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MULTISTEP SYNTHESIS OF PYRIDO[3',2':4,5]PYRROLO[3,2–*d*][1,3]OXAZIN-4(5*H*)-ONE FROM 2–AMINONICOTINONITRILES[†]

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Abstract - Pyrido[3',2':4,5]pyrrolo[3,2–*d*][1,3]oxazin-4(5*H*)-ones (**7)** were synthesized starting from 2-aminonicotinonitriles (**1)** through multistep synthesis involving Sandmeyer reaction, amination, Thorpe-Ziegler reaction, hydrolysis and cyclisation.

INTRODUCTION

The pyrrolo[2,3-*b*]pyridines are also known as 7-azaindoles and have similar chemical properties to that of imidazoles which form the basic skeleton of alkaloids.[1] The primary interest in azaindoles is mainly based on their use as potential antimetabolites compared to naturally occurring indole derivatives.[2] The 7-azaindoles are also considered as anti-malarial agents due to their similarity in structure with quinoline derivatives[3] and some are multidrug resistance associated specific protein (MRP1) inhibitors.[4] Synthesis of 7-azaindoles and fusion of another ring over 7-azaindoles in order to see the influence of additional ring over activity is of current interest. Our continued interest on fusion of oxazine ring over furo [2,3–*b*] pyridines,[5] indoles[6] prompted us to synthesize a number of new 7-azaindoles and fusion of 1,3-oxazine ring over it. Thus the 2-aminonicotinonitriles (**1)**[7] is choosen as starting material and synthesized pyrido[3',2':4,5]pyrrolo[3,2–*d*][1,3]oxazin-4-(5*H*)-ones (**7)** *via* Sandmeyer reaction, amination, Thorpe-Ziegler reaction, hydrolysis followed by cyclisation. The interesting aspect of these studies is mainly to have trifluoromethyl group at a specific position of each molecule and its influence in altering the reactivity apart from increasing solubility in lipid system due to its high liphophilicity. The strategies adopted in each step of the methodology is compatible with the predicted products except in one case where alkylation of amine resulted in dialkylation product.

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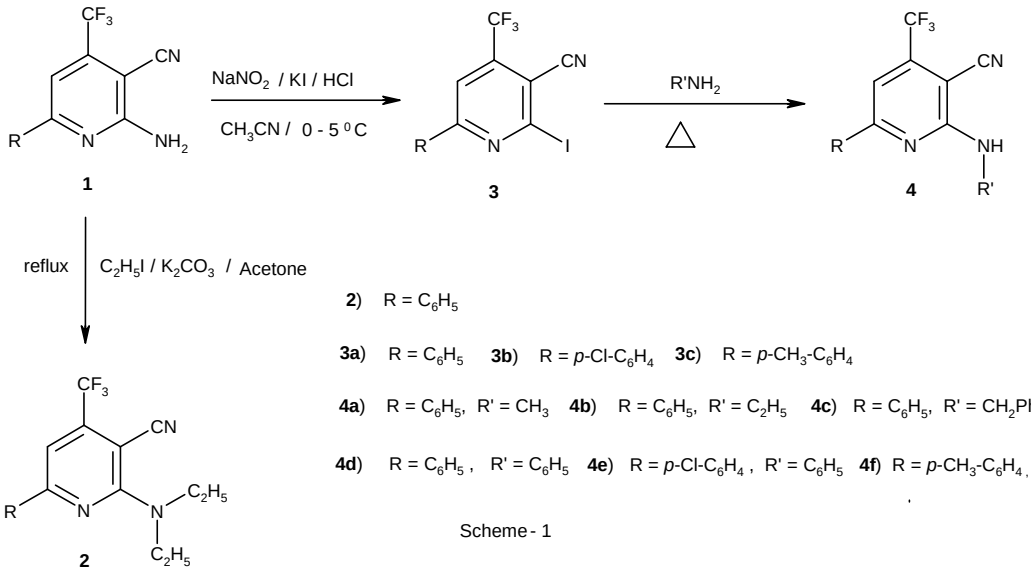
RESULTS AND DISCUSSION

The 2-amino-4- trifluoromethyl- 6-substituted nicotinonitriles (**1)** on reaction with ethyl iodide under basic conditions resulted in exclusively *N*-diethyl product (**2)**, irrespective of stoichiometric quantity used and obtained in low yield (45%). In order to have monoalkylated products, number of procedures were examined using ethyl iodide with potassium carbonate in DMF, sodium carbonate / Cu powder in acetone, sodium hydride in DMF and so on. In all the cases dialkylated products were formed exclusively. Therefore an alternate strategy is applied to obtain monoalkylated products. Thus 2-amino-4-trifluoromethyl-6-substituted nicotinonitriles (**1)** was reacted with sodium nitrite and 33% HCl solution at 0 ^{0}C.

