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Synthesis and Characterisation of 3-Hydroxy-4, 5-dihydro[1,2,3] Oxadiazolo [3,4-A]Quinolin-10-ium and its Fluoro derivative.

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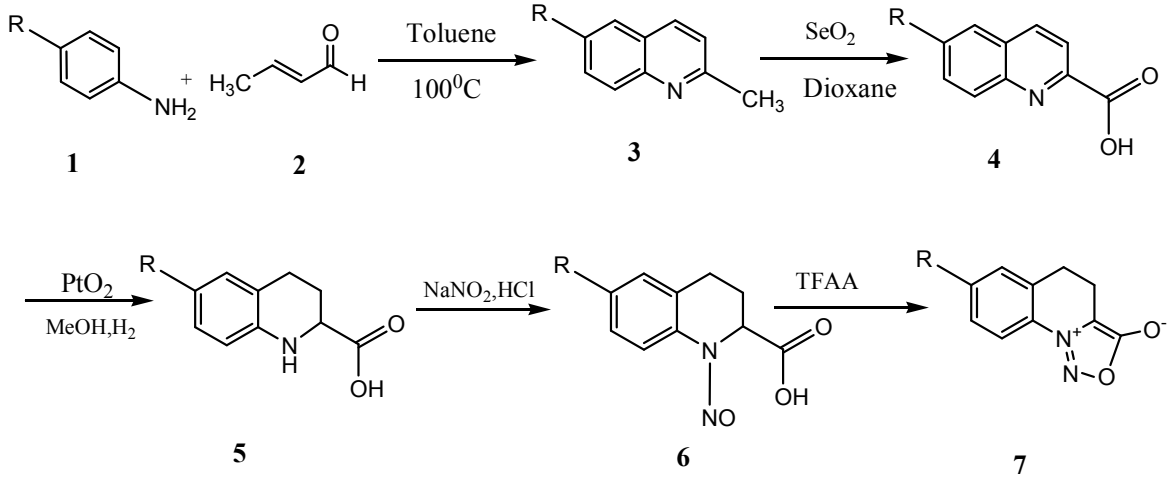
Abstract: 3-hydroxy-4,5-dihydro[1,2,3]oxadiazolo[3,4-a]quinolin-10-ium and its derivative,7-fluoro-3-hydroxy-4,5-dihydrooxadiazolo[3,4-a]quinolin-10-ium were synthesized by N-nitrosation of 1,2,3,4-tetrahydorquinoline-2-carboxylic acid and 6-fluoro-1,2,3,4-tetrahydro quinoline-2-carboxylic acid using sodium nitrite and concentrated HCl followed by cyclisation with trifluoroacetic anhydride. The 1,2,3,4-tetrahydorquinoline-2-carboxylic acid and its 7-fluoro derivative were synthesized from aniline and p-fluoroaniline via Doebner-miller synthesis followed by oxidation with selenium dioxide and reduction. Both the compounds were characterized using Mass, NMR and IR studies.
Keywords: 6-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, quinoline, N-nitrosation.

INTRODUCTION

Mesoionic compounds as exemplified by sydnones, sydnonimines, etc., have unique electronic structures and biological activities[1, 2].Considerable attention has been given to the preparation of sydnones because of their mesoionic character and biological activity which include antimicrobial[3], antineoplastic[4], antinflammatory[5], anticonvulsant[6], hypotensive[7a,7b] and analgesic[8]. We report here the synthesis of two such sydnones, namely, 3-hydroxy-4, 5-dihydro [1,2,3]oxadiazolo[3,4-a]quinolin-10-ium and 7-fluoro-3-hydroxy-4,5-dihydro oxadiazolo[3,4-a]quinolin-10-ium by N-nitrosation of 1,2,3,4-tetrahydroquinoline-2-carboxylicacid and its fluoro derivative using sodium nitrite and concentrated HCl followed by cyclisation using trifluoroacetic anhydride at low temperature. The starting material 1, 2, 3, 4-tetrahydroquinoline-2-carboxylic acid and its fluoro derivative were synthesized from aniline and 4-fluoroaniline respectively (SCHEME 1).

MATERIALS AND METHODS

All the starting materials and reagents were purchased from Lancaster chemicals, Aldrich and Alfa-aesar. Solvents used for the synthesis and work up were LR grade and GR grade from Merck and Rankem laboratories. All the solvents used for the purification were of commercial grade. The progress of the reaction was monitored by thin layer chromatography (TLC) and by visualization using short wavelength UV light. The melting points of the compounds were checked using capillary method using Buchi melting point B-540 apparatus and are uncorrected. Mass spectrums of the compounds were recorded using Perkin-Elmer Mass-API-ES with both positive and negative modes of scanning. ^{1}H NMR spectra were recorded using Bruker NMR spectrometer, at 400 MHz. The IR spectrum of the compounds was recorded using Perkin-Elmer FTIR spectrometer.



