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Efficient route to 6-CF_3-substituted nicotinic acid derivatives

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Abstract

A novel synthetic sequence for preparation of CF_3-pyridines is presented. Reaction of α,β-unsaturated trifluoromethylketones with α-cyanoketones leads to α-hydroxydihydropyranes **1** containing CF_3-group. α-Hydroxydihydropyranes can be easily transformed to α-hydroxytetrahydropyridines, 1,4-dihydropyridines and CF_3-pyridines. All CF_3-pyridine derivatives were obtained in good yields. This route can be applied for preparation of CF_3-pyridines containing various substituents with further possible modification on cyano-group.

Keywords: α,β-Unsaturated trifluoromethylketones; α-Hydroxydihydropyranes; α-Hydroxytetrahydropyridines; 1,4-Dihydropyridines; CF_3-pyridines

1. Introduction

1.1. On importance of CF_3-pyridine derivatives

Substituted pyridines and their hydrogenated derivatives are very important compounds as candidates in drug research. For example, 1,4-dihydropyridines possess high biological activity as NO-donor and calcium channel agonist properties [1], anti-hypoxic, anti-ischemic, acaricidal, insecticidal, bactericidal and herbicidal activities [2,3].

Introduction of fluorine into organic compounds is well-known methodology to enhance their physiological activity [4,5]. In this aspect methods for synthesis of trifluoromethyl derivatives of pyridine can serve as very useful tool for modification of existing drugs and for obtaining novel drug candidates. One of the useful methods for synthesis of CF_3-derivatives of heterocyclic compounds is application of α,β-unsaturated trifluoromethylketones as building blocks [6].

Nicotinic acid (Vitamin B3) and its derivatives such as nicotinoamide (Vitamin PP, niacine) play very important role in biochemical processes in life processes. Also nicotinic acid is very important structural fragment of coenzymes (NAD and NADH). Nicotinic acid by itself is a hypolipidemic agent appears unique due to its potential to increase HDL cholesterol levels to a greater extent than other drugs [7] and lowers ADMA level [8]. So the approaches for preparation of various 6-CF_3-nicotinic acid derivatives, including hydrogenated compounds, using simple, available and inexpensive reagents – α,β-unsaturated trifluoromethylketones – may be very useful.

2. Results an discussion

2.1. Synthesis of starting CF_3-dihydropyranes **1**

In spite of the fact that there are a lot of well-known, widely used methods for synthesis of pyridine cycle, such as Hantzsch synthesis and related condensation of 1,5-dicarbonyl compounds with ammonia, methods for producing pyridines containing trifluoromethyl group are not widely described. Existing methods have some disadvantages such as formation of mixture of isomers [9,10], low yields [11], use of complex and hardly available reagents [12]. Synthesis of CF_3-tetrahydropyridones using reaction of α,β-unsaturated CF_3-ketones was described in work [13]. Also 4-arylsubstituted 1,4-dihydro 2,6-di-CF_3-pyridines were prepared in low yields by modified Hantzsch synthesis from corresponding arylaldehyde, trifluoroacetoacetic acid ethyl ester and ammonia [14] Rare examples of preparation of 6-trifluoromethylnicotinonitryles are known [15,16]. Now we present new general method for synthesis of substituted CF_3-nicotinic acid and their hydrogenated derivatives.

Recently we have found that α-hydroxydihydropyranes **1** containing cyano- and trifluoromethyl group can be readily obtained in the form of single diastereomer in good yields by

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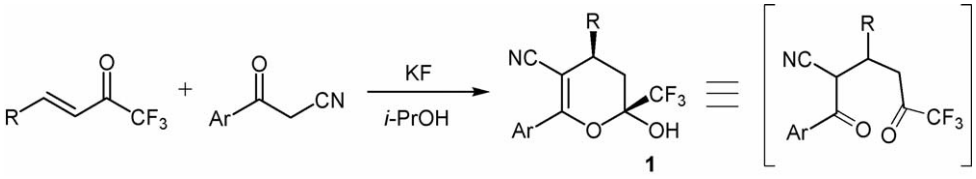
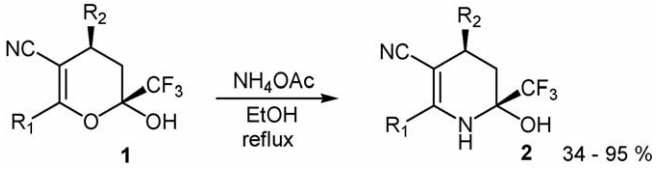


Scheme 1. Synthesis of α-hydroxydihydropyranes **1**.