The resulting diazonium salt is treated with potassium iodide solution at room temperature and gave 2-iodo-4-trifluoromethyl-6-substituted nicotinonitriles (**3**). In order to see the role of substituents of the phenyl ring in formation of products (**3**)**,** the phenyl is *para* substituents with electron releasing methyl group, electron withdrawing chloro group were tested, however there was no effect of substituent on yield or rate of reaction. The iodo compounds (**3**) were further reacted with alkyl / arylamine which gave the corresponding *N*-monoalkylated/monoarylated nicotinonitriles (**4**) leaving the nitrile group intact. This is due to facile nucleophilic substitution at 2-position in pyridine ring. The yield of products with alkyl amines are comparatively higher than with aryl amines and it is attributed to steric factors.

The 2-*N*-substituted aminonicotinonitriles (**4)** have active functional groups *ortho* to each other and considered as active synthons to facilitate fusion of five membered ring and to have novel 7-azaindoles of promising activity. Thus 2-*N*-substituted aminonicotinonitriles (**4**) were further reacted with ethyl bromoacetate in DMF using potassium carbonate as base at 110 ^{0}C and formed 2,3- bifunctionalised 7-azaindole derivatives (**5**)**.** The reaction involves initial alkylation of substituted amine followed by abstraction of methylene hydrogen to generate carbanion and cyclisation on to nitrile carbon to give the corresponding azaindole derivatives (**5**) in single step. This type of cyclisation is also known as Thorpe – Ziegler reaction. The compounds (**5**) have active functional groups *ortho* to each other and are further utilized to build up oxazine ring. Compounds (**5**) are subjected to alkaline hydrolysis to afford the acids (**6**)**.**

The presence of amino and carboxylic acid functional groups *ortho* to each other in compound (**6**) is conveniently utilized for the formation of oxazine ring. Thus compounds (**6**) on reaction with acetic anhydride/ trifluoroacetic anhydride gave the corresponding pyrido[3',2':4,5]pyrrolo[3,2–*d*][1,3]oxazin (5*H*)-ones (**7**) in high yields. The reaction is initially *N*-acylation followed by cyclisation. The reactions are drawn in Scheme 1and 2.



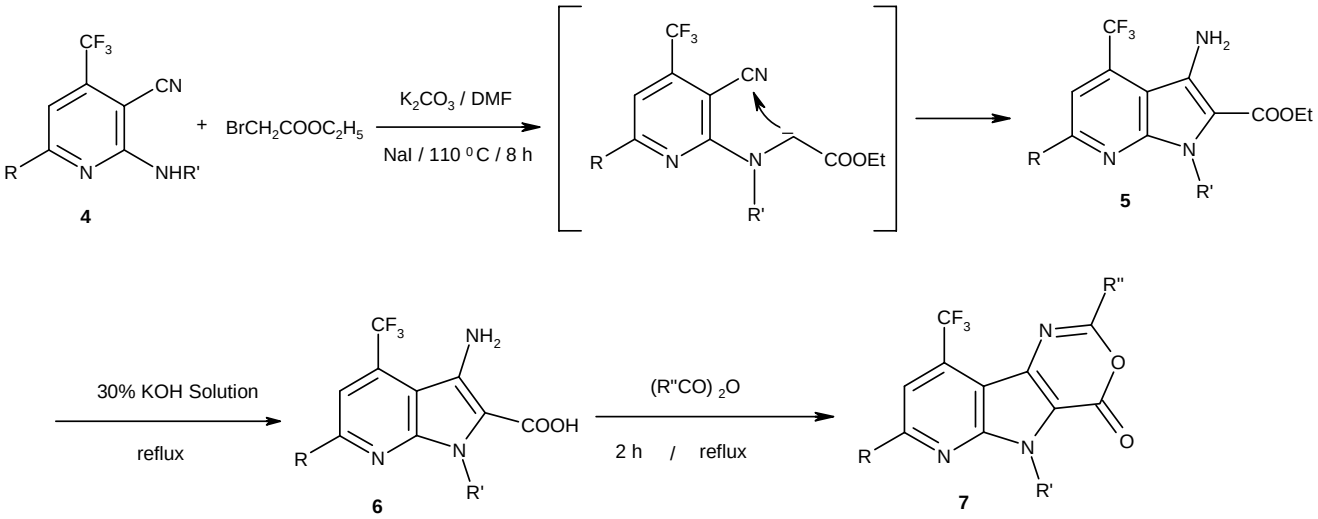
2) R = C_6H_5

3a) R = C_6H_5 **3b**) R = *p*-Cl-C_6H_4 **3c**) R = *p*-CH_3-C_6H_4

4a) R = C_6H_5, R' = CH_3 **4b**) R = C_6H_5, R' = C_2H_5 **4c**) R = C_6H_5, R' = CH_2Ph

4d) R = C_6H_5 , R' = C_6H_5 **4e**) R = *p*-Cl-C_6H_4 , R' = C_6H_5 **4f**) R = *p*-CH_3-C_6H_4 , R' = C_6H_5

