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Synthesis of 10-substituted-3,4,10,10a-tetrahydro-2H-1,9-dioxa-4a-azaphenanthrenes

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ABSTRACT

*Commercially available 2-nitrophenol **1** was treated with ethyl bromoacetate to obtain the (2-ntrophenoxy)acetic acid ethyl ester **(2)**. Then, **2** was reduced with Fe/AcOH to yield 4H-benzo[1,4]oxazin-3-one **(3)**, which on treatment with ethyl 3-bromopropionate led to the formation of 3-(3-oxo-2,3-dihydrobenzo[1,4]oxazin-4–yl)propionic acid ethyl ester **(4)**. Reduction of **4** with lithium aluminiumhydride gave 3,4,10,10a–tetrahydro-2H-1,9-dioxa-4a-azaphenanthrene (**5**). All the new products obtained in the above sequences of reactions have been adequately characterized by spectral data.*

Key words: Synthesis, substituted azaphenanthrenes, Reductive cyclization.

INTRODUCTION

1,4-Benzoxazin-3(4H)-ones are very important bioactive compounds, which find applications such as cardiotonic properties[1], SGLT2 inhibitors[2], mineral corticoid receptor-modulating agents[3], anti-inflammatory[4], antiulcer[5], antiplatelet[6], antihypertensive[7], antifungal[8], antimicrobial[9], neuropeptide Y (NPY) Y5 receptor antagonist[10], serotonin reuptake inhibitors[11], prostacyclin receptor agonist[12]. They are also useful for the treatment of diabetes mellitus and obesity related problems[13] etc. Keeping in view the biological activities of various 1,4-benzoxazin-3-(4H)-ones, it was considered worthwhile to prepare fused derivatives of benzoxazines as potentially biologically active compounds and as new chemicals entities.

MATERIALS AND METHODS

General

All experiments were conducted under nitrogen atmosphere unless stated otherwise. All solvents and reagents were of reagent grade and used without further purification. All melting points were determined on Poloman MP-96 melting point apparatus. ^{1}H NMR spectra were recorded using a Bruker 300 MHz spectrometer with TMS as internal standard in DMSO-d_6 or $CDCl_3$. Mass spectra were recorded on an Agilent 6120 single quadrupole LCMS instrument giving M^+ values either on $[M + H]^+$ or $[M - H]^-$ modes. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr Pellets). Analytical TLC was conducted on E-Merck- 60 GF-254 aluminium-packed silica gel plates (0.2mm). Developed plates were visualized under UV light or in Iodine chamber.

Preparation of 2 (General Procedure).
A mixture of **1** (5 g, 0.035 mol), K_2CO_3 (6.4 g, 0.039 mol), acetone (150 ml), and ethyl bromoacetate or α-bromo-α-phenyl acetate (0.053 mol) was stirred at 60 °C for 4 h. At the end of this period, the reaction mixture was filtered and the filtrate rotary evaporated to obtain a residue which was diluted with dichloromethane (70 ml) and washed with water (2 x 50 ml). The organic layer was dried over anhyd. Na_2SO_4 and filtered through celite pad. The filtrate was rotary evaporated to obtain pure **2** as a liquid.

2a; Yield= 6 gm (75%); Liquid[14] at RT.
2b; Yield=8 gm (90%); Liquid[14] at RT.

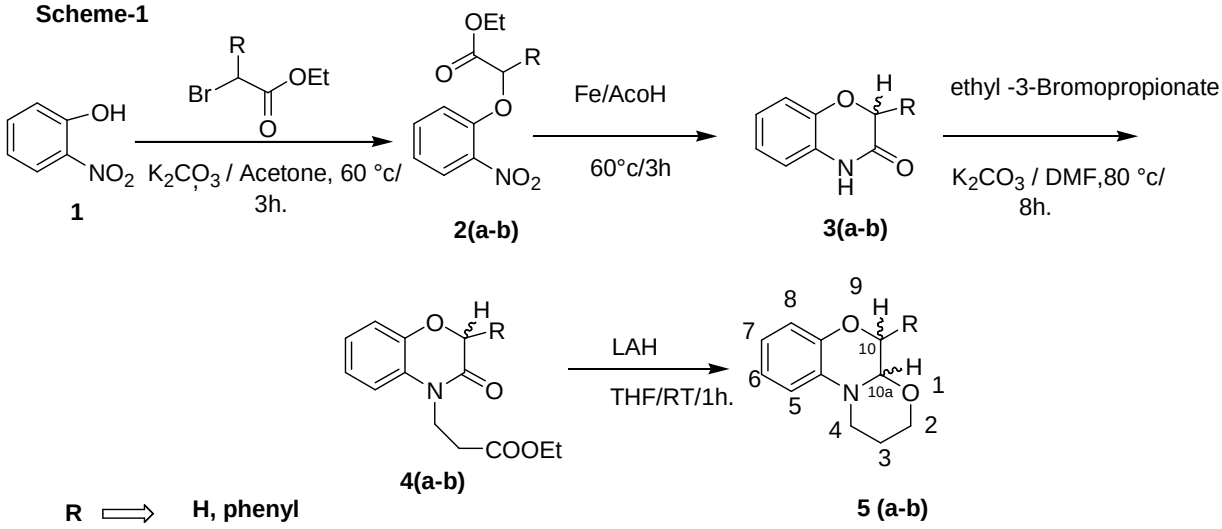
Preparation of 3 (General Procedure) .
A mixture of **2** (0.022 mol), iron powder (8.7 g, 0.155 mol) and acetic acid (20 ml) was refluxed for 8 h. At the end of this period, the reaction mixture was filtered. Acetic acid filtrate was rotary evaporated to obtain a crude residue which was diluted with water. The separated solid was filtered and dried to obtain **3**.

