NEW ROUTES TO PYRANO[2,3-*d*]PYRIMIDINE DERIVATIVES FROM β-ENAMINO NITRILE AND PHOSGENE IMINIUM CHLORIDE

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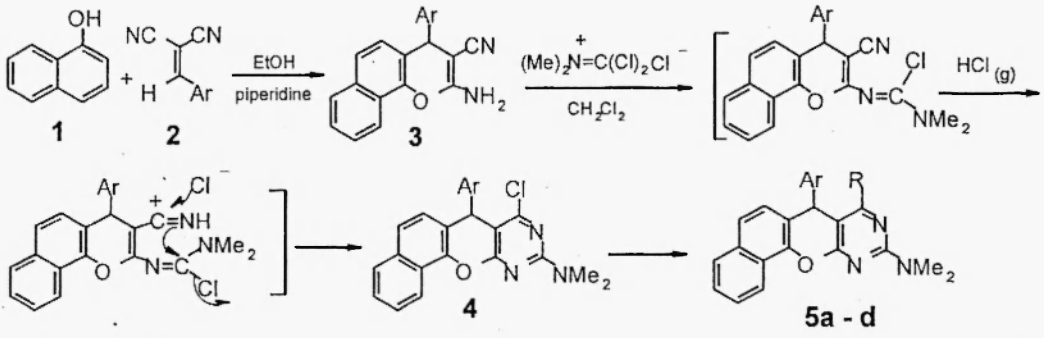
Abstract: The reaction of 2-amino-4-(4-fluorophenyl)-*4H*-benzo[*h*]chromene-3-carbonitrile (**3**) with *N,N*-dimethyldichlo-romethyleniminium chloride gave the tetracyclic chloro compound **4** which reacted readily with nucleophilic agents such as morpholine, piperidine, methylpiperazine to afford **5a-c**. Furthermore, displacement of the halogen atom of compound **4** by hydrazine yielded **5d**. Compound **5d** served as the precursor to pyranopyrimidine derivatives **6-11** by the reactions with triethyl orthoformate, *N,N*-dimethyldichloromethyleniminium chloride, carbon disulfide, ethyl acetoacetate , ethyl cyanoacetate and sodium nitrite in acetic acid.

Introduction

The chemistry of dichloromethyleniminium salts has proved to be very useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a dialkylamino group.[1-5] Pyranopyrimidine derivatives and heterocyclic annelated pyrans continue to attract attention due to a wide variety of interesting physiological biological activities observed.[6] In the search for an efficient method for the preparation of pyrano[2,3-*d*]pyrimidine derivatives and following our work on the synthesis and reactivity and biological activity of polyheterocyclic systems which contain a pyrimidine moiety,[7-9] this paper describes a novel synthesis of some new pyrano[2,3-*d*]pyrimidine derivatives by reaction of heterocyclic aminonitrile with *N,N*-dimethyldichloromethyleneiminium chloride .

Results and Discussions

Heterocyclic β-enamino nitriles are versatile synthons for various cyclization reactions.[10] Some recent reports[11,12] have addressed the biological activity of 2-amino-4-substituted-4*H*-benzo[*h*]chromone-3-carbonitrile. The direct route to the title ring system proved to be the reaction of 2-amino-4-(4-fluorophenyl)-*4H*-benzo[*h*]chromene-3-carbonitrile (**3**) with *N,N*-dimethyldichloromethyleneiminium chloride (phosgene iminium chloride). The aminonitrile **3** has been prepared by Michael addition of α-naphthol (**1**) to 2-(4-fluorobenzylidene)malononitrile (**2**) in the presence of piperidine as a base (Scheme-1). Compound **3** was characterized by microanalysis and spectroscopy.



