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EFFICIENT MULTISTEP SYNTHESIS AND SPECTRAL CHARACTERIZATION OF DIHYDROPYRROLO [3, 2-*c*] PYRIDINE-4-ONE DERIVATIVES

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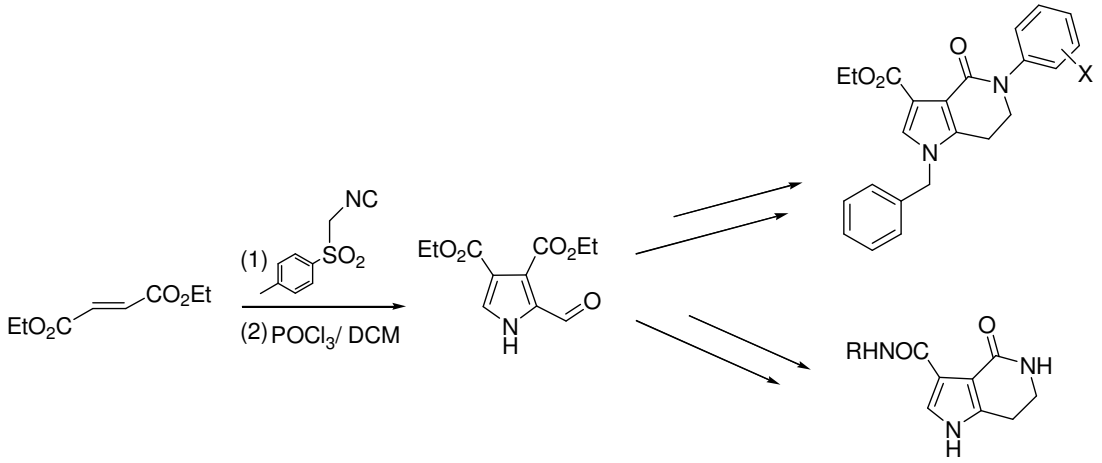
ABSTRACT

Novel dihydropyrrolo[3,2-*c*]pyridine-4-one derivatives were synthesized via multi-step reaction methodology by employing 3,4-bis(ethoxycarbonyl)pyrrole which was generated by the reaction of diethylfumarate with *p*-toluenesulfonylmethylisocyanide followed by formylation using previously reported literature.



Keywords: Multi-step synthesis, dihydropyrrolo [3, 2-*c*] pyridine-4-one, formylation, Buchwald-Hartwig coupling

INTRODUCTION

Pyrrole containing organic scaffolds are of immense synthetic importance as these exhibit promising pharmacological properties such as antimicrobial,[1] anti-inflammatory, antioxidant, antitumor,[2] immune-suppressant, antidepressant activities.[3] Highly functionalised pyrrole are subunit of porphyrins such as heme and chlorophyll, vitamin B_{12}, amino acids, alkaloids etc.[4] These are key constituent of machinery of various enzymatic inhibitors such as prolyl4-hydroxylase, Poly (ADP-ribose) polymerase, topoisomerase inhibitors.[5] Furthermore, the fusion of different pharmacophores like pyridine, thiophene, quinoline, imidazole and pyrimidine in a pyrrole ring system had led to the formation of novel scaffolds with promising biological activities.[6,7] Among these, dihydropyrrolo[3,2-*c*]pyridine-4-one analogues have recently attracted the attention of medicinal chemists for their potential to act as inhibitors of various crucial pathways and enzymes such as p38-MK2 signaling pathway,[8] polo-like kinases,[9] CB-1 receptors,[10]

glycogen synthase kinase-3 (GSK-3)[11] and cell division cycle 7 kinase (Cdc7)[12]. They have been explored extensively and some of these inhibitors have reached clinical trials. Thus such scaffolds have the potential to be used in the treatment of various disorders like rheumatoid arthritis, inflammation, cancer, obesity, diabetes, Alzheimer's disease, mood disorders and other numerous diseases. Prompted by these exciting features of this scaffold and in continuation of our search for biologically potent molecules,[13-15] we laid our attention for the synthesis of this scaffold.

Various methods have been reported in the literature for the synthesis of this scaffold, dihydropyrrolo [3, 2-*c*] pyridine-4-one analogues. One of the method utilized one-pot three-component pyrrole condensation reaction (Hantzsch reaction) between bromoketones and piperidine-2,4-dione in the presence of ammonium acetate.[12] Another method explored the condensation of amino ketone with ketopiperidinone to synthesize bicyclic pyrrolopyridinone scaffold[10] while some methods utilized intramolecular cyclisation (lactamisation) approach in the presence of reagents like lithium hydroxide in ethylene glycol, trimethylaluminium,[16] potassium carbonate.[17] In our study, one-pot lactamisation was executed in the presence of zinc-formic acid which led to the formation of dihydropyrrolo[3,2-*c*]pyridine-4-one as the major product making it very simple and effective method.