Scheme - 1



5a) R = C_6H_5 , R' = $CH_2C_6H_5$ **5 b)** R = C_6H_5, R' = C_6H_5 **5c)** R = *p*-Cl-C_6H_4 , R' = C_6H_5 **5d**) R = *p*-CH_3-C_6H_4, R' = C_6H_5

6a) R = C_6H_5, R' = $CH_2C_6H_5$ **6b**) R = C_6H_5, R' = C_6H_5 **6c**) R = *p*-Cl-C_6H_4 , R' = C_6H_5 **6d**) R = *p*-CH_3-C_6H_4 , R' = C_6H_5

7a) R = C_6H_5, R' = $CH_2C_6H_5$, R" = CH_3 **7b**) R = C_6H_5 , R' = $CH_2C_6H_5$, R" = CF_3 **7c)** R = C_6H_5, R' = C_6H_5 , R" = CH_3

7d) R' = C_6H_5 , R' = C_6H_5 , R" = CF_3 **7e**) R = *p*-Cl-C_6H_4 , R' = C_6H_5 , R" = CH_3 **7f**) R = *p*-Cl-C_6H_4 , R' = C_6H_5 , R" = CF_3

7g) R = *p*-CH_3-C_6H_4 , R' = C_6H_5 , R" = CH_3 **7h**) R = *p*-CH_3-C_6H_4 , R' = C_6H_5 , R" = CF_3

Scheme - 2

CONCLUSION

The sequence of reactions provided active synthons like *N*- substituted nicotinonitriles and 2,3-bifunctionalised indole derivatives, which are useful for further building a variety of heterocycles of biological interest.

EXPERIMENTAL

Melting points were recorded on Casia-siamia (VMP - AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker AV 300 and Unity 400 spectrometer in $CDCl_3$ using TMS as internal standard. Electron impact (EI) and chemical ionization MS spectra were recorded on a VG 7070 H instrument at 70 ev. All reactions were monitored by thin layer chromatography (TLC) on precoated silicagel 60 F_{254} (mesh); Spots were visualized with UV light. Merck silicagel (60-120 and 100-200 mesh) was used for chromatography. CHN analyses were recorded on a Vario EL analyser.

2-Diethylamino-4-trifluoromethyl-6-substituted nicotinonitrile (**2**)

To a solution of **1** (2.0 g, 7.6 mmol) in acetone (25 mL), K_2CO_3 (2.09 g, 15.2 mmol) and ethyl iodide (1.2 g, 7.6 mmol) were added and the resulting mixture was refluxed for 8 h. The reaction mixture was cooled to rt and acetone was evaporated under vacuum. The residual solid was diluted with water, filtered, washed and dried. The crude product was purified by column using 60-120 mesh silica gel and the desired product was eluted using 15% chloroform in hexane.

Yield: 1.0 g (45%); mp 164 ^{0}C, recrystallised from hexane+DCM; IR (KBr): 2220 (CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.4 (6H, t, J = 9.5 Hz , 2 CH_3), 3.8 (4H, quartet, J = 9.5 Hz , 2 CH_2), 7.35 (1H, s , Ar-H), 7.5 (3H, m, Ar-H) , 8.0 (2H , m , Ar-H). EI MS , m/z : 319 (M^+,) , 290 (M^+- C_2H_5). Anal. Calcd for $C_{17}H_{16}N_3F_3$: C, 63.93 ; H, 5.04 ; N, 13.15. Found: C, 63.85; H, 5.15; N, 13.28.

2-Iodo-4-trifluoromethyl-6-substituted nicotinonitrile (**3)**

To a mixture of compounds (**1**) (4 g, 15 mmol) , CH_3CN (8 mL) and conc. HCl (10 mL) at 0^{0}C , a cooled solution of $NaNO_2$ (2.0 g, 30 mmol) in H_2O (12 mL) was added slowly while stirring such that the temperature was maintained below 5 ^{0}C . To the diazonium chloride solution thus formed a solution of KI (5.0 g, 30 mmol) added slowly while stirring and the mixture was stirred for 3 h at rt. Acetonitirile was evaporated under vacuum and the reaction mixture was diluted with ice cold water .The separated crude product was collected and purified by column using 60-120 mesh silica gel. The desired product was eluted with 20% $CHCl_3$ in hexane.

