Synthesis of 1,2-dihydro-6-(1H-imidazo(4,5-b) pyridin-2-yl)-4-aryl-2-oxopyridine-3-carbonitriles and 2-amino-6-(1H-imidazo (4,5-b) pyridin-2-yl)-4-aryl pyridine-3-carbonitriles

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ABSTRACT
1(1H-imidazo[4,5-b]pyridin-2-yl) ethanol (3) is oxidized to form 1-(1H-imidazo[4,5-b]pyridin-2-yl) ethanone (4) by potassium dichromate. This is condensed with different aldehydes to form 1(1H-imidazo[4,5-b]pyridin-2-yl)-3-phenyl prop-2-en-1-ones 5(a-e), which is cyclised to get pyridine derivatives 6(a-e) and 7(a-e).

1. INTRODUCTION
Since the isolation of 5-hydroxy tryptamine (5-HT) or Serotonin more than fifty years ago, countless biological assays have affirmed its influence throughout the human anatomy. The biogenic amine is associated with an array of physiological processes including...
glucose metabolism in the liver and cardio valvular operations as well as those of the central nervous system. Studies have implicated cerebral Serotonin in the regulation of sleep, mood, thermoregulation, feeding, pain-perception, learning, memory and arousal. Its functions are accomplished through the activation of a large family of specific receptors. Of the seven classification of these receptors, the 5-HT7 subtype is the most recently unearthed and its function the most unclear. For thorough understanding of the 5-HT7 receptor, the development of highly selective ligands is imperative to determine its biological significance. In view of this it is essential to synthesis the 1,2-dihydro-6-(1H-imidazo[4,5-b]pyridine-2-yl)-4-aryl-2-oxopyridine-3-carbonitriles and 2-amino-6-(1H-imidazo[4,5-b]pyridin-2-yl)-4-arylpyridine-3-carbonitriles.

2. EXPERIMENTAL

1-(1H-imidazo [4,5-b]pyridin-2-yl)ethanone (4)

Potassium dichromate (0.069 mol) and water (35 ml) were mixed with constant mechanical stirring in a 3-necked flask fitted with a condenser and an addition funnel. The corresponding 1-(1H-imidazo[4,5-b]pyridin-2-yl)ethanol (3) (0.13 mol) was gradually added to the cooled stirring solution and stirring was continued for another 10 minutes. A cooled solution of H2SO4 (30 ml) and water (18 ml) was then added drop wise over a period of 1 hr., after which water (100 ml) was introduced into the reaction mixture. The mixture was extracted with dichloromethane (3 x 150 ml), followed by subsequent washing with water (200 ml) and 5% sodium carbonate (200 ml). The separated organic layer was dried over anhydrous sodium sulfate, filtered and the solvent evaporated in vacuo. The solid obtained was distilled and recrystallised from EtOH.

IR: 3423 cm⁻¹(N-H), 3177 cm⁻¹(C-H aromatic), 1743 cm⁻¹(C=O).

¹H NMR (DMSO-d₆) : δ = 2.18 (S, 3H), 7.72 (d, 1H), 7.88 (t, 1H), 8.41 (d, 1H), 10.32 (brs, 1H).

Mass: m/z 161.9 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-phenylprop-2-en-1-ones (5a-e)

1-(1H-imidazo[4,5-b]pyridin-2-yl)ethanone (4) (0.05 mole), was added with 30 % formaldehyde solution (0.1 moles) and the mixture was treated with conc. HCl (5 ml). After heating at 90-95°C for 4 hrs, the reaction mixture was cooled and neutralized with NaOH. The precipitate formed was filtered and passed through silica gel column and the product was eluted from 60 % ethylacetate and hexane.