EXPERIMENTAL

Chemicals and instruments

All the chemicals and solvents (analytical grade) purchased from sigma-aldrich, spectrochem, merck and SRL were used without further purification. Precoated aluminium sheets (silica gel 60 F_{254}, Merck Germany) were used for thin-layer chromatography (TLC). The IR spectra of compounds were taken on Agilent Cary 630 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were acquired using Bruker Spectrospin DPX-300 MHz with tetramethylsilane (TMS) as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet and m, multiplet. Chemical shift and coupling constants (*J*) values are given in parts per million (ppm) and in Hertz (Hz), respectively. Mass spectra were obtained on AB-Sciex 2000 (Applied Biosystems) electron spray ionization mass spectrometer and on Agilent ion trap-6320 LC/MS spectrometer. Melting points were determined on a digital Buchi M-560 melting point apparatus and were reported uncorrected. Elemental analysis was performed on Elementar Vario Analyzer. Purification of the compounds was done by column chromatography using silica gel (230–400 mesh size). The synthesis of compounds **2, 3, 10** and **11** is described in the literature.[18]

Diethyl 1-benzyl-2-formyl-1*H*-pyrrole-3,4-dicarboxylate (4)

Compound **3** (1 eq) was dissolved in DMF (5 mL) and K_2CO_3 (3 eq) was added to the solution and kept on stirring for 1 h. Benzyl bromide (1.2 eq) was added and the reaction was completed in 6 h. The reaction mixture was treated with ethyl acetate, washed with water and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel using cyclohexane/ethyl acetate (7:3) afforded pure compound.[19]

White soild; M. pt. 105-108 ^{o}C; yield 96%; Anal. calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.56; H, 5.72; N, 4.11%. IR (neat): ν (cm^{-1}) 3136, 2993, 2939, 1708, 1672, 1523, 1447, 1426, 1374, 1257, 1218, 1153, 1061, 1011, 832, 696; ^{1}H-NMR (400 MHz, DMSO) (*δ*, ppm): 9.71 (s, 1H, C*H*O), 8.06 (s, 1H, Ar-*H*), 7.37-7.27 (m, 3H, Ar-*H*), 7.19 (d, *J* = 7.1 Hz, 2H, Ar-*H*), 5.58 (s, 2H, Ar-CH_2),4.28 (q, *J* = 7.1 Hz, 2H, CH_2), 4.21 (q, *J* = 7.1 Hz, 2H, CH_2), 1.29-1.23 (m, 6H, CH_3); ESI-MS (*m/z*): 330.31 $[M+H]^+$.

Synthesis of compounds **5** and **6** was carried out by following the same procedure as given in the literature.[18]

(*E*)-diethyl 1-benzyl-2-(2-nitrovinyl)-1*H*-pyrrole-3,4-dicarboxylate (5)

Yellow solid; M. pt. 102-105 ^{o}C; yield 83%; Anal. calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.10; H, 5.22; N, 7.37%. IR (neat): ν (cm^{-1}) 2985, 2936, 1707, 1607, 1526, 1432, 1387, 1283, 1194,1060, 1030, 974, 866, 825, 769, 702; ^{1}H-NMR (400 MHz, DMSO) (*δ*, ppm): 8.06 (s, 1H, Ar-*H*), 8.02 (s, 1H, Ar-*H*), 7.53 (d, *J* = 13.6 Hz, 1H, =C*H*), 7.40-7.37 (m, 2H, Ar-*H*), 7.33-7.29 (m, 1H, =C*H*), 7.15 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 5.55 (s, 2H, Ar-CH_2), 4.29 (q, *J* = 7.1 Hz, 2H, CH_2), 4.21 (q, *J* = 7.1 Hz,

2H, CH_2),1.27 (t, J = 7.0 Hz, 3H, CH_3),1.24 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm):180.52, 163.74, 162.34, 135.59, 132.72, 129.90, 128.98, 128.58, 128.39, 127.68, 116.12, 61.95, 60.75, 53.05, 14.24, 14.15; ESI-MS (*m/z*): 373.0 $[M+H]^+$.

Diethyl 1-benzyl-2-(2-nitroethyl)-1*H*-pyrrole-3,4-dicarboxylate (6)
Yellow oil; yield 84%: Anal. calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.82; H, 5.76; N, 7.31%. IR (neat): ν (cm^{-1}) 2970, 2836, 1723, 1610, 1521, 1448, 1393, 1245, 1165, 1043, 1003, 956, 876, 821, 778, 702; ^{1}H-NMR (400 MHz, DMSO) (δ, ppm): 7.51 (s, 1H, Ar-*H*), 7.40-7.30 (m, 3H, Ar-*H*), 7.14 (d, J = 7.2 Hz, 2H, Ar-*H*), 5.30 (s, 2H, Ar-CH_2), 4.47 (t, J = 7.4 Hz, 2H, CH_2), 4.20-4.13 (m, 4H, CH_2), 3.34 (t, J = 7.5 Hz, 2H, CH_2), 1.23 (t, J = 7.1 Hz, 6H, CH_3); ESI-MS (*m/z*): 375.2 $[M+H]^+$.