Scheme 2. Reaction of α-hydroxydihydropyranes **1** with ammonium acetate.

reaction of α,β-unsaturated trifluoromethylketones with α-substituted cyanoketones in the presence of potassium fluoride as a base [17] (Scheme 1). More bulky trifluoromethyl and aryl groups in these compounds are arranged in more energy favorable equatorial position while hydroxy-group is arranged in axial position. α-Hydroxydihydropyranes **1** present the hidden cyclic form of 1,5-diketone. Therefore, we proposed that they can be used in Hantzsch pyridine synthesis as analogues of 1,5-dicarbonyl compounds.

2.2. Synthesis of CF_3-α-hydroxytetrahydropyridines 2

We found that reflux of α-hydroxydihydropyranes **1** with ammonium acetate in ethanolic solution leads to formation of the corresponding α-hydroxytetrahydropyridines **2** instead of 1,4-dihydropyridines, which are formed usually in Hantzsch synthesis. The products are formed mainly in up to quantitative yields (Scheme 2). Only in the case of compounds with R_1 = 4-$NO_2C_6H_4$ the reaction proceeds much slower and a lot of tar as the by-product was formed. As the result yields of tetrahydropyridines containing 4-$NO_2C_6H_4$ group were lower (Table 1).

According to spectral data reaction proceeds 100% stereoselectively. α-Hydroxytetrahydropyridines **2** are formed as a single diastereomer. The spectral NMR data for **2** are very similar with structural analogues **1** and some other six-membered having CF_3–C–OH fragment. The structure of compounds **2** was determined by comparison of spectral data with literature [13,17] and starting α-hydroxydihydropyranes **1**, the structure of those was determined using X-ray analysis [18]. Equatorial orientation of R_2 and trifluoromethyl groups and axial orientation of hydroxyl-group in compounds **2** witness of more stable diastereomer formation. Therefore, we believe that the reaction proceeds under thermodynamic control. α-Hydroxytetrahydropyridines **2** were obtained as stable crystalline compounds with relatively high melting points. It is very typical for cyclic CF_3-compounds containing semi-ketal (like in the starting hydroxydihydropyranes **1** [17]), semi-aminal [19,20] or even semi-amidal [21] fragment because of strong electron-withdrawing properties of CF_3-group.

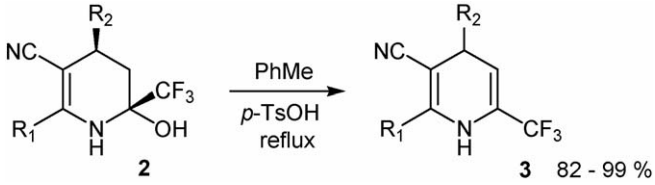
2.3. Dehydration reaction for α-hydroxytetrahydropyridines 2: synthesis of 1,4-dihydropyridines 3

The dehydration reaction for **2** also has been studied [21,13]. Contrary to starting hydroxydihydropyranes **1** α-hydroxyte-

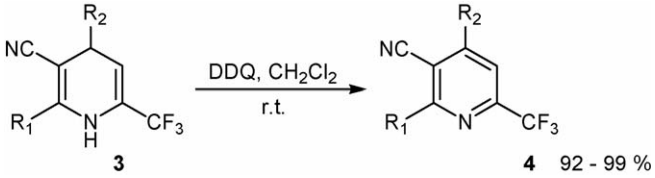
Table 1
Synthesis of CF_3-derivatives **2**, **3** and **4**