3-phenyl-1-(1H-imidazo[4,5-b]pyridin-2-yl)prop-2-en-1-one 5(a)

IR: 3364 cm⁻¹(N-H), 3174 cm⁻¹(C-H aromatic), 1670 cm⁻¹(C=O), 1582 cm⁻¹(C=N).
A mixture of 1-(1H-imidazo[4,5-b]pyridin-2-yl)prop-2-en-1-one (5) (0.02 mol), ethylcyanoacetate (0.02 mol) and ammonium acetate (0.03 mol) were dissolved in EtOH (10 ml) and refluxed for 3-4 hrs. The crude products were purified by recrystallization from 95% ethanol to afford pure products.

1-H NMR (DMSO-d$_6$): $\delta = 6.90$ (d, 1H), 7.40 (m, 4H), 7.71 (d, 1H), 8.02 (d, 1H), 10.50 (brs, 1H). Mass: m/z 285 (M + H).

2-4-(Chlorophenyl)-1-(1H-imidazo[4,5-b]pyridin-2-yl)prop-2-en-1-one 5(b)

$\delta = 7.58$ (m, 3H), 7.81 (d, 1H), 8.16 (s, 1H), 8.79 (d, 1H), 10.10 (brs, 1H). Mass: m/z 349 (M + H).

3-4-(Methoxyphenyl)-1-(1H-imidazo[4,5-b]pyridin-2-yl)prop-2-en-1-one 5(c)

$\delta = 7.95$ (d, 1H), 7.50 (m, 1H), 7.92 (d, 1H), 8.18 (m, 2H), 10.68 (brs, 1H). Mass: m/z 348 (M + H).

4-4-(Nitrophenyl)-1-(1H-imidazo[4,5-b]pyridin-2-yl)prop-2-en-1-one 5(d)

$\delta = 7.86$ (d, 1H), 7.36 (m, 2H), 7.70 (d, 1H), 8.08 (s, 1H), 10.28 (brs, 1H). Mass: m/z 347 (M + H).

5-4-(Dimethylamino)phenyl)-1-(1H-imidazo[4,5-b]pyridin-2-yl)prop-2-en-1-one 5(e)

$\delta = 6.90$ (d, 1H), 7.40 (m, 4H), 7.71 (m, 1H), 7.96 (d, 1H), 8.20 (m, 2H), 10.62 (brs, 1H). Mass: m/z 293 (M + H).

1,2-Dihydro-6-(1H-imidazo[4,5-b]pyridin-2-yl)-4-aryl-2-oxopyridine-3-carbonitriles (6a-e)

A mixture of 1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-phenylprop-2-en-1-one (5) (0.02 mol), ethylcyanoacetate (0.02 mol) and ammonium acetate (0.03 mol) were dissolved in EtOH (10 ml) and refluxed for 3-4 hrs. The crude products were purified by recrystallization from 95% ethanol to afford pure products.

2-Amino-4-phenyl-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridine-3-carbonitrile 6a

IR: 3415 cm$^{-1}$ (N-H), 3118 cm$^{-1}$ (C-H aromatic), 2193 cm$^{-1}$ (CN), 1505 cm$^{-1}$ (C=N).

$\delta = 4.61$ (brs, 2H), 7.24 (m, 5H), 7.41 (t, 1H), 7.58 (d, 1H), 7.86 (d, 1H), 8.40 (s, 1H), 10.28 (brs, 1H). Mass: m/z 312.8 (M + H).

2-Amino-4-(4-chlorophenyl)-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridine-3-carbonitrile 6b

$\delta = 4.70$ (brs, 2H), 7.23 (m, 4H), 7.38 (t, 1H), 7.49 (d, 1H), 8.38 (s, 1H), 10.35 (brs, 1H). Mass: m/z 348 (M + H).

2-Amino-4-(4-methoxyphenyl)-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridine-3-carbonitrile 6c

$\delta = 3.81$ (s, 3H), 4.65 (brs, 2H), 7.22 (m, 4H), 7.40 (t, 1H), 7.52 (d, 1H), 7.85 (d, 1H), 8.40 (s, 1H), 10.42 (brs, 1H). Mass: m/z 343 (M + H).