Diethyl 2-(2-aminoethyl)-1-benzyl-1*H*-pyrrole-3, 4-dicarboxylate (7) and ethyl 1-benzyl-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (8)
Compound **6** (1 eq) was dissolved in ethanol (10 mL), then formic acid (20 eq) was added drop wise. The reaction mixture was kept for 10-15 min at room temperature. After that, Zn (25 eq) was added portion wise at room temperature to this reaction mixture. After completion of the reaction, Zn dust was filtered and the filtrate was concentrated under reduced pressure to give an off-white solid compound, **7.** Under same reaction conditions, ester and amine terminals of compound **6** underwent coupling to form the cyclized product, **8**.

Diethyl 2-(2-aminoethyl)-1-benzyl-1*H*-pyrrole-3, 4-dicarboxylate (7)
Off-white solid; yield 18%; Anal. calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.10; H, 7.21; N, 8.23%. IR (neat): ν (cm^{-1}) 3331, 2928, 1719, 1635, 1520, 1445, 1421, 1391, 1359, 1278, 1231, 1179, 1063, 1024, 970, 863, 782, 751, 703, 693; ^{1}H-NMR (400 MHz, DMSO) (δ, ppm): 7.46 (s, 1H, Ar-*H*), 7.38-7.28 (m, 3H, Ar-*H*), 7.17-7.09 (m, 2H, Ar-*H*), 5.25 (s, 2H, Ar-CH_2), 4.16 (q, J = 5.6 Hz, 2H, CH_2), 4.11 (q, J = 5.8 Hz, 2H, CH_2), 3.30 (brs, 2H, NH_2), 2.71 (t, J = 7.2 Hz, 2H, CH_2), 2.54 (t, J = 7.3 Hz, 2H, CH_2), 1.24-1.20 (m, 6H, CH_3); ESI-MS (*m/z*): 345.2 $[M+H]^+$.

Ethyl 1-benzyl-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (8)
White solid; M. pt. 230-232 ^{o}C; Yield 71%; Anal. calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.27; H, 6.21; N, 9.21%. IR (neat): ν (cm^{-1}) 3260, 3197, 2921, 2854, 2292, 1853, 1700, 1637, 1547, 1499, 1443, 1413, 1343, 1238, 1171, 1100, 963, 758, 713; ^{1}H-NMR (400 MHz, DMSO) (δ, ppm): 7.46 (s, 1H, Ar-*H*), 7.40-7.28 (m, 3H, Ar-*H*), 7.17-7.11 (m, 2H, Ar-*H*), 7.09 (brs, 1H, N*H*), 5.18 (s, 2H, Ar-CH_2), 4.18-4.11 (m, 2H, CH_2), 3.32-3.27 (m, 2H, CH_2), 2.63 (t, J = 6.6 Hz, 2H, CH_2), 1.22 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO) (δ, ppm): 167.72, 163.71, 139.30, 136.90, 130.18, 129.34, 128.39, 127.85, 115.40, 110.24, 62.10, 50.56, 39.40, 20.53, 14.06; ESI-MS (*m/z*): 299.0 $[M+H]^+$.

General procedure for the synthesis of ethyl 1-benzyl-4-oxo-5-phenyl-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate derivatives (9a-e)
To a mixture of aryl halide (1 eq), CuI (0.1 eq), L-Proline (0.2 eq), K_3PO_4 (2.5 eq) and DMSO (4 mL), compound **8** (1.1 eq) was added in a 50 mL RB under nitrogen atmosphere. The mixture was stirred at 110 °C for 20 h. After the completion of reaction, 2 mL water was added and compound was extracted with ethyl acetate and then washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography.