R_1	R_2	Tetrahydropyridine	Yield, %	Dihydropyridine	Yield, %	Pyridine	Yield, %
Ph	Ph	**2a**	90	**3a**	90	**4a**	93
	4-MeC_6H_4	**2b**	87	**3b**	87	**4b**	95
	3-MeC_6H_4	**2c**	87	**3c**	87	**4c**	87
	3-$MeOC_6H_4$	**2d**	84	**3d**	84	**4d**	99
	2-Th	**2e**	88	**3e**	88	**4e**	97
4-$MeOC_6H_4$	Ph	**2f**	95	**3f**	95	**4f**	96
	4-MeC_6H_4	**2g**	91	**3g**	91	**4g**	92
	3-MeC_6H_4	**2h**	92	**3h**	92	**4h**	99
	3-$MeOC_6H_4$	**2i**	88	**3i**	88	**4i**	99
	2-Th	**2j**	93	**5**	–	–	–
4-$NO_2C_6H_4$	Ph	**2k**	46	–[b]	–	–	–
	4-MeC_6H_4	**2l**	38	–[b]	–	–	–
	3-MeC_6H_4	**2m**	38	–[b]	–	–	–
	3-$MeOC_6H_4$	–[a]	–	–[b]	–	–	–
	2-Th	**2n**	34	–[b]	–	–	–

[a] No target product was isolated.
[b] The reaction has no been carried out.



Scheme 3. Dehydration of α-hydroxytetrahydropyridines **2**.



Scheme 5. Oxidation of 1,4-dihydropyridines **3** to pyridines **4**.

trahydropyridines **2** smoothly eliminate water to form corresponding 1,4-dihydropyridines **3**. The reaction was accomplished by refluxing toluene solution of **2** with catalytic amounts of *p*-toluenesulfonic acid (Scheme 3) during 5–6 h. 1,4-Dihydropyridines **3** were obtained as white or slightly yellow solids in nearly quantitative yields (Table 1).

A very unusual result was obtained for the transformation of the hydroxytetrahydropyridine **2j**. Instead of the formation of compound **3j** the reaction did not stop on the stage of dehydration. Elimination of thiophene from the corresponding dihydropyridine **3j** takes place (Scheme 4). This reaction presents a rare example of dihydropyridine transformation with C–C bond cleavage. Several similar examples are described in literature [22]. The driving force for these reactions is the formation of aromatic pyridine ring.

2.4. Oxidation of 1,4-dihydropyridines *3* to pyridines *4*

There are a lot of methods for aromatization of 1,4-dihydropyridines to pyridines [25,26], including 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [27] and sodium persulfate/cobalt(II) nitrate mixture [28]. The attempts to use the air oxygen for oxidizing 1,4-dihydropyridines **3** failed. Trial reaction for oxidizing compounds **3** with sodium persulfate/cobalt nitrate mixture showed comparatively lower yields (~60%) and proceeds with noticeable formation of by-product. The application of DDQ for oxidizing 1,4-dihydropyridines **3** showed excellent results. The oxidation reaction proceeded in methylene chloride for several minutes at room temperature and desired trifluoromethylpyridines **4** were obtained with nearly to quantitative yields (Scheme 5).

So the presented sequence of three reactions severs as an efficient and simple synthetic route to substituted 6-trifluoromethyl derivatives of nicotinic acid nitriles, which are very interesting for medicinal chemistry. The advantage of the presented method is the possibility to isolate intermediate di- and tetrahydropyridines **2** and **3**. Cyano-group in these compounds can be involved into further transformations.

3. Experimental

3.1. Materials and physical methods

NMR spectra were recorded on Varian VXR-400 and Bruker AM 400C spectrometers in $CDCl_3$ with TMS as an internal standard and Me_2SO-d_6. The IR spectra were obtained with UR-20 spectrometer. Chromatography was performed on silica gel (63–200 mesh, Merck). All solvents used were dried and distilled according to the standard procedures.