3a; Yield= 2.5 gm (76%); M. P. = 169-172 °C (Lit[14] .M.P. = 173-175°C).
3b; Yield= 3 gm (80%); M. P. = 177-178 °C (Lit[14] .M.P. = 178-181°C).

Preparation of 4 (General Procedure).
A mixture of **3** (0.0134 mol), K_2CO_3 (3.6 g, 0.268 mol), DMF (15 ml), and ethyl 3-bromopropionate (2.67 g, 0.0147 mol) was stirred at 80 °C for 8 h. At the end of this period, the mixture was diluted with water (45 ml) and extracted with dichloromethane (20 ml). The organic layer was separated, washed with water (20 ml) dried over anh. Na_2SO_4 and filtered through celite pad. The filtrate was rotary evaporated to obtain a crude residue which was purified by column chromatography to obtain pure **4** as thick syrup. For spectral data, please see under Results and Discussion.

4a; Yield = 2.25 gm (67%).
4b; Yield = 1.9 gm (69%); thick syrup.

Scheme-1



Preparation of 5 (General Procedure).
A solution of **4** (4 mmol) in THF (10 ml) was cooled to 10 °C and lithium aluminiumhydride (0.177 g, 4.4 mmol) was added. The mixture was stirred under nitrogen at room temperature for 1 h. At the end of this period, the mixture was quenched with saturated Na_2SO_4 solution (2 ml) at 5°C and the precipitated cake was filtered, washed with ethyl acetate (2 x 20 ml). The organic filtrate was dried over anhyd. Na_2SO_4 and rotary evaporated to obtain a crude residue which was purified by column chromatography to obtain pure **5** as a white solid. For spectral data please see under Results and Discussion.

5a; yield= 0.5 gm (66%); M. P. = 57-59 °C; Purity (HPLC) = 99.80%.

5b; yield= 0.6gm (70%); M. P. = 115-118 °C; Purity (HPLC) = 97.27%.