Ethyl 1-benzyl-5-(4-bromophenyl)-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (9a)
Light brown solid; M. pt. 292-295 ^{o}C; yield 64%; Anal. calcd for $C_{23}H_{21}BrN_2O_3$: C, 60.94; H, 4.67; N, 6.18. Found: C, 60.83; H, 4.43; N, 6.03%. IR (neat): ν (cm^{-1}) 3190, 2925, 2854, 1726, 1655, 1484, 1443, 1324, 1253, 1220, 1197, 1167, 1100, 1063, 1041, 925, 862, 795, 765, 743, 709; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.61 (s, 1H, Ar-*H*), 7.46–7.10 (m, 9H, Ar-*H*), 5.23 (s, 2H, Ar-CH_2), 3.79 (q, J = 7.4 Hz,

2H, CH_2), 3.50 (t, J = 7.8 Hz, 2H, CH_2), 2.76 (t, J = 7.2 Hz, 2H, CH_2), 1.45 (t, J = 14.8 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 166.34, 160.21, 138.86, 129.18, 129.02, 128.85, 128.38, 126.65, 123.26, 122.31, 118.73, 111.19, 110.04, 60.24, 51.60, 40.10, 30.37, 14.15; ESI-MS (*m/z*): 453.3 $[M+H]^+$.

Ethyl 1-benzyl-5-(2-chlorophenyl)-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3 carboxylate (9b)

Brown solid; M. pt.: 280-282 °C; yield 60%; Anal. calcd for $C_{23}H_{21}ClN_2O_3$: C, 67.56; H, 5.18; N, 6.85. Found: C, 67.41; H, 5.04; N, 6.71%. IR (neat): ν (cm^{-1}) 2925, 2854, 1722, 1640, 1480, 1458, 1383, 1324, 1257, 1227, 1197, 1097, 1063, 996, 929, 765, 743, 709; ^{1}H-NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.74 (s, 1H, Ar-*H*), 7.46–7.13 (m, 9H, Ar-*H*), 5.18 (s, 2H, Ar-CH_2), 3.99 (q, J = 8.4 Hz, 2H, CH_2), 3.02 (t, J = 8.8 Hz, 2H, CH_2), 2.76 (t, J = 8.2 Hz, 2H, CH_2), 1.23 (t, J = 12.2 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 164.74, 160.35, 136.37, 129.17, 129.01, 128.38, 128.01, 127.33, 127.04, 126.76, 126.32, 125.91, 124.75, 123.45, 122.71, 118.56, 58.44, 51.62, 40.61, 31.92, 14.11; ESI-MS (*m/z*): 409.13 $[M+H]^+$.

Ethyl 1-benzyl-5-(3-methylphenyl)-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (9c)

Light yellow solid; M. pt. 276-278 °C; yield 70%; Anal. calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.13; H, 6.16; N, 7.09%. IR (neat): ν (cm^{-1}) 2925, 2854, 1707, 1640, 1547, 1480, 1443, 1383, 1328, 1231, 1197, 1115, 1082, 1063, 1045, 929, 765, 709; ^{1}H-NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.70 (s, 1H, Ar-*H*), 7.45–7.11 (m, 9H, Ar-*H*), 5.21 (s, 2H, Ar-CH_2), 3.56 (q, J = 8.2 Hz, 2H, CH_2), 3.51 (t, J = 7.6 Hz, 2H, CH_2), 2.73 (t, J = 7.5 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 1.37 (t, J = 8.8 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 166.78, 134.85, 129.89, 129.27, 128.60, 128.38, 127.03, 126.74, 126.55; 125.83, 124.57, 123.42, 122.78, 119.21, 59.52, 51.27, 40.69, 30.36, 29.68, 20.82; ESI-MS (*m/z*): 389.18 $[M+H]^+$.

Ethyl 1-benzyl-5-(4-fluoro-3-methylphenyl)-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (9d)

Yellow oil; yield 64%; Anal. calcd for $C_{24}H_{23}FN_2O_3$: C, 70.92; H, 5.70; N, 6.89. Found: C, 70.81; H, 5.56; N, 6.71%. IR (neat): ν (cm^{-1}) 2987, 2828, 1713, 1656, 1521, 1456, 1383, 1303, 1209, 1197, 1131, 1065, 1035, 945, 765, 736; ^{1}H-NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.48 (s, 1H, Ar-*H*), 7.42–7.15 (m, 8H, Ar-*H*), 5.29 (s, 2H, Ar-CH_2), 3.98 (q, J = 8.4 Hz, 2H, CH_2), 3.02 (t, J = 8.7 Hz, 2H, CH_2), 2.73 (t, J = 8.2 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.42 (t, J = 8.8 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 165.23, 160.87, 156.21, 138.35, 136.07, 134.22, 129.17, 128.71, 128.33, 126.03, 122.74, 122.51, 120.31, 116.12, 110.20, 61.43, 51.20, 43.64, 22.36, 16.61, 14.12; ESI-MS (*m/z*): 407.17 $[M+H]^+$.