2-Iodo-6-phenyl-4-trifluoromethylnicotinonitrile (**3a**)

Yield: 4.6 g (82%) ; mp 92 ^{0}C , recrystallised from hexane + EtOAc ; IR (KBr): 2248(CN).^{1}H NMR(200 MHz, $CDCl_3$): δ 7.5 – 7.6 (3H, m, Ar-H), 8.0 - 8.15 (3H, m, Ar-H); LSIMS, m/z : 375 (M^++ 1). Anal. Calcd for $C_{13}H_6N_2F_3I$: C, 41.74; H, 1.62; N, 7.49. Found: C, 41.66; H, 1.58; N, 7.55.

2-Iodo-6-(4-chlorophenyl)-4-trifluoromethylnicotinonitrile (**3b**)

Yield: 4.58 g (85%); mp 144 ^{0}C, recrystallised from hexane + EtOAc ; IR (KBr): 2240 (CN).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.5 (2H, d, J = 15 Hz, Ar-H), 7.65(1H, s, Ar-H), 8.05 (2H, d, J = 15 Hz, Ar-H) ; LSIMS,

m/z : 409 (M^++1). Anal. Calcd for $C_{13}H_5N_2ClF_3I$: C, 38.22; H, 1.23; N, 6.86. Found: C, 38.31; H, 1.18; N, 6.78.

2-Iodo-6-(4-methylphenyl)-4-trifluoromethylnicotinonitrile (**3c**)

Yield: 3.92 g (70%); mp 152 ^{0}C, recrystallised from hex + DCM ; IR (KBr): 2245(CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.3 (3H, s , CH_3), 7.25 - 7.3 (2H, m , Ar-H), 8.0 – 8.1 (3H, m , Ar-H) . LSIMS, m/z : 389 (M^++ 1). Anal. Calcd for $C_{14}H_8N_2F_3I$: C, 43.32; H, 2.08; N, 7.22. Found: C, 43.25; H, 2.15; N, 7.18

2 - (*N*-Subtituted amino)-4-trifluoromethyl-6-substituted nicotinonitrile (**4**)

The iodo compound (**3)** (2 g , 5.3 mmol) was taken in excess of alkyl/arylamine (15 mL) and the mixture was stirred for 4 h at rt (in case of aniline the reaction was carried out at 110 ^{0} C for 6 h) . The reaction mixture was diluted with cold water and the solid was collected by filtration, washed and dried (in case of aniline the reaction mixture was cooled to rt, aniline was removed under vacuum and the solid product was washed with hexane and dried. The resulted product was purified by column using 60-120 mesh silica gel. The desired product was eluted with 25% $CHCl_3$ in hexane)

2-Methylamino-6-phenyl-4-trifluoromethylnicotinonitrile (**4a**)

Yield: 1.35 g (91%); mp 138 ^{0}C, recrystallised from hex + EtOAc ; IR (KBr): 3310 (N-H), 2228 (CN). ^{1}H NMR(200 MHz, $CDCl_3$): δ 3.2 (3H, J = 8.2Hz, d) , 6.2 (1H, br s , NH), 7.4 (1H, s, Ar-H), 7.6 - 7.7 (3H, m, Ar-H) , 8.0 – 8.1 (2H , m , Ar-H). EIMS, m/z : 277 (M^+) , 262 (M^+- CH_3). Anal. Calcd for $C_{14}H_{10}N_3F_3$: C, 60.86 ; H, 3.64 ; N, 15.20. Found: C, 60.75; H, 3.55; N, 15.38.

2-Ethylamino-6-phenyl-4-trifluoromethylnicotinonitrile (**4b**)

Yield: 1.32 g (87%); mp 159 ^{0}C, recrystallised from hex + DCM ; IR (KBr): 3315(N-H), 2225(CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.4 (3H, t, J = 10.45 Hz, CH_3), 3.8 (2H, quartet, J = 10.45 Hz, CH_2), 5.6 (1H, br t , NH), 7.35 (1H, s , Ar-H), 7.7 – 7.8 (3H, m, Ar-H) , 8.0- 8.05 (2H , m , Ar-H). EIMS , m/z(%); 291 (M^+) , 276 (M^+-CH_3). Anal. Calcd for $C_{15}H_{12}N_3F_3$: C, 61.98 ; H, 4.15 ; N, 14.42 Found: C, 61.82; H, 4.22; N, 14.55.