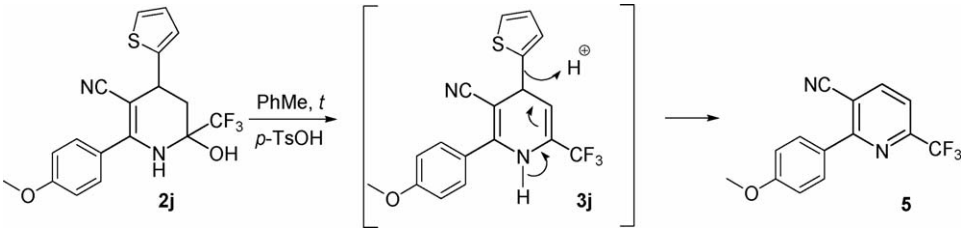
3.2. Experimental procedures

3.2.1. Typical procedure for preparation of α-hydroxytetrahydropyridines (*2*)

The solution of 3 mmol of α-hydroxydihydropyrane (**1**) and 30 mmol of ammonium acetate in 30 ml of ethanol was refluxed for several hours until complete of reaction (TLC monitoring, hexane–ethylacetate 3:1). The solvent was evaporated and the mixture was taken up in 30 ml of water. The product was extracted with methylene chloride (2 × 20 ml). Combined organic layers were passed through thin silica gel layer and evaporated to result the product as light solid.

*3.2.1.1. 6-Hydroxy-2,4-diphenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2a**).* Yield 930 mg (90%), white solid: m.p. 190–191 °C; IR (nujol): ν 1620 (C=C–N), 2215 (CN), 3365 (–NH); ^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.83 (b.d.d, 1H, $–CH_2–$, J = 12.7 Hz, J = 12.5 Hz); 2.13 (d.d, 1H, $–CH_2–$, J = 12.7 Hz, J = 5.1 Hz); 3.86 (d.d, 1H, –CH–, J = 12.5 Hz, J = 5.1 Hz); 7.21 (b.s, 1H, NH); 7.24–7.33 (m, 1H, Ph); 7.33–7.42 (m, 4H, Ph); 7.43–7.50 (m, 3H, Ph); 7.51–7.58 (m, 2H, Ph); 8.05 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 35.5 (CH); 36.3 (CH_2); 78.8 (q, C–OH, J = 31.5 Hz); 80.6 (C–CN); 120.5 (CN); 124.0 (q, CF_3, J = 286.0 Hz); 127.2, 128.0, 128.1, 128.7, 128.8, 128.9, 134.7, 141.8 (Ph, Ph); 155.0 (C=C–N).



Scheme 4. Formation of compound **5**.

Anal. calcd. for $C_{19}H_{15}F_3N_2O$: C, 66.27; H, 4.39. Found: C, 66.51; H, 4.57.

*3.2.1.2. 6-Hydroxy-4-(4-methylphenyl)-2-phenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2b**).* Yield 940 mg (88%), white solid: m.p. 118–119 °C; IR (nujol): ν 1615 (C=C–N), 2220 (CN), 3375 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.85 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.9 Hz); 2.14 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 5.1 Hz); 2.31 (s, CH_3); 3.86 (d.d, 1H, –CH–, J = 12.9 Hz, J = 5.1 Hz); 7.15–7.31 (m, 4H, 4-MeC_6H_4, Ph, NH); 7.44–7.60 (m, 6H, 4-MeC_6H_4, Ph); 8.02 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 20.6 (CH_3); 35.5 (CH); 35.8 (CH_2); 78.8 (q, C–OH, J = 30.7 Hz); 80.9 (C–CN); 120.4 (CN); 124.1 (q, CF_3, J = 286.0 Hz); 127.9, 128.0, 128.7, 129.2, 129.8, 134.8, 136.2, 138.7 (4-MeC_6H_4, Ph); 154.7 (C=C–N).

Anal. calcd. for $C_{20}H_{17}F_3N_2O$: C, 67.03; H, 4.78. Found: C, 66.90; H, 4.90.