Ethyl 1-benzyl-5-(3, 5-dimethylphenyl)-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (9e)

Dark brown solid; M. pt. 291-293 °C; yield 84%; Anal. calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.51; H, 6.37; N, 6.81%. IR (neat): ν (cm^{-1}) 3268, 2925, 2858, 1704, 1637, 1551, 1503, 1443, 1339, 1238, 1171, 1022, 955, 758, 709; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.59 (s, 1H, Ar-*H*), 7.33–6.98 (m, 8H, Ar-*H*), 5.27 (s, 2H, Ar-CH_2), 3.60 (q, J = 7.4 Hz, 2H, CH_2), 3.35 (t, J = 7.2 Hz, 2H, CH_2), 2.78 (t, J = 8.2 Hz, 2H, CH_2), 2.38 (s, 6H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 167.85, 160.86, 137.98, 134.84, 130.19, 129.27, 128.60, 128.04, 127.03, 126.23, 123.42, 122.21, 116.00, 109.20, 61.43, 51.53, 40.98, 29.67, 24.82, 14.12; ESI-MS (*m/z*): 403.5 $[M+H]^+$.

The compounds **12** and **13** have been synthesized according to the procedure adopted for the synthesis of compounds **7** and **8**.

Diethyl 2-(2-aminoethyl)-1*H*-pyrrole-3, 4-dicarboxylate (12)

Light yellow solid, M. pt.: 226-228 °C; yield: 24%; Anal. calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.54; H, 7.02; N, 11.23%. IR (neat): ν (cm^{-1}) 3226, 1708, 1654, 1660, 1528, 1484, 1452, 1421, 1389, 1324, 1261, 1231, 1189, 1140, 1059, 1039, 901, 819, 786, 765, 720, 683; ^{1}H-NMR

(300 MHz, DMSO) (δ, ppm): 11.63 (brs, 1H, N*H*), 7.26 (s, 2H, NH_2), 6.99 (s, 1H, Ar-*H*), 4.15-4.03 (m, 4H, CH_2), 2.70 (t, *J* = 6.3 Hz, 4H, CH_2), 1.22 (t, *J* = 6.4 Hz, 6H, CH_3); ESI-MS (*m/z*): 255.3 $[M+H]^+$.

Ethyl 4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylate (13)
Light yellow oil; yield 71%; Anal. calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.54; H, 5.67; N, 13.32%. IR (neat): ν (cm^{-1}) 3330, 2976, 2881, 2041, 1458, 1382, 1277, 1089, 1048, 883, 806, 786, 657; ^{1}H-NMR (400 MHz, DMSO) (δ, ppm): 11.61 (s, 1H, N*H*), 7.26 (s, 1H, Ar-*H*), 6.99 (s, 1H, N*H*), 4.12 (q, *J* = 6.9 Hz, 2H, CH_2), 3.31 (m, 2H, CH_2), 2.70 (t, *J* = 6.6 Hz, 2H, CH_2), 1.22 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 178.14, 164.44, 140.42, 134.38, 121.53, 108.22, 61.84, 34.92, 30.02, 14.20; ESI-MS (*m/z*): 209.3 $[M+H]^+$.

1-*tert*-butyl 3-ethyl 4-oxo-4, 5, 6, 7-tetrahydropyrrolo[3,2-*c*]pyridine-1,3-dicarboxylate (14) To a solution of compound **13** (1 eq) in acetonitrile (10 ml), boc anhydride (1.5 eq) and DMAP (1 eq) were added. The resulting solution was stirred for 24 h. After completion of the reaction, water was added and the compound was extracted with ethyl acetate. The combined organic layers were washed with 1M HCl and brine which were further dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the boc protected compound.[20]
Light yellow oil; yield 85%; Anal. calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.23; H, 6.42; N, 9.24%. IR (neat): ν (cm^{-1}) 3330, 3156, 2976, 2878, 2041, 1853, 1756, 1646, 1532, 1458, 1382, 1277, 1089, 1048, 883, 806, 786, 657; ^{1}H-NMR (400 MHz, DMSO) (δ, ppm): 7.58 (s, 1H, Ar-*H*), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2), 3.37-3.35 (m, 2H, CH_2), 3.04 (t, *J* = 6.7 Hz, 2H, CH_2), 1.57 (s, 9H, Boc), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3); ESI-MS (*m/z*): 309.0 $[M+H]^+$.