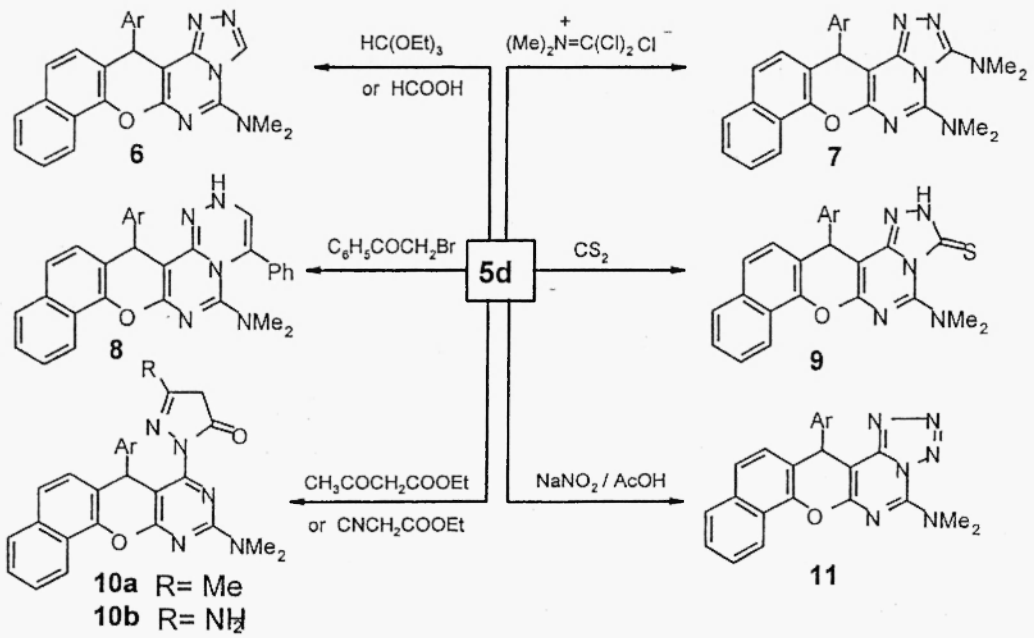
Ar = 4-FC_6H_4
R = a) Morpholino, b) piperidino, c) methylpiperazino, d) $NHNH_2$

Scheme -1

Treatment of reactive compound **3** with *N,N*-dimethyldichloromethyleneiminium chloride in 1,2-dichloroethane at room temperature provided [8-chloro-7-(4-fluorophenyl)-*7H*-12-oxa-9,11-diazabenzo[*a*]-anthracen-10-yl]dimethylamine (**4**) through the pathway outlined in Scheme **1**.[13] The structure of compound **4** was consistent with elemental analysis and spectral data. Its mass spectrum showed the expected molecular ion

peak at *m/z* 405 and its IR spectrum showed the absence of nitrile and NH_2 signals. Also, the structure of compound **4** was confirmed by analysis of the ^1H NMR spectrum. The chloride bearing group in the tetracyclic compound **4** reacts readily with nucleophilic agents such as morpholine, piperidine, methylpiperazine to afford **5a-c** in good yields (Scheme-1). The structures of compounds **5a-c** were determined by microanalytical and spectral data. Mass spectra of compounds **5a-c** show the expected molecular ion peaks at *m/z* 454, 456 and 469, respectively. Also, their IR spectra show the absence of NH and NH_2 signals. The ^1H NMR spectrum of [7-(4-fluorophenyl)-8-morpholino-12*H*-7-oxa-9,11-diazabenzo[*a*]-anthracen-10-yl]dimethylamine (**5a**), given as an example, show signals at δ 3.15 (s, 6H, $N(CH_3)_2$), 3.35- 3.65 (m, 8H, $4CH_2$), 5.50 (s, 1H, pyran proton) and 6.98- 8.25 (m, 10H, aromatic protons).