*3.2.1.3. 6-Hydroxy-4-(3-methylphenyl)-2-phenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2c**).* Yield 930 mg (87%), white solid: m.p. 188–189 °C; IR (nujol): ν 1615 (C=C–N), 2215 (CN), 3320 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.85 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.5 Hz); 2.14 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 4.5 Hz); 2.33 (s, CH_3); 3.86 (d.d, 1H, –CH–, J = 12.5 Hz, J = 4.5 Hz); 7.05–7.30 (m, 4H, 3-MeC_6H_4, Ph, NH); 7.40–7.62 (m, 6H, 3-MeC_6H_4, Ph); 8.02 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 21.0 (CH_3); 35.5 (CH); 36.2 (CH_2); 78.8 (q, C–OH, J = 30.7 Hz); 80.7 (C–CN); 120.4 (CN); 124.0 (q, CF_3, J = 286.0 Hz); 127.8, 128.0, 128.4, 128.5, 128.7, 129.8, 134.7, 137.7, 141.7 (3-MeC_6H_4, Ph); 154.8 (C=C–N).

Anal. calcd. for $C_{20}H_{17}F_3N_2O$: C, 67.03; H 4.78. Found: C, 67.27, H, 4.79.

*3.2.1.4. 6-Hydroxy-4-(3-methoxyphenyl)-2-phenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2d**).* Yield 940 mg (84%), white solid: m.p. 186–187 °C; IR (nujol): ν 1615 (C=C–N), 2215 (CN), 3300 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.86 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.5 Hz); 2.16 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 4.5 Hz); 3.77 (s, OCH_3); 3.86 (d.d, 1H, –CH–, J = 12.5 Hz, J = 4.5 Hz); 7.05–7.30 (m, 3H, 3-MeOC_6H_4); 7.20 (b.s, NH); 7.29 (t, 1H, 3-MeOC_6H_4, J = 7.6 Hz); 7.40–7.62 (m, 5H, Ph); 8.02 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 35.3 (CH); 36.3 (CH_2); 55.0 (OCH_3); 78.8 (q, C–OH, J = 30.7 Hz); 80.5 (C–CN); 112.5, 113.9, 128.3, 128.5, 128.8, 129.7, 129.9, 134.7, 143.4, 159.4 (3-MeOC_6H_4, Ph); 120.2 (CN); 124.0 (q, CF_3, J = 286.0 Hz); 154.9 (C=C–N).

Anal. calcd. for $C_{20}H_{17}F_3N_2O_2$: C, 64.17; H, 4.58. Found: C, 64.28; H, 4.80.

*3.2.1.5. 6-Hydroxy-2-phenyl-4-(2-thienyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2e**).* Yield 940 mg (87%), white solid, m.p. 138–139 °C; IR (nujol): ν 1620 (C=C–N); 2220 (CN); 3320 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.93 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.5 Hz); 2.29 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 5.0 Hz); 4.24 (d.d, 1H, –CH–, J = 12.5 Hz, J = 5.0 Hz); 6.93–7.08 (m, 2H, C_4H_3S); 7.09–7.18 (m, 1H, C_4H_3S); 7.28 (b.s, NH); 7.40–7.57 (m, 5H, Ph); 8.15 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 31.5 (CH); 36.0 (CH_2); 78.8 (q, C–OH, J = 31.5 Hz); 80.1 (C–CN); 120.0 (CN); 123.8 (q, CF_3, J = 286.0 Hz); 124.8, 126.0, 126.9, 128.1, 128.7, 130.0, 134.4, 144.5 (C_4H_3S, Ph); 154.4 (C=C–N).

Anal. calcd. for $C_{17}H_{13}F_3N_2OS$: C, 58.28; H, 3.74. Found: C, 58.02; H, 3.66.

