NITRILES IN ORGANIC SYNTHESIS:FACILE and GENERAL SYNTHESES of FUSED TETRAAZA-BENZO [*a*] CYCLOPENTA [*h*]ANTHRACENE and TETRAAZA-DIBENZO[*a,h*] ANTHRACENE

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Abstract

Cyclocondensation of **(5)** with different reagents gave 6-oxa-1,3,3a-5-tetraaza-benzo[a]cyclopenta[h]anthracene derivatives **(6,7,9a-f)** and 2-(4-fluorophenyl)-14-(4-nitrophenyl)-4H-14H-7-oxa-1,4,4a,6- tetraaza-dibenzo[a,h]anthracene and 3,3-dichloro-14-(4-nitrophenyl)-3,4-dihydro-14H-7-oxa-1,4,4a,6-tetraaza dibenzo[a-h]anthracen-2-ylideneamine **(10,11)** respectively.

Introduction

Some recent reports[1,2] have adressed the biological and pharmacological activity of 2-amino-4-substituted-4H-benzo[h]chromene-3-carbonitrile. These products have been prepared by Michael addition of α-naphthol **(1)** to arylidene malononitrile namely 2-(4-nitrobenzylidene)-malononitrile **(2)** using piperidine as a base (Scheme 1). Moreover, triazolo[1,5-c]pyrimidine moeities show some of the useful pharmacological properties of theophylline to a greater extent. The latter were shown to protect guinea pigs against the toxic effects of inhaled histamine spray.[3,4]

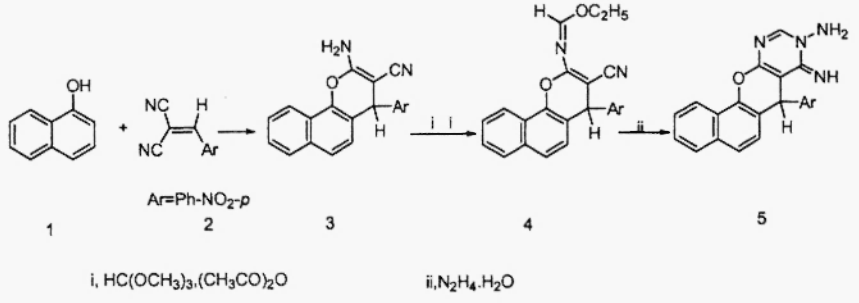
Results and Discussion

In the present study and in continuation of our previous work on the synthesis of polyfunctionally substituted heteroaromatics for potential utility as pharmaceuticals[5-8] In the past few years, we have involved in a program aimed at developing new efficient synthesis of these heteroaromatic compounds utilizing inexpensive starting materials. During this phase of our research, we shown that 8-imino-7-(4-nitrophenyl)-7H,8H-12-oxa-9,11-diaza-benzo[*a*]anthracen-9-ylamine **(5)** considered as a key intermediate, to prepare fused heterocycles, was prepared by treating N-3-cyano-4-(4-nitrophenyl)-4-H-benzo[*h*]chromen-2-yl]formimidic acid ethyl ester **(4)** with hydrazine hydrate[9,10]. In turn, compound **(4)** was prepared by reaction of **(3)** with an equimolar amount of triethyl orthoformate and acetic anhydride (Scheme 1).

When compound **(5)** reacted with one carbon donor cyclizing agents orthoesters, formic acid or acetic anhydride gave 13-(3-nitrophenyl)-13H-6-oxa-1,3,3a-5-tetraaza-benzo [*a*]cyclopenta [h] anthracene **(6)** and 2-methyl-13-(4-nitrophenyl)-13H-6-oxa-1,3,3a-5-tetraaza-benzo[*a*] cyclopenta[*h*] anthracene **(7)** respectively. (Scheme 2).

However, This current pharmacological interest has led us to seek novel methods to the synthesis of such tricyclic systems, in order to prepare new and biological active molecules.

Compund **(4)** was reacted with acetohydrazide and isonicotinic acid hydrazide[5-7 11] in refluxing ethanol to give 2-methyl-13-(4-nitrophenyl)-13H-6-oxa-1,3,3a-5-tetraaza-benzo[a] cyclopenta[h]anthracene,13-(4-nitrophenyl)-2-pyridin-4-yl-13H-6-oxa-1,3,3a,5-tetraaza-benzo[*a*] cyclopenta[*h*]anthracene **(7), (9c)** respectively.