Furthermore, displacement of the halogen atom of compound **4** by treatment with hydrazine hydrate in refluxing EtOH/DMF (4:1) yielded **5d** (Scheme 1). The structure of product **5d** was consistent with elemental analysis and spectral data. Compound **5d** was used for the direct synthesis of several new compounds. Thus, compound **5d** was converted into **6** by reaction with triethyl orthoformate. Product **6** was also obtained by reaction of **5d** with formic acid. The two products were found to be identical in all respects (mp, mixed mp, IR, ^1H NMR). A particular aspect of the reactivity of *N,N*-dimethyldichloromethyleniminium chloride is its ability to undergo condensation with **5d** to yield **7**. The reaction of **5d** with phenacyl bromide in presence of sodium carbonate led to the formation of compound **8**. Compound **5d** was also reacted with carbon disulfide to yield 5-dimethylamino-14-(4-fluorophenyl)-2*H*,14*H*-7-oxa-1,2,4,6-tetraazabenzo[*a*]-cyclopenta[*h*]-anthracene-3-thione (**9**). Refluxing compound **5d** with ethyl acetoacetate and ethyl cyanoacetate led to the formation of products **10a** and **10b**, respectively.[7] Finally, the product **11** was obtained by refluxing **5d** with sodium nitrite in acetic acid. (Scheme-2) Structural assignments of all compounds **6-11** were based on elemental analyses, ^{1}HNMR, IR and mass spectra.



Scheme-2

Experimental

All melting points are uncorrected and were measured using an Electrothermal IA 9100 apparatus. IR spectra were recorded on a Nexcus 670 FT-IR spectrometer using potassium bromide pellets. ^{1}H NMR spectra were determined on a Jeol 270 MHz spectrometer with TMS as internal reference. Mass spectra were recorded on an EI + Q1 MSLMR UPLR instrument. Microanalyses were performed on a Vario El Elemental apparatus.

2-Amino-4-(4-fluorophenyl)-4*H*-benzo[*h*]chromone-3-carbonitrile (3)

A solution of 2-(fluorobenzylidene) malononitrile (1.72 g, 10 mmol) and α-naphthol (1.44 g, 10 mmol) in 50 ml absolute ethanol in the presence of a catalytic amount of piperidine was refluxed for 3-5 h. The solid product was collected by filtration and crystallized from EtOH to afford 2.46 g (78%) of yellow crystals; mp 236-238 °C; IR ν 3381, 3365 (NH_2), 2220 cm^{-1} (CN); ^{1}H-NMR (DMSO-d_6) δ 5.00 (s, 1H, pyran proton), 7.10- 8.25 (m, 12 H, aromatic protons + NH_2, exchangeable with D_2O); MS, *m/z* (%): 316 (M^+, 37), 317 (9), 222 (16), 221 (100). *Anal.* Calcd. for $C_{20}H_{13}FN_2O$ (316.3): C, 75.94; H, 4.14; N, 8.86. Found: C, 76.01; H, 4.13; N, 8.97.

[8-Chloro-7-(4-fluorophenyl)-7*H*-12-oxa-9,11-diazabenzo[*a*]anthracen-10-yl]dimethylamine (4)

A solution of **3** (3.16 g, 10 mmol) and phosogen iminiumchloride (1.78 g, 11 mmol) in dry 1,2-dichloroethane (100 ml) was stirred overnight at room temperature. The precipitated solid was collected by filtration and crystallized from dioxane to give **4** (3.69 g, 91%) as colorless powder; mp 273-275 °C; IR ν 3010, 3040, 2930, 2889, 1650, 1450 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 3.23 (s, 6H, $N(CH_3)_2$, 5.55 (s, 1H, pyran proton), 7.00- 8.40 (m, 10H, aromatic protons); MS, *m/z* (%): 405 (M^+, 32%), 310 (100%), 312 (33%). *Anal.* Calcd. for $C_{23}H_{17}ClFN_3O$ (405.9): C, 68.07; H, 4.22; N, 10.35. Found: C, 67.99; H, 4.21; N, 10.38.

General procedure for 5a-c. A solution of **4** (10 mmol) and the appropriate amine [a - piperidine, b - morpholine, c - 4-methylpiperazine] (11 mmol) in ethanol (50 ml) was refluxed until the starting material **4** had disappeared (TLC analysis, 20-30 h). The product **5** was collected by filtration and crystallized from ethanol.

