction mixture was refluxed for 8 h, then left to cool to rt. The triethylamine hydrobromide salt was removed by filtration and the filtrate was evaporated under vacuum. The residue was triturated with methanol where a precipitate was formed that was filtered off, washed with MeOH and dried. Recrystallization from MeOH afforded 2,3,5,6-tetrahydro-8,9-dimethoxy-2-oxopyrrolo[2,1-*a*]isoquinoline **8** as dark brown powder (0.31 g). Yield (64%); mp 243-244 °C, IR (KBr) υ 1742 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 2H, Oxopyrrolo-CH_2), 3.03 (m, 2H,

Isoquinoline-CH_2), 3.83 (m, 2H, Isoquinoline-CH_2), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 1H, Oxopyrrolo-CH), 6.82 (s, 1H, Isoquinoline-CH), 7.15 (s, 1H, Isoquinoline-CH); MS *m/z* (%) 245 (M^+,100), 219 (27.5), 205 (47.5), 160 (21.2). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 57.14; H, 6.12; N, 5.71. Found: C, 57.34; H, 6.25; N, 5.63 %.

Synthesis of the Isoquinolinium Salt 11

These compounds were prepared by the same method described for the synthesis of **3** *via* reaction of α-bromoketone derivatives **2a,b,d** with 3,4-dihydro-6,7-diethoxyisoquinolin-1-acetonitrile **10**. The compounds prepared with their data are listed below.

Isoquinolinium salt 11a: Yield (71%); mp 130-132 ^oC (MeOH); IR (KBr) υ 2205 (C≡N), 1688 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.37 (m, 6H, Isoquinoline-$2CH_3$), 2.84 (s, 2H, CH_2CO), 2.95 (m, 2H, Isoquinoline-CH_2), 4.07 (m, 2H, Isoquinoline-CH_2), 4.19 (m, 4H, Isoquinoline-$2CH_2O$), 5.58 (s, 2H, CH_2CN), 6.49 (s, 1H, Isoquinoline-CH), 6.75 (s,1H, Isoquinoline-CH), 7.27-7.76 (m, 5H, Ar H). Anal. Calcd for $C_{23}H_{25}BrN_2O_3$: C, 60.40; H, 5.51; N, 6.13. Found: C, 60.12; H, 5.56; N, 6.28%.

Isoquinolinium salt 11b: Yield (63%); mp 219-220 ^oC (DMF-EtOH); IR (KBr) υ 2209 (C≡N),1677 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (m, 6H, Isoquinoline-$2CH_3$), 2.51 (s, 4H, CH_2CO, CH_2CN), 3.05 (t, 2H, *J* = 9 Hz, Isoquinoline-CH_2), 4.09 (m, 4H, Isoquinoline-$2CH_2O$), 4.20 (t, 2H, *J* = 9 Hz, Isoquinoline-CH_2), 7.03 (s, 1H, Isoquinoline-CH), 7.41-7.46 (m, 2H, Ar H), 7.63 (s, 1H, Isoquinoline-CH), 7.95 (d, 1H, J = 7.2 Hz, Ar H), 8.09 (d, 1H, J = 7.2 Hz, Ar H). Anal. Calcd for $C_{24}H_{24}BrN_3O_3S$: C, 56.03; H, 4.70; N, 8.17; S, 6.23; Found: C, 56.17; H, 4.52; N, 7.95; S, 6.48 %.

Isoquinolinium salt 11d: Yield (63%); mp 204-206 ^oC (AcOH); IR (KBr) υ 2211 (C≡N), 1646 (C=O), cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.35 (m, 6H, Isoquinoline-$2CH_3$), 2.48 (s, 2H, CH_2CO), 2.76 (t, 2H, *J* = 6 Hz, Isoquinoline-CH_2), 3.25 (t, 2H, *J* = 6 Hz, Isoquinoline-CH_2), 4.11 (m, 4H, Isoquinoline-$2CH_2O$), 4.94 (s, 2H, CH_2CN), 6.92 (s, 1H, Isoquinoline-CH), 6.96 (s, 1H, Isoquinoline-CH), 7.09 (s, 1H, Ar H), 7.26 (s, 1H, Ar H), 7.36 (s, 1H, Ar H), 7.46 (s, 1H, Ar H), 7.59 (s, 1H, Benzofuryl-CH). Anal. Calcd for $C_{25}H_{25}BrN_2O_4$: C, 60.37; H, 5.07; N, 5.63. Found: C, 60.55; H, 5.13; N, 5.69 %.