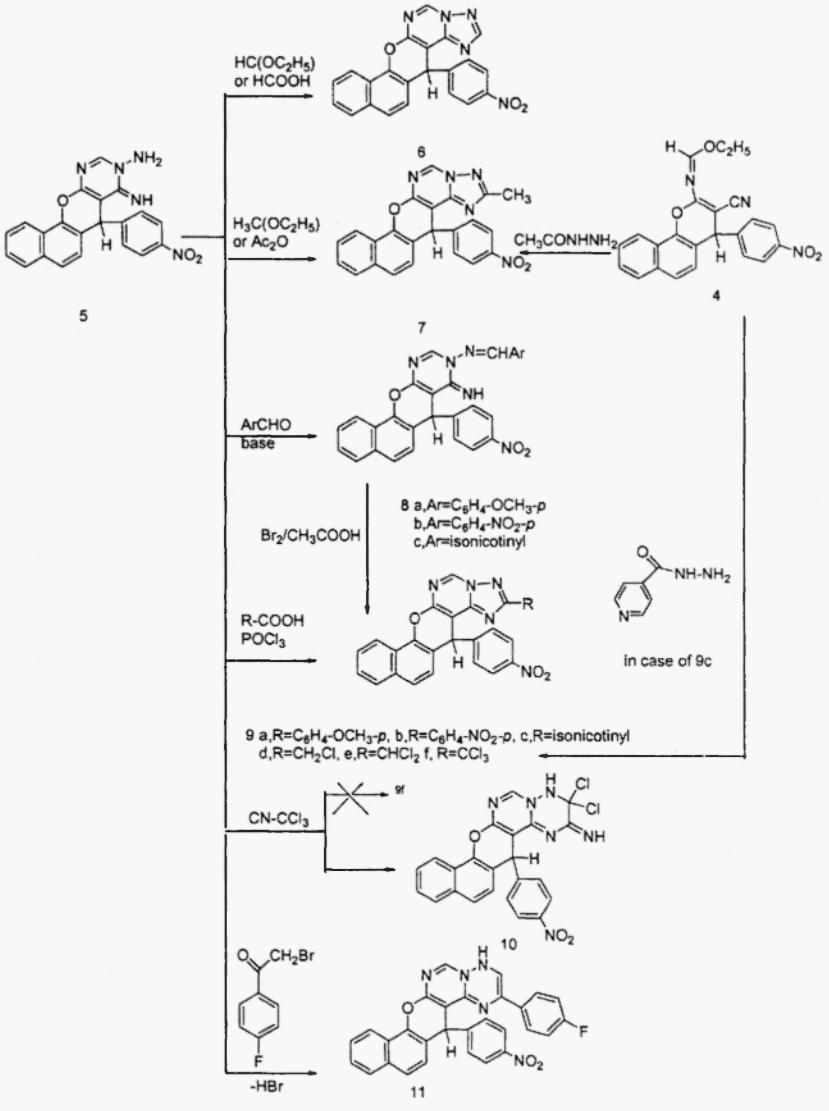
Scheme 1

Reaction of compound **(5)** with appropriate aldehydes in presence of base afforded [8-imino-7-(4-nitrophenyl)-7H,8H-12-oxa-9,11-diaza-benzo[*a*]anthracen-9-yl]-(arylidene)amine, and [8-imino-7-(4-nitrophenyl)-7H,8H-12-oxa-9,11-diaza-benzo[*a*]anthracen-9-yl]-pyridin-4-yl methylene amine **(8a-c)**, respectively as a thermodinamically stable compound. As an unexpected result, Taylor-Loeffler rearrangement did not take place as a result of using base in the medium.[9]The proposed structure of **(8a-c)** were supported by the following spectral features, the ^{1}H NMR spectrum of **(8a)** as an example showed the presence of NH imino signal at δ 11.02 ppm and N=CH- at δ 8.52 ppm.