[7-(4-Fluorophenyl)-8-piperidino-7*H*-12-oxa-9,11-diazabenzo[*a*]anthracen-10-yl]dimethylamine (5a)

Yield 3.63 g (80%); colorless powder; mp 231-233 °C; ^{1}HNMR (DMSO-d_6) δ 1.35-1.65 (m, 6H, $3CH_2$), 3.15 (s, 6H, $N(CH_3)_2$), 3.20-3.50 (m, 4H, $2CH_2$), 5.40 (s, 1H, pyran proton), 7.10-8.30 (m, 10H, aromatic protons); MS *m/z* (%) 453 (10), 454 (65), 455 (28), 456 (6), 412 (9), 411 (31), 360 (25), 359 (100), 317 (9), 164 (5), 84 (2). *Anal.* Calcd. for $C_{28}H_{27}FN_4O$ (454.6): C, 73.99; H, 5.99; N, 12.33. Found: C, 47.08; H, 5.98; N, 12.30.

[7-(4-Fluorophenyl)-8-morpholino-12*H*-7-oxa-9,11-diazabenzo[*a*]anthracen-10-yl]dimethylamine (5b)

Yield 3.92 g (86%); colorless powder; mp 218-220 ^{0}C; ^{1}HNMR (DMSO-d_6): 3.15 (s, 6H, N(CH_3)$_2$), 3.35- 3.65 (m, 8H, 4CH_2), 5.50 (s, 1H, pyran proton), 6.98- 8.25 (m, 10H, aromatic protons); MS *m/z* (%) 458 (3), 457 (14), 456 (46), 455 (4), 411 (8), 398 (12), 362 (24), 361 (100), 303 (8), 172 (6). *Anal.* Calcd. for $C_{27}H_{25}FN_4O_2$ (456.5): C, 71.04; H, 5.52; N, 12.27. Found: 71.29; H, 5.71; N, 12.31.

[7-(4-Fluorophenyl)-8-(4-methylpiperazino)-12*H*-7-oxa-9,11-diazabenzo[*a*]anthracen-10-yl]-dimethylamine (5c)

Yield 3.24 g (69%); colorless powder; mp 237-239 ^{0}C; ^{1}HNMR (DMSO-d_6): 2.15 (s, 3H, NCH_3), 2.30- 2.45(m, 4H, 2CH_2), 3.15 (s, 6H, N($\mathbf{CH_3}$)$_2$), 3.20- 3.49 (m, 4H, 2CH_2), 5.50 (s, 1H, pyran proton), 7.00- 8.30 (m, 10H, aromatic protons); MS *m/z* (%) 471 (5), 470 (66), 469 (44), 468 (3), 400 (28) , 399 (100), 386 (16), 317 (7), 303 (7), 291 (6), 260 (4), 169 (3). *Anal.* Calcd. for $C_{28}H_{28}FN_5O$ (469.6): C, 71.62; H, 6.01; N, 14.91. Found: C, 71.77; H, 6.20; N, 14.97.

[7-(4-Fluorophenyl)-8-hydrazino-7*H*-12-oxa-9,11-diazabenzo[*a*]anthracen-10-yl]dimethylamine (5d)

A solution of **4** (10 mmol) and hydrazine hydrate (11 mmol) in EtOH (40 ml) and DMF (10 ml) was refluxed for 8 h). The product **5d** was collected by filtration and crystallized from dioxane to afford 3.52 g (88%) of colorless powder; mp 202 -204 ^{0}C; IR ν 3389, 3360 cm^{-1} (NH+NH_2); ^{1}HNMR (DMSO-d_6) δ 3.14 (6H, NMe_2), 5.20 (s, 1H, pyran proton), 5.45 (br, 1H, NH, exchangeable with D_2O), 6.15 (br, 2H, NH_2, exchangeable with D_2O), 6.88 – 8.43 (m, 10H, Ar protons). *Anal.* Calcd. for $C_{23}H_{20}FN_5O$ (401.5): C, 68.82; H, 5.02; N, 17.45. Found: C, 68.77; H, 5.04; N, 17.49.