1 **2** **3** **4**

5 **6** **7**

a: R = H; b: R = F

SCHEME -1

3-Hydroxy-4, 5-dihydro [1,2,3]oxadiazolo[3,4-a]quinolin-10-ium (7a)

Preparation of 2-methylquinoline (3a)

To a solution of aniline **1a** (1.12 g, 4.46 mmol) in 6M HCl (22.4ml) at 100^{0}C (bath temperature) a mixture of toluene (5.8 ml) and crotonaldehyde **2** (0.74 ml, 8.92 mmol) was added drop wise with vigorous stirring. Stirring was continued for 3 h at 100 ^{o}C. The reaction mixture was allowed to attain the room temperature. The aqueous layer was separated and neutralized with aqueous NaOH to obtain crude **3a**. The crude product was purified by column chromatography over silica gel (60-120 mesh).

Yield: 70%; MASS: m/z 144.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.75(s, 3H), 7.26-7.30(t, 1H), 7.46-7.50(t, 1H), 7.66-7.70(m, 1H), 7.76-7.78 (d, 1H, *J* = 8.16 Hz), 8.01-8.06(m, 2H).

6-Fluoro- 2-methylquinoline (3b)

6-Fluoro- 2-methylquinoline was also prepared adopting the same procedure.

MASS: m/z 162.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.73(s, 3H), 7.29-7.31 (m, 1H), 7.37-7.7.40 (m, 1H), 7.42-7.47 (m, 1H), 7.99-8.02 (m, 2H).

Quinoline-2-carboxylic acid (4a)

To a solution of **3a** (0.57 g, 5.18 mmol) in dry 1, 4-dioxane (30 ml), selenium dioxide (0.7 g, 4.89 mmol) was added and the reaction mixture was refluxed for 2h.It was then cooled to room temperature and filtered through a pad of celite. The filtrate collected was concentrated and few drops of water was added to the concentrated reaction mixture and extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated. The concentrate was then basified with aqueous saturated sodium bicarbonate and extracted with ether (2 X 5 ml). The bicarbonate layer after acidification with concentrated HCl was extracted with ethyl acetate (3 X 5 ml). The ethyl acetate layer was then dried and concentrated to get the pure quinoline-2-carboxylic acid **(4a)**.

Yield: 35%;MASS: m/z 174.1 (M+1);^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.72-7.74(d, 1H, *J* = 8.0Hz), 7.84-7.85(d, 1H, *J* = 7.16Hz), 7.95-7.97 (d, 1H, *J* = 8.2Hz), 8.16-8.18 (d, 1H, *J* = 8.5Hz), 8.28-8.30 (d, 1H, *J* = 8.4Hz), 8.42-8.44 (d, 1H, *J* = 8.4Hz).

Preparation of 6-Fluoroquinoline-2-carboxylic acid (4b)

6-Fluoroquinoline- 2-carboxylic acid was also prepared adopting the same procedure.

MASS: m/z 192.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.56-7.59 (m, 1H); 7.61-7.65 (m, 1H); 8.17-8.21 (m, 1H); 8.30-8.32 (d, 1H, *J* = 8.4Hz); 8.37-8.39 (d, 1H, *J* = 8.5Hz).

1,2,3,4-Tetrahydroquinoline-2-carboxylicacid (5a)

Quinoline-2-carboxylic acid **4a** (1 g, 5.7 mmol) in methanol (6 ml) was hydrogenated over platinum oxide (0.03 g) under atmospheric pressure of hydrogen at ambient temperature until the theoretical amount of hydrogen was consumed. The completion of the reaction was checked by TLC. The mixture was

filtered through celite and the filtrate was concentrated to get 1,2,3,4-tetrahydoquinoline-2-carboxylic acid **(5a).** The crude product was used as such for the further reaction without purification.

Yield: 0.8 g (80 %); MASS: m/z 176.1 (M-1).

6-Fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylicacid (5b)

6-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid was also prepared adopting the same procedure

MASS: m/z 194.1 (M-1).