Synthesis of 5,6-dihydro-8,9-diethoxy -2-arylpyrrolo[2,1-a]isoquinoline-1-carbonitrile 12

These compounds were prepared by the same method described for the synthesis of **4a-c** using isoquinolinium salt derivatives **11a,b,d** instead of **3a-c**. The compounds prepared with their data are listed below.

5,6-Dihydro-8,9-diethoxy-2-phenylpyrrolo[2,1-a]isoquinoline-1-carbonitrile 12a

Yield (73%); mp 158-160 °C (MeOH); IR (KBr) υ 2178 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.37 (m, 6H, Isoquinoline-2CH_3), 2.96 (m, 2H, Isoquinoline-CH_2), 3.45 (m, 2H, Isoquinoline-CH_2), 4.07 (m, 4H, Isoquinoline-2CH_2O), 6.68 (s, 1H, Isoquinoline-CH), 7.01 (s, 1H, Isoquinoline-CH), 7.40-7.49 (m, 5H, Ar H), 7.58 (s, 1H, Pyrrole-CH); ^{13}C NMR (DMSO-d_6): δ 14.60, 27.96, 54.06, 63.80, 64.09, 85.60, 108.22, 110.23, 112.20, 113.10, 120.13, 121.38, 125.87, 128.62, 130.33, 133.93, 135.78, 147.01, 148.51, 150.55, 156.70; MS *m/z* (%) 358 (M^+, 25), 301(14.6), 101(16.0). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.26; H, 6.39; N, 7.64 %.

5,6-Dihydro-8,9-diethoxy-2-(benzothiazol-2-yl)pyrrolo[2,1-a]isoquinoline-1-carbonitrile 12b

Yield (67%); mp 243-244 °C (EtOH) IR (KBr) υ 2202 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (m, 6H, Isoquinoline-2CH_3), 3.09 (t, 2H, *J* = 6.9 Hz, Isoquinoline-CH_2), 4.20 (m, 4H, Isoquinoline-2CH_2O), 4.91 (t, 2H , *J* = 6.9 Hz, Isoquinoline-CH_2), 6.80 (s, 1H, Isoquinoline-CH), 7.08 (s, 1H, Isoquinoline-CH), 7.38 (m, 1H, Ar H), 7.48 (m, 1H, Ar H), 7.85 (s, 1H, Pyrrole-CH), 7.88 (d, 1H, *J* = 6 Hz, Ar H), 7.97 (d, 1H, *J* = 6 Hz, Ar H); MS *m/z* (%) 415 (M^+, 50), 358 (72.7), 181 (28.8). Anal. Calcd for $C_{24}H_{21}N_3O_2S$: C, 69.37; H, 5.09; N, 10.11; S, 7.72. Found: C, 69.42; H, 5.33; N, 10.26; S, 7.51%.

5,6-Dihydro-8,9-diethoxy-2-(2-benzofuryl)pyrrolo[2,1-a]isoquinoline-1-carbonitrile 12d

Yield (66%); mp 164-165 °C (EtOH) IR (KBr) υ 2212 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (m, 6H, Isoquinoline-2CH_3), 3.17 (t, 2H, *J* = 7.2 Hz, Isoquinoline-CH_2), 3.79 (m, 4H, Isoquinoline-2CH_2O), 4.25 (t, 2H, *J* = 7.2 Hz, Isoquinoline-CH_2), 5.32 (s, 1H, Benzofuryl-CH), 6.66 (s, 1H, Isoquinoline-CH), 6.89 (s, 1H, Isoquinoline-CH), 7.18-7.63 (m, 4H, Ar H), 8.58 (s, 1H, Pyrrole-CH); ^{13}C NMR ($CDCl_3$): δ 14.69, 46.23, 55.19, 58.99, 64.64, 104.0, 112.21, 119.43, 124.30, 124.36, 126.55, 129.77, 148.92, 156.12, 180.65; MS *m/z* (%) 398 (M^+, 20), 217 (6.4), 86 (100). Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.51; H, 5.42; N, 7.19 %.