2-Amino-4-(4-nitrophenyl)-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridine-3-carbonitrile 6d

$\delta = 4.68$ (brs, 2H), 7.28 (m, 4H), 7.35 (t, 1H), 7.50 (d, 1H), 8.38 (s, 1H), 10.35 (brs, 1H). Mass: m/z 358 (M + H).

2-Amino-4-(4-dimethylamino)phenyl)-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridine-3-carbonitrile 6e

$\delta = 2.78$ (s, 6H), 4.72 (brs, 2H), 7.29 (m, 4H), 7.38 (t, 1H), 7.51 (d, 1H), 7.83 (d, 1H), 8.39 (s, 1H), 10.45 (brs, 1H). Mass: m/z 356 (M + H).

2-Amino-6-(1H-imidazo[4,5-b]pyridin-2-yl)-4-arylpypyridine-3-carbonitriles (7a-e)

A mixture of 1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-phenylprop-2-en-1-one (5) (0.02 mol), malononitrile (0.02 mol) and ammonium acetate (0.03 mol) were dissolved in EtOH (10 ml) and refluxed for 3-4 hrs. The crude products were purified by recrystallization from 95% ethanol to afford pure products.

Phenyl-1,2-dihydro-6-(1H-imidazo[4,5-b]pyridin-2-yl)-2-oxopyridine-3-carbonitrile 7a

IR: 3336 cm$^{-1}$ (N-H), 3063 cm$^{-1}$ (C-H aromatic), 2279 cm$^{-1}$ (CN), 1615 cm$^{-1}$ (C=O), 1593 cm$^{-1}$ (C=N).

$\delta = 7.56$ (m, 4H), 7.80 (d, 1H), 8.18 (d, 2H), 8.31 (s, 1H), 8.78 (d, 1H), 10.05 (brs, 1H), 10.40 (brs, 1H). Mass: m/z 313.9 (M + H).

4-(4-Chlorophenyl)-1,2-dihydro-6-(1H-imidazo[4,5-b]pyridin-2-yl)-2-oxopyridine-3-carbonitrile 7b

$\delta = 7.58$ (m, 3H), 7.81 (d, 1H), 8.16 (d, 2H), 8.28 (s, 1H), 8.79 (d, 1H), 10.10 (brs, 1H), 10.42 (brs, 1H). Mass: m/z 349 (M + H).

4-(4-Methoxyphenyl)-1,2-dihydro-6-(1H-imidazo[4,5-b]pyridin-2-yl)-2-oxopyridine-3-carbonitrile 7c

$\delta = 3.79$ (s, 3H), 7.58 (m, 3H), 7.82 (d, 1H), 8.18 (d, 2H), 8.30 (s, 1H), 8.78 (d, 1H), 10.05 (brs, 1H), 10.41 (brs, 1H). Mass: m/z 344 (M + H).
4-(4-Nitrophenyl)-1,2-dihydro-6-(1H-imidazo[4,5-b]pyridin-2-yl)-2-oxopyridine-3-carbonitrile 7(d)

$^1$H NMR (DMSO-d$_6$): $\delta$ = 7.28 (m, 3H), 7.80 (d, 1H), 8.17 (d, 2H), 8.32 (s, 1H), 8.79 (d, 1H), 10.08 (brs, 1H), 10.42 (brs, 1H).
Mass: m/z 359 (M + H).

4-(4-Dimethylamino)phenyl)-1,2-dihydro-6-(1H-imidazo[4,5-b]pyridin-2-yl)-2-oxopyridine-3-carbonitrile 7(e)

$^1$H NMR (DMSO-d$_6$): $\delta$ = 2.75 (s, 6H), 7.29 (m, 3H), 7.81 (d, 1H), 8.19 (d, 2H), 8.30 (s, 1H), 8.80 (d, 1H), 10.02 (brs, 1H).
Mass: m/z 357 (M + H).

The PMR spectrum is completely in agreement with proposed structure. The mass spectrum showed the molecular ion which appeared as base peak.

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