3-Hydroxy-4,5-dihydro[1,2,3]oxadiazolo[3,4-a]quinolin-10-ium (7a)

To a suspension of **5a (**1 g, 5.6 mmol) in water (3 ml), cooled to -5^{0}C, concentrated sulphuric acid (0.6ml) was added. To the above mixture a solution of sodium nitrite (0.42 g, 6.1 mmol) in water (2 ml) was then added and stirred at room temperature for 2h. The reaction mixture was then extracted twice with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give the intermediate **6a**. Trifluoroacetic anhydride (1.1 ml, 6.1 mmol) was added to a cooled (-3 ^{o}C) solution of the intermediate **6a** in ether (20 ml) and stirred at room temperature for 12h. The reaction mixture was concentrated under reduced pressure and the crude product thus obtained was purified by column chromatography over silica gel (60-120 mesh)**.**

Yield: 0.7 g (70%); MASS: m/z 189.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.97-2.98 (t, 2H), 3.06-3.08 (t, 2H); 7.48-7.52(m, 2H); 7.96-7.98(d, 2H, *J* = 7.4Hz); IR (KBr): 1724 cm^{-1} (C=O stretching).

7-Fluoro-3-hydroxy-4,5-dihydro[1,2,3]oxadiazolo[3,4-a]quinolin-10-ium (7b)

7-Fluoro-3-hydroxy-4,5-dihydro[1,2,3]oxadiazolo[3,4-a]quinolin-10-ium was also prepared adopting the same procedure.

Yield: 70%; MASS: m/z 207.1 (M+1); ^{1}H NMR 400 MHz ($CDCl_3$) δ ppm: 2.95-2.98(t, 2H); 3.06-3.09(t, 2H); 7.14-7.26(m, 2H); 7.96-8.0(m, 1H); IR (KBr): 1737 cm^{-1} (C=O stretching).

RESULTS AND DICUSSION

The primary objective of this paper was to find a method of synthesis of sydnones from the commercially available aniline and substituted anilines. The preparation was carried out via N-nitrosation using sodium nitrite and concentrated HCl, followed by cyclisation using trifluoroacetic anhydride at low temperature. The starting materials 1,2,3,4-tetrahydroquinoline-2-carboxylic acid and 6-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid was prepared from aniline and 4-fluoroaniline respectively via doebner-miller synthesis of quinolines.

1,2,3,4-Tetrahydroquinoline-2-carboxylic acid (**5)** was prepared from aniline. The fluoro derivative was prepared and the staring compound was 4-fluoro aniline.

Aniline (**1a)** was heated HCl followed by the addition of toluene and crotonaldehyde to give (**3a)** which was characterized using mass and ^{1}H NMR data. In the mass the M+1 peak of 144.1amu was seen. The ^{1}H NMR spectrum showed the 3 methyl protons at δ 2.75 ppm the 6 aromatic protons appear in the region δ 7.26 - 8 ppm.

The compound **(3a)** was then oxidized to **(4a)** using selenium dioxide in dioxane. The structure of the acid was confirmed by the spectral data. The mass spectrum showed the M+1 peak at 174.1amu. The ^{1}H NMR data showed 6 aromatic protons between δ 7.72-8.43 ppm. The compound **(5a)** was dissolved in methanol and platinum oxide catalyst was added to it and the reduction was carried out in the presence of hydrogen to give (**6a)**. This was confirmed using mass spectrum as the M-1 peak of 176.1amu was seen.

The nitrosation reaction on crude was performed with sodium nitrite and conc.HCl to give the intermediate **(6a)**, which was further cyclized using trifluoroacetic anhydride to give the final compound **(7a).** The product **(7a)** was purified by column chromatography and characterized by mass and ^{1}H NMR spectra. The mass spectrum showed the M-1 peak of 176.1amu. The ^{1}H NMR spectrum showed peaks at δ 2.97-2.98 ppm for two protons, two protons at δ 3.06-3.08 ppm, two aromatic protons at δ 7.48-7.52 ppm and two aromatic protons at δ 7.96-7.98 ppm. The IR spectrum showed 3438 cm^{-1} (O-H stretching) and 1724 cm^{-1} (C=O stretching).

The same procedure was followed to give the corresponding fluoro derivative. The structure of the compound **(7b)** was confirmed by IR, ^{1}H NMR and mass spectra. The mass spectrum showed the M+1 peak of 207.1. The ^{1}H NMR showed four methylene protons between 2.95-3.09 ppm and also four aromatic protons between 7.14-8.00 ppm. The IR spectrum showed 3440 cm^{-1} (O-H stretching), 1737 cm^{-1} (C=O stretching).

The biological evaluations of the synthesized compounds are under progress.

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