Synthesis of 3-(p-tolylazo)-5,6-dihydro-8,9-diethoxy-2-phenylpyrrolo[2,1-a]isoquinoline-1-carbnitrile 14

To a cold solution of 5,6-dihydro-8,9-diethoxy-2-phenylpyrrolo[2,1-*a*]isoquinoline-1-carbonitrile **12a** (0.71g, 2 mmol) in pyridine (20 mL), *p*-tolyldiazonium salt (0.21g, 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 rt overnight then diluted with water (10 mL). The precipitate was filtered off, washed with MeOH and dried. Recrystallization from EtOH afforded **14** Yield (69%); mp 197-198 °C (EtOH) IR (KBr) υ 2183 (C≡N), 1390 (N=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.37 (m, 6H, Isoquinoline-2CH_3), 2.34 (s, 3H, CH_3), 2.96 (t,

2H, *J* = 12 Hz, Isoquinoline-CH_2), 3.47 (t, 2H, *J* = 12 Hz, Isoquinoline-CH_2), 4.09 (m, 4H, Isoquinoline-2CH_2O), 6.68 (s,1H, Isoquinoline-CH), 7.0 (s,1H, Isoquinoline-CH), 7.22-7.25 (d, 2H, *J* = 7.8 Hz, Ar H), 7.48-7.58 (m, Ar H), 7.66-7.69 (d, 2H, *J* = 7.8 Hz, Ar H), 7.87 (s,1H, Ar H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.54, 14.65, 20.80, 27.85, 42.09, 63.90, 64.07, 108.24, 111.21, 112.43, 113.14, 117.49, 118.03, 121.53, 123.88, 125.90, 127.93, 128.66, 129.44, 130.36, 133.97, 137.53, 145.97, 149.54, 150.81, 151.74. Anal. Calcd for $C_{30}H_{28}N_4O_2$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.49; H, 5.93; N, 11.58 %.

2,3,5,6-Tetrahydro-8,9-diethoxy-3-(p-tolyl)-[1,2,3]triazolo[5,1-a]isoquinoline-1-carbonitrile 16

To a cold solution of the appropriate isoquinolinium bromide salts **11a,b,d** (2 mmol) in base-free absolute EtOH (20 mL), *p*-tolyldiazonium salt (2 mmol) was added portionwise over 1 h at 0-5 ^{o}C. After the addition was completed, the reaction mixture was left to stir at rt overnight then diluted with 10 mL water. The precipitate so formed was filtered off, washed with MeOH and dried. Recrystallization from EtOH afforded the corresponding 1,2,3-triazolo[5,1-*a*]isoquinoline-1-carbonitrile **16** Yield (65%); mp 193-195 ^{o}C (DMF-EtOH); IR (KBr) υ 3380 (NH), 2205 (C≡N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.38 (m, 6H, Isoquinoline-2CH_3), 2.17 (s, 3H, CH_3), 2.34 (t, 2H, *J* = 6.9 Hz, Isoquinoline-CH_2), 3.52 (t, 2H, *J* = 6.9 Hz, Isoquinoline-CH_2), 4.10 (m, 4H, Isoquinoline-2CH_2O), 5.13 (s, 1H, Triazole-NH), 6.66 (s, 1H, Isoquinoline-CH), 6.90 (s, 1H, Isoquinoline-CH), 7.25 (d, 1H, *J* = 8.7 Hz, Ar H), 7.47-7.65 (m, 1H, Ar H), 7.86 (s, 1H, Ar H), 8.0 (d, 1H, *J* = 8.7 Hz, Ar H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.52, 14.61, 20.79, 27.81, 42.09, 45.33, 64.07, 112.48, 113.20, 117.48, 120.68, 121.57, 128.66, 129.41, 133.26, 137.50, 145.95, 151.73; MS *m/z* (%) 376 (M^+, 78), 301 (37.4), 258 (19.9), 91 (78). Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.34; H, 6.29; N, 14.69 %.

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