2-Benzylamino-6-phenyl-4-trifluoromethylnicotinonitrile (**4c**)

Yield: 1.55 g (82%); mp 168 ^{0}C, recrystallised from hex + EtOAc ; IR (KBr): 3322 (N-H), 2220 (CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 4.9 (2H, d, J = 12.5 Hz, N-CH_2), 5.9 (1H, br t , NH), 7.3 – 7.5 (9H, m , Ar-H), 8.0 (2H, m, Ar-H) . LSIMS, m/z : 354 (M^+ + 1), 262 (M^+- CH_2Ph). Anal. Calcd for $C_{20}H_{14}N_3F_3$: C, 67.98 ; H, 3.99 ; N, 11.89. Found: C, 67.85; H, 3.85; N, 11.92.

2-Phenylamino-6-phenyl-4-trifluoromethylnicotinonitrile (**4d**)

Yield: 1.52 g (84%); mp 134 ^{0}C recrystallised from $CHCl_3$; IR (KBr): 3320 (N-H), 2225(CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.15 - 7.2 (1H, m , Ar-H), 7.4 – 7.5 (6H, m, Ar-H), 7.65 (2H , d, J = 18.5 Hz, Ar-H), 8.0 – 8.05 (2H , m , Ar - H) . LSIMS, m/z : 340 (M^++ 1),. Anal. Calcd for $C_{19}H_{12}N_3F_3$: C, 67.26 ; H, 3.56 ; N, 12.38. Found: C, 67.32; H, 3.66; N, 12.45.

2-Phenylamino-6-(4-chlorophenyl)-4-trifluoromethylnicotinonitrile (**4e**)

Yield: 1.43 g (79%); mp 181 ^{0}C, recrystallised from $CHCl_3$; IR (KBr): 3319 (N-H), 2226 (CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.2 (1H, s , Ar-H), 7.4 – 7.5 (5H, m, Ar-H), 7.6 (2H , d , J = 22.8 Hz, Ar-H) , 7.95 (2H , d , J = 22.8 Hz, Ar - H) . LSIMS, m/z : 374 (M^++ 1), 296 (M^+- Ph). Anal. Calcd for $C_{19}H_{11}N_3ClF_3$: C, 61.06 ; H, 2.97 ; N, 11.27. Found: C, 61.15; H, 2.86; N, 11.35.

2-Phenylamino-6-(4-methylphenyl)-4-trifluoromethylnicotinonitrile (**4f**)

Yield: 1.48 g (81%); mp 184 ^{0}C, recrystallised from $CHCl_3$; IR (KBr): 3317 (N-H), 2223 (CN). ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.4 (3H, s) , 7.15 (1H, s , Ar-H), 7.3 – 7.5 (5H, m, Ar-H), 7.65 (2H , d , J = 18.8 Hz, Ar - H) , 7.9 (2H , d , J = 18.8 Hz, Ar – H) ; LSIMS, m/z : 354 (M^++1) . Anal. Calcd for $C_{20}H_{14}N_3F_3$: C, 67.98 ; H, 3.99 ; N, 11.89. Found: C, 67.85; H, 3.86; N, 11.75.

Ethyl 3-amino-1,6-disubstituted 4-trifluoromethyl-1*H*-pyrrolo[2,3- *b*]pyridine-2-carboxylate *(*5*)*

To a solution of compounds (**4**) (900 mg, 2.6 mmol) in DMF (5 mL), K_2CO_3 (730 mg, 5.3 mmol), ethyl bromoacetate (850 mg, 5.3 mmol) and a pinch of NaI were added and the resulting mixture was heated to 120 ^{0} C for 8 h while stirring under N_2 atmosphere. The reaction mixture was cooled to rt and DMF was removed under vacuo. The residual solid was diluted with water, filtered, washed with water until washings were neutral to pH. The crude product was purified by column using 60 – 120 mesh silica gel. The desired product was eluted with 15% $CHCl_3$ in hexane solvent mixture

Ethyl 3-amino-1-benzyl-6-phenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (**5a**)

Yield: 786 mg (70%); mp 131^0 C, recrystallised from MeOH ; IR (KBr): 3490, 3370 (NH_2), 1735 (C=O); ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.2 (3H, t, J = 10.72 Hz, CH_3), 4.3 (2H, quartet, J = 8.92 Hz, CH_2) , 5.35 (2H, br s, NH_2), 5.95 (s, 2H, CH_2Ph), 7.1- 7.3 (m, 5H, Ar-H), 7.4 – 7.5 (3H, m, Ar- H), 7.75 (1H, s ,Ar-H) , 8.05 - 8.1 (2H , m, Ar-H) ; LSIMS, m/z ; 439 (M^+). 348 (M^+- CH_2Ph) ; Anal. Calcd for $C_{24}H_{20}N_3O_2F_3$: C, 65.45; H, 4.81; N, 9.54. Found: C, 65.56; H, 4.77; N, 9.62.