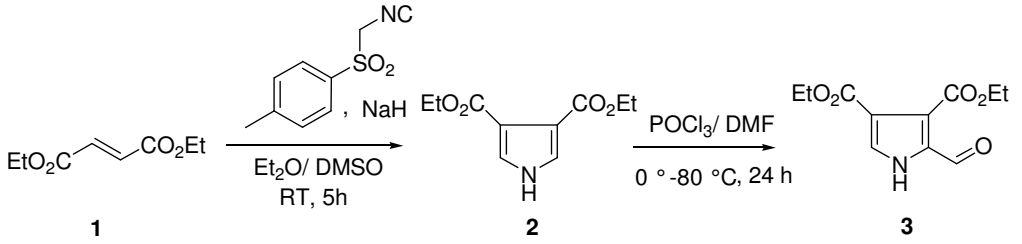
1-(*tert*-butoxycarbonyl)-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxylic acid (15)
To a solution of **14** (1 eq) in tetrahydrofuran, water and 2M LiOH solution (4.5 eq) was added with the help of the dropping funnel. The reaction was continued for 2 hours. After completion of the reaction, pH of the reaction was adjusted to 2-3 by adding 1N HCl. The compound was extracted with diethyl ether, dried over sodium sulfate, concentrated to give desired compound, **15.** [15]
White solid; M. pt. 146-148 ºC; yield 74%; Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.62; H, 5.65; N, 9.84%. ^{1}H-NMR (400 MHz, DMSO) (δ, ppm): 11.05 (brs, 1H, COO*H*), 7.66 (s, 1H, Ar-*H*), 3.31 (t, *J* = 8.2 Hz, 2H, CH_2), 2.92 (t, *J* = 8.1 Hz, 2H, CH_2), 1.62 (s, 9H, Boc); ESI-MS (*m/z*): 281.1 $[M+H]^+$.

***Tert*-butyl 3-(butylcarbamoyl)-4-oxo-4, 5, 6, 7-tetrahydropyrrolo [3, 2-*c*] pyridine-1-carboxylate (16)**
In a 50 ml round bottom flask, compound **15** (1 eq) and n-butylamine (1.2 eq) were dissolved in acetonitrile and cooled to 0 °C. To this solution, NMM (2 eq), HOBt (2 eq) were added and EDC.HCl (3 eq) was added in small portions. The reaction mixture was brought to room temperature and stirred at 4 °C. The progress of the reaction was checked by TLC. After completion of the reaction, solvent is removed under vaccum and ethyl acetate was added to the residue, washed with 10% citric acid solution, 5% sodium bicarbonate solution, water and then with brine and dried over $MgSO_4$. The organic layer was concentrated under vaccum. The crude product obtained was purified by column chromatography using methanol: DCM (1:10) as eluent to obtain pure compound, **16.**).[15]
Yellow oil; yield 63%; Anal. calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.71; H, 7.34; N, 12.41%. IR (neat): ν (cm^{-1}) 2924, 2853, 1991, 1703, 1462, 1380, 1279, 1166, 1123, 843, 745, 724, 672; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.86 (s, 1H, N*H*), 7.71 (s, 1H, N*H*), 7.38 (s, 1H, Ar-*H*), 3.09-3.05 (m, 2H, CH_2), 2.37-2.20 (m, 4H, CH_2), 1.76 (t, *J* = 6.6 Hz, 2H, CH_2), 1.65 (s, 9H, Boc),1.61-1.58 (m, 2H, CH_2), 1.29 (s, 9H, CH_3), 0.91-0.88 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 164.76, 156.06, 139.94, 129.80, 121.38, 119.87, 114.80, 72.44, 65.81, 40.42, 34.29, 31.94, 29.71, 22.70, 15.11; ESI-MS (*m/z*): 258.2 $[(M-Boc)+Na]^+$.