The above results encouraged us to seek a novel, simple and an one pot reaction to synthesis 2-(substituted)-6-oxa-1,3,3a-tetraaza benzo[*a*]cyclopenta[*h*]anthracene **(9a-f)** in good yield starting from the imino-amino derivatives. Thus, by reacting **(5)** with appropriate carboxylic acid in phosphorus oxychloride as cyclizing agent. As well as **(8a-c)** cyclized in presence of bromine/acetic acid[12,13] affording**(9a-c)**. 2-(Substituted)-13-(4-nitrophenyl)-13H-6-oxa- 1,3,3a-tetraazabenzo[*a*]cyclopenta [*h*] anthracene **(9a-f)** were established by the absence of NH or NH_2 in its ir, and Hnmr. The structure of compound **(9f)**was established according to absence of signals corresponding to NH and NH_2, and presence of signals at δ 6.1 ppm and at 9.5 ppm corresponding to H-pyran and H-pyrimidine respectively.

El-Agrody et al. [14], postulated that 13-(4-nitrophenyl)-2-trichloromethyl-13H-6-oxa-1,3,3a,5-tetraaza-benzo[*a*]cyclopenta[*h*]anthracene (reported as 3-trichloromethyl[1,2,4]triazolo-[1,5-c]pyrimidine) **(9f)** as a product from the interaction of **(5)** with trichloroacetonitrile ,but, in fact we isolated 3,3-dichloro-14-(4-nitrophenyl)-3,4-dihydro-14H-7-oxa-1,4,4a,6-tetraaza dibenzo[*a-h*]anthracen-2-ylideneamine **(10)** . The isolated product was established by the following: in its ^{1}H NMR showed broad signals at 8.45 and 6.75 ppm, exchangeable with D_2O. Moreover, the mass spectrum for the isolated product showed molecular ion peak (m/z) at 395 [$(M^+ - HN - CCL2)^+$, 10%].

Interaction of (**5**) with *p*-fluorophenacyl bromide in presence of sodium carbonate afforded 2-(4-fluorophenyl)-14-(4-nitrophenyl)-4H-14H-7-oxa-1,4,4a,6- tetraaza-dibenzo[*a,h*]anthracene (**11**) (Scheme 2).



Scheme 2

Experimental

Melting points were uncorrected. Elemental analysis was carried out in the Microanalytical Unit National research Centre. IR spectra were recorded on Mattson 5000 FT-IR spectrometer using KBr wafer technique. ^{1}H NMR spectra were determined on JEOL 270 MHz spectrometers using TMS as an internal standard with (δ = 0 ppm). Mass spectra were determined on FiniganSQ 700 (Japan).

2-amino-4-(4-nitrophenyl)-4-*H*-benzo[h]chromene-3-carbonitrile (3): A solution of equimolecular amounts of α-naphthol (**1**) (0.01mole) and 2-(3-nitrobenzylidene)-malononitrile (**2**) (0.01mole) in 50ml absolute ethanol and a catalytic amount of piperidine was refluxed for 3 h. A white precepitate was formed collected by filtration and recrystallized from ethanol affording (**3**), 85%,m.p. 151-153 ^{0}C, $C_{20}H_{13}N_3O_3$ (343.34),IR (γ/cm^{-1}) 3390-3362 (NH_2),2230(CN), ^{1}H-NMR(DMSO-d_6) 8.32-7.25 (m,

10H, aromatic protons), 6.25 (s, 1H, pyran) and 5.25 (bs, 2H, exchangeable with D_2O,NH_2), Ms:m/z(%) 343 (M^+ 25%),277(100%).

N-3-cyano-4-(4-nitrophenyl)-4-H-benzo[h]chromen-2-yl]formimidic acid ethyl ester (4):

A solution of **(3)** (0.01 mole) in a mixture of triethyl orthoformate and acetic anhydride (1:1 *vol*) was refluxed for 6h.Then ,the reaction mixture was cooled .A colourless preceipitate was formed and filtered off affording **(4)**, 87%,m.p. 240-242^{0}C, $C_{23}H_{17}N_3O_4$ (399.41), IR (γ/cm^{-1}) 2225 (CN),1659 (CO ester), ^{1}H-NMR(DMSO-d_2) 8.96 (s, 1H, N=CH), 8.25-7.45 (m, 10H, aromatic protons), 5.59 (s, 1H, pyran), 4.39 (q,2H, CH_2),1.48 (t,3H,CH_3). Ms:m/z(%)399 (M^+ ,73%), 277,(100%).