Ethyl 3-amino-1,6-diphenyl-4-trifluoromethyl- 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (**5b**)

Yield: 852 mg (76%); mp 139 ^{0}C, recrystallised from MeOH ; IR (KBr): 3465, 3390 (NH_2), 1730 (C=O); ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.1 (3H, t, J= 15 Hz, CH_3), 4.1 (2H, quartet, J = 11.6 Hz , OCH_2) , 5.45 (2H, br s, NH_2), 7.3- 7.5 (8H, m, Ar-H), 7.75 (1H, s, Ar- H), 7.9 - 8.0 (2H , m, Ar-H) ; LSIMS), m/z ; 425 (M^+). Anal. Calcd for $C_{23}H_{18}N_3O_2F_3$: C, 64.94; H, 4.26; N,9.88. Found: C, 64.82; H, 4.38; N, 6.78.

Ethyl 3-amino-6-(4-ch1orophenyl)-1-phenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate *(* 5c*)*

Yield: 956 mg (86%); mp 144 ^{0}C, recrystallised from MeOH ; IR (KBr): 3485, 3360 (NH_2), 1733 (C=O) ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.1 (3H, t, J= 7.5 Hz, CH_3), 4.3 (2H, quartet, J= 7.5 Hz , OCH_2) , 5.5 (2H, br s, NH_2), 7.3- 7.5 (7H, m, Ar-H), 7.7 (1H, s, Ar- H), 7.85 - 7.9 (2H, m , Ar-H) ; LSIMS, m/z : 459 (M^+), 461(M^+ + 2) Anal. Calcd for $C_{23}H_{17}N_3O_2ClF_3$: C, 60.07; H, 3.73; N, 9.14. Found:C, 60.15; H, 3.61; N, 9.28.

Ethyl 3-amino-6-(4-methylphenyl)-1-phenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (**5d**)

Yield: 775 mg (70%); mp 135 ^{0}C, recrystallised from MeOH ; IR (KBr): 3475, 3345 (NH_2), 1730(C=O) ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3H, t, J= 8.82 Hz, CH_3), 2.4 (3H, s) , 4.1 (2H, quartet, J= 5.88 Hz , OCH_2) , 5.5 (2H, br s, NH_2), 7.15 - 7.2 (2H, m, Ar-H), 7.3 - 7.35 (3H, m, Ar- H), 7.4 – 7.5 (2H, m , Ar-H), 7.75 (1H , s , Ar- H), 7.8 - 7.85 (2H, m , Ar – H) ; LSIMS, m/z : 439 (M^+), 362 (M^+- Ph). Anal. Calcd for $C_{24}H_{20}N_3O_2F_3$: C, 65.60; H, 4.59; N, 9.56. Found: C, 65.75; H, 4.66; N, 9.68.

3-Amino-1,6-disubstituted 4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (**6**)

Compounds (**5**) (650 mg , 1.5 mmol) was suspended in 30% KOH solution (10 mL) and heated to reflux while stirring for 6 h. The reaction mixture was cooled to rt diluted with cold water and neutralized with 5% HCl solution. The separated solid was filtered, washed with water, dried and recrystallised in methanol.

3-Amino-1-benzyl-6-phenyl-4-trifluoromethyl-*1H*-pyrrolo[2,3-*b*]pyridine-2- carboxylic acid (**6a**)

Yield: 475 mg (76%); mp 255 ^{0}C, recrystallised from MeOH ; IR (KBr):3400 – 3600 (O-H), 1725 (C=O). ^{1}H NMR(200 MHz, DMSO- d_6): δ 5.3 (2H, br s, NH_2), 6.1 (2H, s, CH_2Ph), 7.2- 7.3 (m, 4H, Ar-H), 7.5 – 7.6 (4H, Ar- H), 7.75 (1H, s, Ar-H), 8.2 (2H , m, Ar-H) ; LSIMS, m/z : 411 (M^+), 393 ($M^+ – H_2O$), 367 (M^+- CO_2) Anal. Calcd for $C_{22}H_{16}N_3O_2F_3$: C, 64.23; H, 3.92; N, 10.21. Found: C, 64.38; H, 3.88; N, 10.33.

3-Amino-1,6-diphenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (**6b**)

Yield: 480 mg (78%) ; mp 268 ^{0}C, recrystallised from EtOH ; IR (KBr): 3400 – 3550 (O-H), 1720 (C=O) ^{1}H NMR (200 MHz, DMSO- d_6): δ 5.1 (2H, br s, NH_2), 7.2 (2H, m, Ar-H), 7.35 (3H, m, Ar-H), 7.4 – 7.5 (3H, m, Ar-H), 7.75 (1H, s, Ar- H), 7.85 (2H, m, Ar – H); .LSIMS, m/z : 397(M^+), 379(M^+- H_2O), 353 (M^+– CO_2). Anal. Calcd for $C_{21}H_{14}N_3O_2F_3$: C, 63.48; H, 3.55; N, 10.58. Found: C, 66.55; H, 3.67; N, 10.44.