RESULTS AND DISCUSSION

Commercially available 2-nitrophenol **1** was treated with ethyl bromoacetate in the presence of K_2CO_3 in acetone at 60 °C to obtain (2-nitrophenoxy)acetic acid ethyl ester (**2a)**. Using the same method, **1** was treated with α-bromo-α-phenyl acetate to obtain (2-nitrophenoxy)phenyl acetic acid ethyl ester **(2b).** Each of **2a** and **2b** were then treated, independently with Fe/AcOH at 60 °C to obtain 4*H*-benzo[1,4]oxazin-3-one and 2-phenyl-4*H*-benzo[1,4]oxazin-3-one (**3a** and **3b)** respectively. The latter, (ie. **3a** and **3b)** on treatment with ethyl 3-bromopropionate in the presence of K_2CO_3 in DMF at 80 °C for 8 h, gave crude products which on purification by column chromatography yielded as 3-(3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)propionic acid ethyl ester (**4a)** and 3-(3-oxo-2-phenyl-2,3-dihydrobenzo[1,4]oxazin-4-yl)propionic acid ethyl ester (**4b)** respectively which were characterized on the basis of their spectral data. Thus, the IR (KBr pellet) spectrum of **4a** showed diagnostic peaks at 1731 cm^{-1} (due to ester carbonyl stretching) and at 1691 (due to amide carbonyl stretching). Its ^{1}H-NMR ($CDCl_3$/TMS, 300 MHz) spectrum showed signals at δ 1.22-1.25 (t, *J* = 4.2 Hz, 3H -O-CH_2-C**H**$_3$), 2.67-2.70 (t, *J* = 5.1 Hz ,2H, -N-C**H**$_2$),4.12-4.14 (q, 2H, –O-C**H**$_2$-CH_3), 4.22-4.23 (t, *J* = 4.5 Hz, 2H, -N-CH_2-C**H**$_2$), 4.58 (s, 2H, -O-C**H**$_2$-CO-), 6.99-6.99 (d, *J* = 1.8 Hz, 2H, Ar-**H**), 7.02-7.03 (d, *J* = 2.1 Hz, 2H, Ar-**H**). Its LCMS showed the molecular ion (M^++1) peak at *m/z* 250 corresponding to a molecular mass of 249 when recorded in the Q+1 mode. The IR (KBr pellet) spectrum of **4b** showed diagnostic peaks at 1731 cm^{-1} (due to ester carbonyl stretching) and at 1682 (due to amide carbonyl stretching). Its ^{1}H-NMR ($CDCl_3$/TMS, 300 MHz) spectrum showed signals at δ 1.20-1.23 (t, *J* = 4.5 Hz, 3H, –O-CH_2-C**H**$_3$), 2.71-2.72 (t, *J* = 3 Hz, 2H, -N-C**H**$_2$-), 4.128-4.143 (q, 2H, –O-C**H**$_2$-CH_3), 4.28-4.30 (t, *J* = 3.2 Hz, 2H, -N-CH_2-C**H**$_2$-), 5.70 (s,1H**,**-O-C**H**-Ar), 6.99-7.12 (m, 4H, Ar-**H**), 7.30-7.37 (m, 5H**,** Ar-**H**). Its LCMS showed the molecular ion (M^++1) peak at *m/z* 326 corresponding to a molecular mass of 325 when recorded in the Q+1 mode. Both **4a** and **4b** on individual reduction with lithium aluminiumhydride gave products which have been characterized respectively as 3,4,10,10a-tetrahydro-2*H*-1,9-dioxa-4a-azaphenanthrene (**5a)** and 10-phenyl-3,4,10,10a-tetrahydro-2*H*-1,9-dioxa-4a-azaphenanthrene (**5b)** on the basis of their spectral data. Thus, the IR (KBr) spectrum of **5a** did **not** show any diagnostic peaks due to –NH- and –CO- groups. Its ^{1}H-NMR ($CDCl_3$/TMS,300 MHz) spectrum showed signals (as a diasteromeric mixture) at δ 1.38-1.40 (d, *J* = 8.1 Hz, 1H, one proton of 3-C**H**$_2$), 2.01-2.03 (m, 1H, one proton of 3-C**H**$_2$), 3.15-3.16 (t, *J* = 9 Hz 1H, -N-C**H**$_2$-), 3.88-3.94 (t, *J* =8.7 Hz, 1H, -N-C**H**$_2$-), 4.14-4.15 (d, *J* = 4.8 Hz, 1H, one proton of 10a-C**H**), 4.16-4.17 (m, 3H**,** one of the protons of 2-C**H**$_2$ and 10-C**H**), 4.65 (s, 1H, one proton of 10-C**H**), 6.72-6.74 (d, *J* = 4.2 Hz, 1H, Ar-**H**), 6.82-6.87 (m, 3H, Ar-**H**). Its LCMS showed the molecular ion (M^++1) peak at *m/z* 192 corresponding to a molecular mass of 191 when recorded in the Q+1 mode. Spectal data for (5**b)** in its IR (KBr pellet) spectrum did **not** show any diagnostic peaks due to –NH- and –CO- groups. Its ^{1}H-NMR ($CDCl_3$/TMS,300 MHz) spectrum showed signals at (as a diasteromeric mixture) δ 1.38-1.40 (d, *J* = 5.7 Hz, 1H, one of the proton of 3-C**H**$_2$), 2.15-2.20 (m, 1H, one proton of 3-C**H**$_2$), 3.15-3.16 (t, *J* = 10.5 Hz, 1H, one proton of -N-C**H**$_2$-), 3.69-3.72 (t, *J* =7.5 Hz, 1H, one proton of -N-C**H**$_2$-), 4.03-4.06 (d, *J* = 10.5 Hz, 1H, one of the proton of 2-C**H**$_2$), 4.16-4.17 (m, 1H, one proton of 2-C**H**$_2$), 4.50-4051 (d, *J* =3 Hz, 1H, one proton of 10-C**H**$_2$), 5.06-5.07 (d, *J* =3 Hz, 1H, one proton of 10a-C**H**), 6.77-6.94 (m, 4H, Ar-**H**), 7.33-7.44 (m, 5H, Ar-**H**). Its LCMS showed the molecular ion (M^++1) peak at *m/z* 268 corresponding to a molecular mass of 267 when recorded in the Q+1 mode. All the above reactions are shown in Scheme-1.

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