8-imino-7-(4-nitrophenyl)-7H,8H-12-oxa-9,11-diaza-benzo[a]anthracen-9-ylamine (5):

Hydrazine hydrate (3ml) was added to a solution of **(4)** in 20 ml absolute ethanol in ice bath .The reaction mixture was stirred for 4h. Then the reaction mixture was diluted with cold water .The solid formed was collected by filtration and crystallized from dioxane affording (**5**). 90%,m.p. 220-22^{0}C, $C_{21}H_{15}N_5O_3$ (385.38), IR (γ/cm^{-1}) 3377-3315 (NH_2),3199 (NH), ^{1}H-NMR(DMSO-d_6) 9.85 (s, 1H, exchangeable with D_2O, NH), 9.5 (s, 1H, pyrim.), 8.40-6.95 (m, 10H, aromatic protons), 6.82 (b, 2H,exchangeable with D_2O, NH_2), and 6.25 (s, 1H, pyran). Ms:m/z(%)M^+ 386 (M^+ ,40%), 277, (100%).

13-(4-nitrophenyl)-13H-6-oxa-1,3,3a-5-tetraaza-benzo[a]cyclopenta[h]anthracene (6) , 2-methyl-13-(4-nitrophenyl)-13H-6-oxa-1,3,3a-5-tetraazabenzo[a]cyclopenta[h]anthracene (7):

General method : A mixture of (**5**) (0.01 mole) and 10 ml of either triethyl orthoformate, triethyl orthoacetate, formic acid or acetic anhydride was heated under reflux for 8h.(under TLC control).The reaction mixture was cooled . the precepitate was colleceted by filtration and crystallized from ethanol yielding (6) , 89%,m.p. 295-97^{0}C , $C_{22}H_{13}N_5O_3$ (395.38), ^{1}H-NMR(DMSO-d_6) 9.58 (s, 1H, pyrim.), 8.51 (s, 1H, triazoloe), 8.48-7.20 (m, 10H, aromatic protons), and 6.35 (s, 1H, pyran),Ms:m/z(%) 395 (M^+ , 99%), 277, (100%), **(7)** 75%,m.p. 270-72^{0}C, $C_{23}H_{15}N_5O_3$ (409.41)^1 H-NMR(DMSO-d_6) 9.25 (s, 1H, pyrim.), 8.35-7.45 (m, 10H, aromatic protons), 5.95 (s, 1H, pyran) and 2.75 (s, 3H, CH_3). Ms:m/z(%), 410 (M^{+1} 37%,286 (100%)

Method B: A mixture of **(3)** (0.01 mole) and (0.01 mole) of acetohydrazide was heated under reflux for 8h.(under TLC control).The reaction mixture was cooled . the precepitate was colleceted by filteration and crystallized from ethanol yielding 85% from **(7).**

[8-imino-7-(4-nitrophenyl)-7H,8H-12-oxa-9,11-diaza-benzo[a]anthracen-9-yl]-(arylidene)amine, [8-imino-7-(4-nitrophenyl)-7H,8H-12-oxa-9,11-diaza-benzo[a]anthracen-9-yl]-pyridin-4-yl methylene amine (8a-c):

General Method A mixture of (5) (1g,2.4 mmol) and p-anisaldehyde p-nitrobenzaldehyde or pyridine-4-carbox-aldehyde (2.5 mmol) in dioxane and piperidine as a catalyst, was refluxed for 8 h (TLC control) on cooling a solid product separated which was filtred and crystallized from the appropriate solvent to afford **(8a-c).**

(8a): 60% from dioxane,m.p 240-2 ^{0}C , $C_{29}H_{21}N_5O_4$ (503.52), IR (γ/cm^{-1}) 3284 (NH), ^{1}H-NMR(DMSO-d_6) 11.02 (s, 1H, exchangeable by D_2O,NH), 9.25 (s, 1H, pyrim.), 8.52 (s, 1H, N=CH), 8.40-7.65 (m, 14H, aromatic protons), 6.32 (s, 1H, pyran) and 3.82 (s, 3H, OCH_3). Ms:m/z(%) 369 (M^+ -N=CHPh-OCH3-*p*,54%),137 (100%).