3-Amino-6-(4-chlorophenyl)-1-phenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (**6c**)

Yield: 535 mg (86%); mp 272 ^{0}C, recrystallised from EtOH , IR (KBr): 3455 – 3600 (O-H), 1725 (C=O). ^{1}H NMR(200 MHz, DMSO- d_6): δ 5.5 (2H, br s, NH_2) 7.3- 7.5 (7H, m, Ar-H), 7.7 (1H, s, Ar- H), 7.85 - 7.9 (2H, m , Ar-H). LSIMS, m/z : 431 (M^+), 413 (M^+- H_2O), 387 (M^+- CO_2) . Anal. Calcd for $C_{21}H_{13}N_3O_2ClF_3$: C, 58.41; H, 3.03; N, 9.73. Found: C, 58.55; H, 3.15; N, 9.88.

3-Amino-6-(4-methylphenyl)-1-phenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (6d)

Yield: 433 mg (70%) ; mp 248 ^{0}C, recrystallised from MeOH ; IR (KBr): 3400 – 3580 (O-H) , 1720 (C=O). ^{1}H NMR(200 MHz, DMSO- d_6): δ 2.45 (3H, s, CH_3), 5.25 (2H, br s, NH_2), 7.15 - 7.2 (2H, m, Ar-H), 7.25 - 7.35 (3H, m, Ar- H), 7.4 – 7.5 (2H, m , Ar- H), 7.75 (1H , s , Ar- H), 7.80 - 7.85 (2H, m,

Ar – H); LSIMS, m/z : 411 (M^+), 393(M^+-H_2O), 367 (M^+-CO_2). Anal. Calcd for $C_{22}H_{16}N_3O_2F_3$: C, 64.23; H, 3.92; N, 10.21. Found: C, 64.33; H, 3.85; N, 10.35.

2,5,7-Trisubstituted 9-trifluoromethylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)- one (**7**)

Compounds (**6**) (420 mg , 1 mmol) was taken in acetic anhydride (5 mL, 48 mmol)/trifluoroacetic anhydride (5 mL, 34 mmol) and the mixture was heated to 110 ^{0}C (40^{0}C in case of trifluoroacetic anhydride) while stirring for 2 h. The reaction mixture was cooled to rt and poured on to crushed ice. The separated solid was filtered, washed with water until neutral to pH (7) and dried. The crude product was purified by column using 60-120 mesh silica gel and the desired product was eluted with 10% $CHCl_3$ in hexane.

2-Methyl-5-benzyl-7-phenyl-9-trifluoromethylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)-one(**7a**)

Yield: 350 mg (79%), mp 282 ^{0}C, recrystallised from MeOH ; IR (KBr): 1751 (C=O). ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.55 (3H, s, CH_3), 6.0 (2H , s , CH_2Ph), 7.15 - 7.25 (4H, m, Ar-H), 7.5 – 7.6 (4H, m, Ar- H), 8.0 (1H , s , Ar – H), 8.2 (2H , m , Ar – H) ; MS (LSIMS), m/z : 437 (M^++1), 392 (M^+ - CO_2) , 421 (M^+ – CH_3) ; Anal Calcd for $C_{24}H_{16}N_3O_2F_3$: C, 66.21; H, 3.70; N, 9.65. Found: C, 66.15; H, 3.88; N, 9.78.

2,9-Bis(trifluoromethyl)-5-benzyl-7-phenylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)- one (**7b**)

Yield: 445 mg (87%) , mp 224 ^{0}C, recrystallised from MeOH ; IR (KBr): 1750 (C=O). ^{1}H NMR(300 MHz, $CDCl_3$): δ 6.05 (2H , s , CH_2Ph), 7.2 – 7.3 (4H, m, Ar-H), 7.5 – 7.6 (4H, m, Ar- H), 8.1 (1H , s , Ar – H), 8.20 - 8.25 (2H , m , Ar – H); LSIMS, m/z : 490 (M^++1), 420 (M^+- CF_3) , 445 (M^+ - CO_2) . Anal. Calcd for $C_{24}H_{13}N_3O_2F_6$: C, 58.90; H, 2.60; N, 8.59. Found: C, 58.84; H, 2.77; N, 8.66.