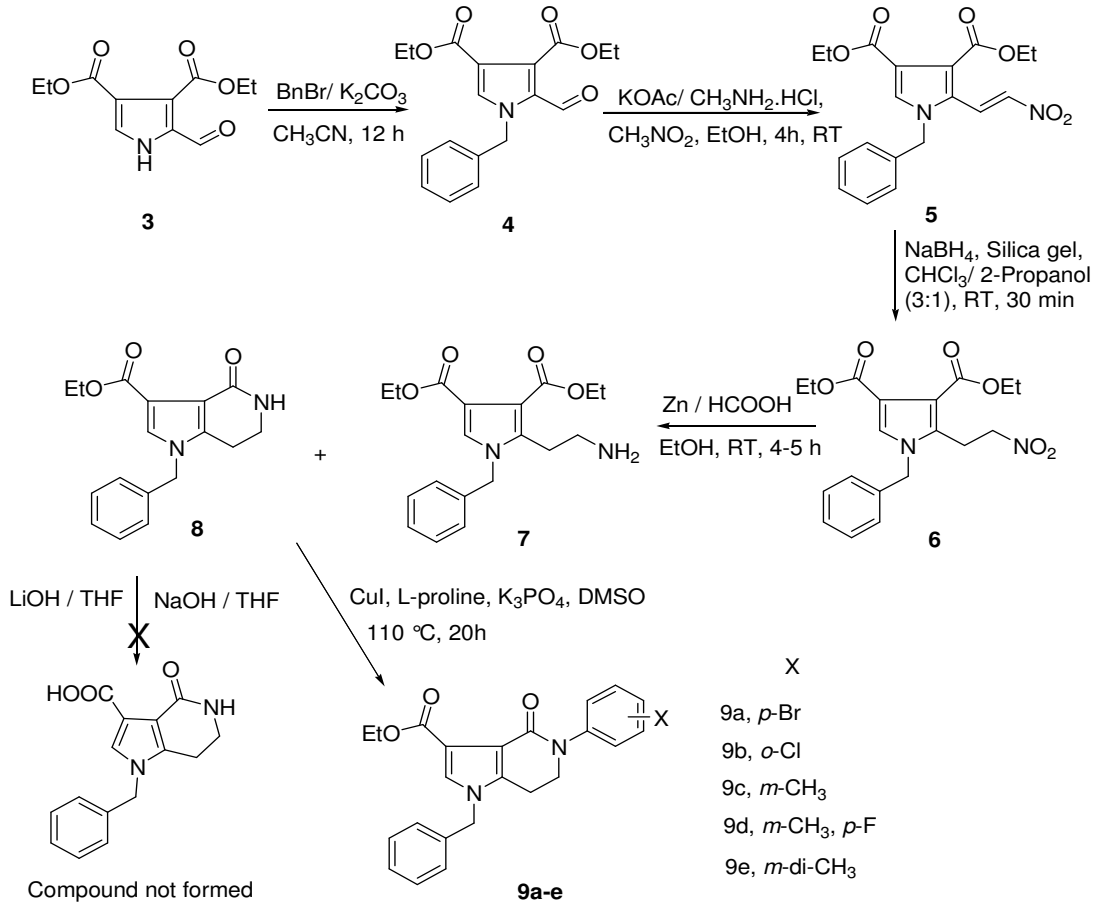
***N*-butyl-4-oxo-4, 5, 6, 7-tetrahydro-1*H*-pyrrolo [3, 2-*c*] pyridine-3-carboxamide (17)**

To a solution of compound **16** (1 eq) in DCM was added TFA (2 mL). The reaction mixture was stirred for 2 h at RT. After completion of reaction, DCM was evaporated and to the residue ethyl acetate was added, the mixture was neutralized by saturated sodium bicarbonate, washed with brine and organic layers were concentrated to give the final compound, **17.**[21]

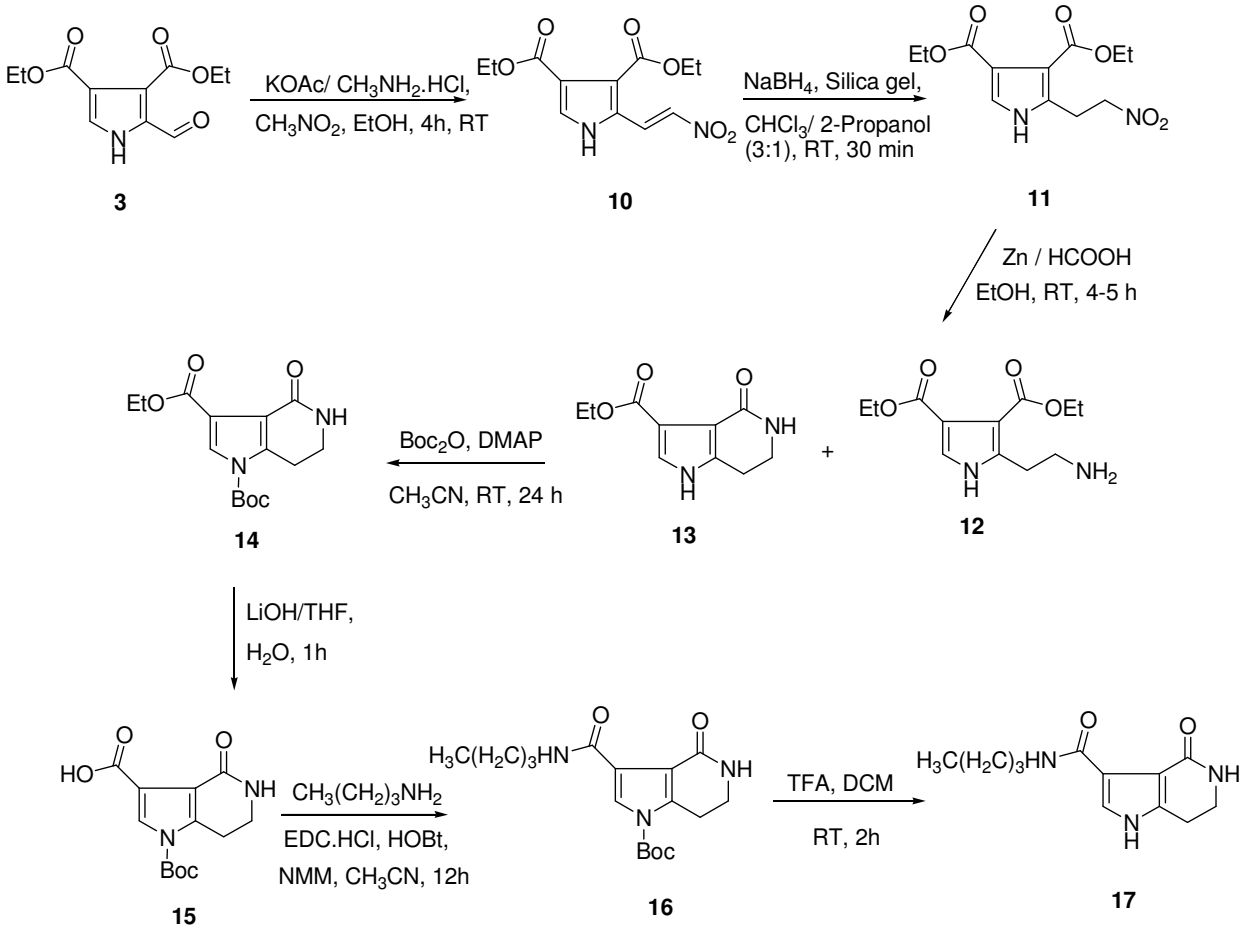
Light yellow oil; yield: 84%; Anal. calcd for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.17; H, 7.16; N, 17.52%. ^{1}H-NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.02 (brs, 1H, N*H*), 7.93 (brs, 1H, N*H*), 7.61 (s, 1H, Ar-*H*), 6.91 (brs, 1H, N*H*), 3.31 (t, *J* = 7.1 Hz, 2H, CH_2), 2.91 (t, *J* = 7.2 Hz, 2H, CH_2), 2.73 (t, *J* = 8.1 Hz, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 0.94-0.90 (m, 3H, CH_3); ESI-MS (*m/z*): 236.4 $[M+H]^+$.