(8b): 50% from dioxane,m.p 250-2 ^{0}C, $C_{28}H_{18}N_6O_5$ 518.49, IR (γ/cm^{-1}) 3120 (NH), ^{1}H-NMR(DMSO-d_6) 11.31 (s, 1H, exchangeaable by D_2O,NH), 9.75 (s, 1H, pyrim.), 8.62 (s, 1H, N=CH), 8.32-7.56 (m, 14H, aromatic protons) and 6.42 (s, 1H, pyran).Ms:m/z(%)396 (M^+ - Ph-NO_2-*p* 30%),394, (100%).

(8c): 65% from dioxane,m.p 260-2^{0}C , $C_{27}H_{18}N_6O_3$ 474.48, IR (γ/cm^1) 3172 (NH)), ^{1} H-NMR(DMSO-d_6) 11.35 (s, 1H, exchangeaable by D_2O, NH), 9.62 (s, 1H, pyrim.), 8.53 (s, 1H, N=CH), 8.35-7.42 (m, 14H, aromatic protons) and 6.52 (s, 1H, pyran).

2-(Substituted)-13-(4-nitrophenyl)-13*H*-6-oxa-1,3,3a-tetraaza benzo[*a*]cyclopenta[*h*]anthracene 9a-f:

Method A: A mixture of **(5)** (1g, 2.4 mmol) and *p*-anisic acid, *p*-nitrobenzoic acid isonicotinic acid, monochloroacetic acid, dichloroacetic acid and trichloroacetic acid (2.5 mmol) in freshly distilled phosphoryl chloride (15 ml) was refluxed for 5 h. After cooling the reaction mixture poured onto crushed ice to give a precipitate which was filtered, washed several times with water and crystallized from the appropriate solvent to afford **(9a,f).**

2-(4-Methoxyphenyl)-13-(4-nitrophenyl)-13*H*-6-oxa-1,3,3a-5-tetraazabenzo[*a*]cyclopenta[*h*] anthracene (9a): 55% from dioxane,m.p 230-2^{0}C , $C_{28}H_{19}N_5O_4$ (501.47), ^{1}H-NMR(DMSO-d_6) 9.25 (s, 1H, pyrim.), 8.42-7.55 (m, 14H, aromatic protons), 6.42 (s, 1H, pyran) and 3.70 (s, 3H, OCH_3), Ms:m/z(%)502(M+, 12%).

2,13-Bis-(4-nitrophenyl)-13*H*-6-oxa-1,3,3a,5- tetraazabenzo[*a*]cyclopenta[*h*]anthracene (9b): 45% from acetic acid ,m.p 255-7^{0}C , $C_{28}H_{16}N_6O_5$ (516.47), ^{1} H-NMR(DMSO-d_6) 9.32 (s, 1H, pyrim.), 8.32-7.45 (m,14H, aromatic protons) and 6.32 (s, 1H, pyran).

13-(4-Nitrophenyl)-2-pyridin-4-y)-13*H*-6-oxa-1,3,3a,5-tetraazabenzo[*a*]cyclopenta[*h*]anthracene (9c): 52% from acetic acid ,m.p 280-2^{0}C , $C_{27}H_{16}N_6O_3$ (472.46), ^{1} H-NMR(DMSO-d_6) 9.35 (s, 1H, pyrim.), 8.31-7.62 (m,14H, aromatic protons) and 6.22 (s, 1H, pyran).

2-chloromethyl-13-(4-nitrophenyl)-13*H*-6-oxa-1,3,3a,5-tetraazabenzo[*a*]cyclopenta[*h*]anthracene (9d): 77% from acetic acid ,m.p 289-290^{0}C , $C_{23}H_{14}ClN_5O_3$ (443.85), ^{1}H-NMR(DMSO-d_6) 8.58(s,1H, pyrim.), 8.25-7.45 (m,10H, aromatic protons), and 5.85 (s, 1H, pyran),4.75 (s, 2H, CH_2).