2-Methyl-5,7-diphenyl-9-trifluoromethylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)- one (**7c**)

Yield: 356 mg (78%), mp 266 ^{0}C, recrystallised from MeOH ; IR (KBr): 1755 (C=O). ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.6 (3H , s , CH_3), 7.3 - 7.4 (4H, m, Ar-H), 7.5 - 7.6 (4H, m, Ar- H), 8.0 - 8.05 (3H , m , Ar – H) ; LSIMS, m/z : 422 (M^+ + 1), 406 (M^+ – CH_3) , 377 (M^+ - CO_2) . Anal. Calcd for $C_{23}H_{14}N_3O_2F_3$: C, 65.56; H, 3.35; N, 9.97. Found: C, 65.44; H, 3.28; N, 9.88.

2,9-Bis(trifluoromethyl)-5,7-diphenylpyrido[3',2':4,5]pyrrolo[3,2- *d*][1,3]oxazin- 4(5*H*)- one (**7d**)

Yield: 422 mg (85%), mp 268 ^{0}C, recrystallised from MeOH ; IR (KBr): 1752 (C=O). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.4 – 7.6 (6H, m, Ar-H), 7.75 - 7.8 (2H, m, Ar- H), 7.9 (1H , s , Ar- H), 8.0 - 8.05 (2H , m , Ar – H) LSIMS, m/z : 476 (M^++1), 406 (M^+ – CH_3) , 377 (M^+– CO_2) . Anal. Calcd for $C_{23}H_{11}N_3O_2F_6$: C, 58.12; H, 2.33; N, 8.84. Found: C, 58.22; H, 2.45; N, 8.95

2-Methyl-5-phenyl-7-(4-chlorophenyl)-9-trifluoromethylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)- one (**7e**)

Yield: 375 mg (82%), mp 274 ^{0}C, recrystallised from MeOH ; IR (KBr): 1784(C=O). ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.6 (3H , s , CH_3), 7.45 (2H, m, Ar-H), 7.5 - 7.6 (5H, m, Ar- H), 7.9 - 8.0 (3H , m , Ar – H) . LSIMS, m/z ; 456 (M^++1), 440(M^+ – CH_3) , 411 (M^+ - CO_2) . Anal. Calcd for $C_{23}H_{13}N_3O_2ClF_3$: C, 60.61; H, 2.87; N, 9.22. Found: C, 60.72; H, 2.95; N, 9.38.

2,9-Bis(trifluoromethyl)7-(4-chlorophenyl)-5-phenylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)-one (**7f**)

Yield: 462 mg (88%), mp 177 ^{0}C, recrystallised from MeOH ; IR (KBr): 1745 (C=O). ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.4 - 7.45 (3H, m, Ar-H), 7.45 - 7.6 (4H, m, Ar-H), 7.9 - 8.0 (3H , m , Ar – H) ; . LSIMS), m/z : 510 (M^++1), 440 (M^+-CF_3), 490 (M^+-F) . Anal. Calcd for $C_{23}H_{10}N_3O_2ClF_6$: C, 54.19; H, 1.98; N, 8.24. Found: C, 54.28; H, 1.85; N, 8.33

2-Methyl-7-(4-methylphenyl)-5-phenyl-9-trifluoromethylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)- one (**7g**)

Yield: 384 mg (82%), mp 257 ^{0}C, recrystallised from MeOH ; IR (KBr): 1751(C=O). ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.4 (3H , s , CH_3), 2.6 (3H, s , CH_3- C (2)), 7.2 – 7.3 (2H, m, Ar-H), 7.5 - 7.6 (6H, m, Ar-H), 7.95 - 8.0 (2H , m , Ar – H); LSIMS, m/z : 436 (M^++1), 420 (M^+– CH_3); 391(M^+ – CO_2). Anal Calcd for $C_{24}H_{16}N_3O_2F_3$: C, 66.21; H, 3.70; N, 9.65. Found: C, 66.38; H, 3.85; N, 9.55.

2,9-Bis(trifluoromethyl)-7-(4-methylphenyl)-5-phenylpyrido[3',2':4,5]pyrrolo[3,2-*d*][1,3]oxazin-4(5*H*)-one (**7h**)

Yield: 420 mg (83%), mp 265 ^{0}C, recrystallised from MeOH ; IR (KBr): 1735(C=O). ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.4 (3H , s , CH_3), 7.3 – 7.4 (3H, m, Ar-H), 7.55 - 7.6 (3H, m, Ar- H), 7.8 - 8.0 (4H , m , Ar – H) ; LSIMS, m/z : 490 (M^++1), 470 (M^+-F), 420 (M^+– CF_3). Anal Calcd for $C_{24}H_{13}N_3O_2F_6$: C, 58.90; H, 2.68; N,8.59. Found: C, 58.85; H, 2.55; N, 8.65.

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