[14-(4-Fluorophenyl)-14*H*-7-oxa-1,2,4,6-tetraazabenzo[*a*]cyclopenta[*h*]anthracen-5-yl]dimethylamine (6)

A solution of **5d** (10 mmol) in triethyl orthoformate (25 ml) was stirred at 70 ^{0}C for 9 h and then cooled overnight. The solid product **6** was collected by filtration and crystallized from methanol to yield 2.34 g (57%) of colorless powder; mp 286-288 ^{0}C; IR ν 1615 cm^{-1}(C=N). ^{1}HNMR (DMSO-d_6): 3.19 (s, 6H, N(CH_3)$_2$, 5.20 (s, 1H, pyran proton), 6.90- 8.22 (m, 10H, aromatic protons), 8.68 (s, 1H, -CH=N-); MS *m/z* (%) 411 (98), 277 (100). *Anal.* Calcd. for $C_{24}H_{18}FN_5O$ (411.4): C, 70.06; H, 4.41; N, 17.02. Found: C, 70.11; H, 4.52; N, 17.09.

14-(4-Fluorophenyl)-14*H*-7-oxa-1,2,4,6-tetraaza-3,5-bis(dimethylamino)benzo[*a*]cyclopenta[*h*]-anthracene (7)

A solution of **5d** (10 mmol) in 1,2-dichloroethane (10ml) was added to a stirred suspension of phosgen iminium chloride (10 mmol) in 1,2-dichloroethane (30 ml) at room temperature. The mixture

was then refluxed for 4 h. The solid product 7 was collected by filtration, washed with saturated solution of $NaHCO_3$, H_2O, dried and crystallized from EtOH to afford 3.38 g (74%); mp 283-285 ^{0}C; IR ν 3040, 3010, 2998, 1607, 1590, 1562, 1420 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 3.09 (s, 6H, $N(CH_3)_2$, 3.14 (s, 6H, $N(CH_3)_2$, 5.01 (s, 1H, pyran proton), 6.94-8.32 (m, 10H, aromatic protons). *Anal.* Calcd. for $C_{26}H_{23}FN_6O$ (454.5): C, 68.71; H, 5.10; N, 18.49. Found: C, 68.99; H, 5.08; N, 18.69.

[14-(4-Fluorophenyl)-4-phenyl-2*H*,14*H*-7-oxa-1,2,5,7-tetraazadibenzo[*a,h*]anthracen-5-yl]dimethylamine (8)

A mixture of **5d** (10 mmol), phenacyl bromide (10 mmol), and sodium acetate in dry dioxane (30 ml) was heated under reflux for 12 h. The solid precipitate that separated upon cooling was filtered off and crystallized from dioxane to afford 2.20 g (44%); mp 288-290 ^{0}C; IR ν 3391, 1603, 1558 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 3.16 (s, 6H, $N(CH_3)_2$, 5.30 (s, 1H, pyran proton), 6.62 (s, 1H, =CH-NH), 7.00-8.42 (m, 16H, aromatic protons), 9.11 (br, 1H, NH, exchangeable with D_2O); MS *m/z* (%) 501 (14). *Anal.* Calcd. for $C_{31}H_{24}FN_5O$ (501.6): C, 74.24; H, 4.82; N, 13.96. Found: C, 74.45; H, 4.83; N, 14.01.