Scheme-1



Scheme-2



Scheme-3

RESULTS AND DISCUSSION

The 3,4-bis-(ethoxycarbonyl)-2-formylpyrrole, **3** was prepared according to the method reported previously [15] using *α*, *β*-unsaturated esters, **1** as the starting material (Scheme 1). Compound **1** upon treatment with *p*-toluenesulfonylmethylisocyanide (TosMIC) via van Leusen method afforded 3,4-bis-(ethoxycarbonyl) pyrrole, **2** which upon Vilsmeier-Haack formylation yielded compound **3** in 56% yield. For the synthesis of dihydropyrrolo [3, 2-*c*] pyridine-4-one analogues, two possibilities were explored with different protecting groups as given in scheme 2 and 3. Benzyl protection of **3** followed by Henry condensation of resulting compound **4** gave nitrovinylpyrrole, **5**. Subsequent reduction of **5** with $NaBH_4$ afforded 3, 4-bis (ethoxycarbonyl)-2-(2-nitroethyl)-1-benzyl pyrrole, **6**. Further reduction of nitro group gave two types of compounds: 3,4-bis(ethoxycarbonyl)-2-(2-aminoethyl)-1-benzyl pyrrole, **7** in less amount while ethyl 1-benzyl-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate, **8** was obtained in major amount. Failure of hydrolysis of **8** even by utilizing strong base did not result into desired compound, amide substituted dihydropyrrolo [3, 2-*c*] pyridine-4-one. In order to explore further applicability of compound **8,** Buchwald-Hartwig cross-coupling reaction was utilized for the formation of C-N bonds by reacting it with different aryl iodides in the presence of CuI, L-proline, potassium phosphate at 110 °C (Scheme-2).

Formation of amide substituted dihydropyrrolo [3, 2-*c*] pyridine-4-one was accomplished by utilizing boc protection of compound **13.** This methodology has certain advantages over to benzyl protection method as boc group can be easily removed by using TFA/DCM mixture and amide coupling prior to removal of boc group eradicates the possibility of formation of side products. Compound **11** on reduction yielded two

products: diethyl 2-(2-aminoethyl)-1*H*-pyrrole-3,4-dicarboxylate, **12** in less amount while ethyl 4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-3-carboxylate, **13** was obtained in major amount. Hydrolysis of **13** followed by coupling with n-butylamine gave desired product, **16** in good yield which was further deprotected to yield the amide substituted dihydropyrrolo [3, 2-*c*] pyridine-4-one, **17** (Scheme-3).

To conclude, a mild method was demonstrated for the synthesis of desired amide substituted dihydropyrrolo [3, 2-*c*] pyridine-4-one analogues starting from diethylfumarate. Boc protection method was successful for the synthesis of desired analogues as compared to benzyl protection method. We have elaborated the use of Buchwald-Hartwig cross-coupling reaction for the formation of C-N bonds in the presence of CuI, L-proline and potassium phosphate.

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