2-Dichlorormethyl-13-(4-nitrophenyl)-13*H*-6-oxa-1,3,3a,5-tetraazabenzo[*a*]cyclopenta[*h*] anthracene (9e): 82% from acetic acid ,m.p 250-2^{0}C , $C_{23}H_{13}Cl_2N_5O_3$ (478.30), ^{1} H-NMR(DMSO-d_6) 8.80 (s, 1H, pyrim.), 8.30-7.40 (m,10H, aromatic protons), 6.50 (s, 1H, $CHCl_2$) and 5.90 (s, 1H, pyran).

13-(4-Nitrophenyl)-2-trichloromethyl-13*H*-6-oxa-1,3,3a,5tetraazabenzo[*a*]cyclopenta [*h*]anthracene (9f): 75% from acetic acid ,m.p 265-7^{0}C , $C_{23}H_{12}Cl_3N_5O_3$ (12.86), ^{1} H-NMR(DMSO-d_6 9.82 (s, 1H, pyrim.), 8.45-7.82 (m, 10H, Aromatic protons) and 6.30 (s, 1H, pyran). Ms:m/z(%) 395 [(M, Cl^{37}, Cl^{37}, Cl^{37}-Ar)$^+$, 5.84%] 393 [M, Cl^{37}, Cl^{37}, Cl^{37} – Ar)$^+$, 32.17], 391 [M, Cl^{37}, Cl^{35}, Cl^{35} – Ar)$^+$, 93%] and 389 [M, Cl^{35}, Cl^{35}, Cl^{35} – Ar)$^+$, 100%].

Method B: A mixture of **(8a,c)** (10 mmol), anhydrous sodium acetate (2g) and bromine (10 mmol) in acetic acid (20 ml) was heated at 80°C for 5 h. The reaction mixture was then poured into water, and the solid formed filtered off and crystallized from dioxane to afford 60 and 65% from **(9a,c)** respectively.

Method C: A mixture of **(3)** (1g, 2.4 mmol) and isonicotinic acid hydrazide (3 mmol) in (20 ml) ethanol was refluxed for 10 h (TLC control). On cooling a solid product separated which was filtered and crystallized from ethanol to afford 85**%(9c)**.

3,3-dichloro-14-(4-nitrophenyl)-3,4-dihydro-14H-7-oxa-1,4,4a,6-tetraaza dibenzo[a-h]anthracen-2-ylideneamine 10: A mixture of **(5)** (1g,2.4 mmol) and trichloroacetonitrile (2.5 mmol) in dioxane and piperidine as a catalyst, was refluxed for 8 h (TLC control) on cooling a solid product separates which is filtered and crystallized from the appropriate solvent to afford **(10)**: 70% from dioxane,m.p 293-5 ^{0}C , $C_{23}H_{14}Cl_2N_6O_3$ (493.31), IR (γ/cm^{-1}) 3120 (NH), ^{1}H-NMR(DMSO-d_6) 8.85 (s, 1H, pyrim.), 8.45 (bs, 1H, exchangeaable by D_2O, NH), 8.39-7. 2 (m, 10H, aromatic protons), 6.75 (s, 1H, exchangeaable by D_2O, NH) and 6.20 (s, 1H, pyran).Ms:m/z(%)399 [(M, Cl^{37},Cl^{37}, , 1.4%] 397 [M, Cl^{37}, Cl^{35}, 6.3], 395 [M, Cl^{35},Cl^{35},10%], 385,35%, 364,100%.

2-(4-fluorophenyl)-14-(4-nitrophenyl)-4H-14H-7-oxa-1,4,4a,6- tetraaza-dibenzo[a,h]anthracene (11): A mixture of **(5)** (1g,2.4 mmol) and *p*-fluorophenacyl bromide (2.5 mmol) in dioxane and sodium carbonate , was refluxed for 8 h (TLC control) on cooling a solid product separated which was filtered, washed with cold water and crystallized from the appropriate solvent to afford **(11)**. 65% from dioxane,m.p 280-2^{0}C , $C_{29}H_{18}FN_5O_3$ (503.47), ^{1}H-NMR(DMSO-d_6) 9.62 (s, 1H, pyrim), 8.45-7.32 (m, 15H, aromatic protons) and 6.45 (s, 1H, pyran), Ms:m/z(%) 504 (M+ ,15%), 248 (100%).

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Received on September 27, 2002