5-Dimethylamino-14-(4-fluorophenyl)-2H,14H-6-oxa-1,2,4,6-tetraazabenzo[*a*]cyclopenta[*h*]anthracene-3-thione (9)

To a warm ethanolic sodium hydroxide solution [prepared by refluxing (0.40 g, 10 mol) of NaOH in abs. EtOH (50 ml)] was added (10 mmol) of compound **5d** and carbon disulfide (15 mmol). The mixture was heated on a water bath for 6 h, then allowed to cool , poured into water, and neutralized with diluted HCl. The solid product **9** was collected by filtration and crystallized from benzene to give 2.97 g (67%); mp 228-230 ^{0}C. IR, KBr ν 3331, 1613, 1583 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 3.14 (s, 6H, $N(CH_3)_2$, 5.20 (s, 1H, pyran proton), 6.93 -8.46 (m, 10H, aromatic protons), 12.40 (br, 1H, NH, exchangeable with D_2O). *Anal.* Calcd. for $C_{24}H_{18}FN_5OS$ (443.5): C, 65.00; H, 4.09; N, 15.79. Found: 65.09; H, 4.16; N, 15.81.

2-[10-Dimethylamino-7-(4-fluorophenyl)-7*H*-12-oxa-9,11-diazabenzo [a]anthracen-8-yl]-5-methyl-2,4-dihydro-pyrazole-3-one (10a)

A solution of compound **5d** (10 mmol) and ethyl acetoacetate (10 mmol) in sodium ethoxide solution [prepared by dissolving (0.23 g, 10 mmol) of sodium metal in absolute ethanol (30 ml)] was refluxed for 9 h. The mixture was allowed to cool, poured into cold water, and neutralized with acetic acid. A solid precipitate was filtered off and crystallized from dioxane to give 3.79 g(81%); mp 217-219 ^{0}C; IR ν 1669, 1601, 1550, 1452 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 3.15 (s, 6H, $N(CH_3)_2$, 3.34(dd, 2H, CH_2), 5.60 (s, 1H, pyran proton), 7.03 -8.42 (m, 10H, aromatic protons); MS *m/z* (%) 467. *Anal.* Calcd. for $C_{27}H_{22}FN_5O_2$ (467.5): C, 69.37; H, 4.74; N, 14.98. Found: C, 69.44; H, 4.76; N, 14.97.

5-Amino-2-[10-Dimethylamino-7-(4-fluorophenyl)-7H-12-oxa-9,11-diaza-benzo[a]anthracen-8-yl]-2,4-dihydro-pyrazole-3-one (10b)

This compound was obtained by using ethyl cyanoacetate instead of ethyl acetoacetate in the procedure described above; yield 3.42 g (73%); mp 237-239 ^{0}C; IR, KBr ν 3290, 688, 1606, 1527 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 3.14 (s, 6H, N(CH_3)$_2$, 3.49 (dd, 2H, CH_2), 5.59 (s, 1H, pyran proton), 6.40 (br, 2H, NH_2, exchangeable with D_2O); 7.03 -8.42 (m, 10H, aromatic protons); *Anal.* Calcd. for $C_{26}H_{21}FN_6O_2$ (468.5): C, 66.66; H, 4.52; N, 17.94. Found: C, 66.47; H, 4.54; N, 17.96.

[14-(4-Fluorophenyl)-14*H*-7-oxo-1,2,3,4,6-pentaazabenzo[*a*]cyclopenta[*h*]anthracen-4-yl]-dimethylamine(11)

A solution of **5** (4.01 g, 10 mmol) and sodium nitrite (0.69 g, mmol) in acetic acid (50 ml) was stirred at room temperature for 24 h. Cold distilled water was added and the precipitate was collected by filtration and crystallized from dioxane to afford **11** (2.72 g, 66 %); mp 197-199 ^{0}C; IR, KBr ν 3010, 3070, 2890, 1629, 1591, 1562, 1480 cm^{-1}. ^{1}HNMR (DMSO-d_6) δ 3.10 (s, 6H, N(CH_3)$_2$, 5.15 (s, 1H, pyran proton), 7.10 - 8.41 (m, 11H, aromatic protons); MS *m/z* (%) 412. *Anal.* Calcd. for $C_{23}H_{17}FN_6O$ (412.43): C, 66.98; H, 4.15; N, 20.38. Found: C, 67.01; H, 4.16; N, 20.39.

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