*3.2.1.6. 6-Hydroxy-2-(4-methoxyphenyl)-4-phenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2f**).* Yield 1060 mg (94%), light-yellow solid: m.p. 168–169 °C; IR (nujol): ν 1620 (C=C–N), 2220 (CN), 3330 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.84 (b.d.d, 1H, –CH_2–, J = 12.9 Hz, J = 12.7 Hz); 2.15 (d.d, 1H, –CH_2–, J = 12.9 Hz, J = 5.0 Hz); 3.8 (s, OCH_3); 3.87 (d.d, 1H, –CH–, J = 12.7 Hz, J = 5.0 Hz); 7.02 (d, 2H, 4-MeOC_6H_4, J = 8.6 Hz); 7.14 (b.s, 1H, NH); 7.24–7.43 (m, 5H, Ph); 7.51 (d, 2H, 4-MeOC_6H_4, J = 8.6 Hz); 7.86 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 35.5 (CH); 36.3 (CH_2); 55.3 (OCH_3); 78.8 (q, C-OH, J = 30.7 Hz); 80.1 (C-CN); 113.4, 126.9, 127.1, 128.0, 128.6, 130.2, 141.9, 160.5 (4-MeOC_6H_4, Ph); 120.7 (CN); 123.9 (q, CF_3, J = 286.0 Hz); 154.5 (C=C–N).

Anal. calcd. for $C_{20}H_{17}F_3N_2O_2$: C, 64.17; H, 4.58. Found: C, 64.38; H, 4.37.

*3.2.1.7. 6-Hydroxy-2-(4-methoxyphenyl)-4-(4-methylphenyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2g**).* Yield 1060 mg (91%), white solid: m.p. 140–141 °C; IR (nujol): ν 1615 (C=C–N), 2215 (CN), 3330 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.83 (b.d.d, 1H, –CH_2–, J = 12.9 Hz, J = 12.7 Hz); 2.12 (d.d, 1H, –CH_2–, J = 12.9 Hz, J = 4.8 Hz); 2.30 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 3.81 (d.d, 1H, –CH–, J = 12.7 Hz, J = 5.0 Hz); 7.02 (d, 2H, 4-MeOC_6H_4, J = 8.6 Hz); 7.13 (b.s, 1H, NH); 7.17 (d, 2H, 4-MeC_6H_4, J = 7.8 Hz); 7.26 (d, 2H, 4-MeC_6H_4, J = 7.8 Hz); 7.51 (d, 2H, 4-MeOC_6H_4, J = 8.6 Hz); 7.82 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 20.2 (s, CH_3), 35.6 (CH); 35.9 (CH_2); 55.3 (OCH_3); 78.8 (q, C–OH, J = 30.7 Hz); 80.1 (C–CN); 113.4, 126.9, 127.9, 129.2, 130.2, 136.1, 138.8, 160.5 (4-MeOC_6H_4, 4-MeC_6H_4); 120.7 (CN); 123.8 (q, CF_3, J = 286.0 Hz); 154.4 (C=C–N).

Anal. calcd. for $C_{21}H_{19}F_3N_2O_2$: C, 64.94; H, 4.93. Found: C, 64.84; H, 5.17.

*3.2.1.8. 6-Hydroxy-2-(4-methoxyphenyl)-4-(3-methylphenyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2h**).* Yield 1070 mg (92%), light-yellow solid: m.p. 102–103 °C; IR (nujol): ν 1615 (C=C–N), 2220 (CN), 3280 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.82 (b.d.d, 1H, –CH_2–, J = 12.9 Hz, J = 12.7 Hz); 2.12 (d.d, 1H, –CH_2–, J = 12.9 Hz, J = 5.0 Hz); 2.32 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 3.81 (d.d, 1H, –CH–, J = 12.7 Hz, J = 5.0 Hz); 7.02 (d, 2H, 4-MeOC_6H_4, J = 8.6 Hz); 7.17 (d, 1H, 3-MeC_6H_4, J = 7.4 Hz); 7.14 (b.s, 1H,

NH); 7.14–7.21 (m, 2H, 3-MeC_6H_4); 7.25 (t, 1H, 3-MeC_6H_4, J = 7.4 Hz); 7.51 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz); 7.86 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 21.1 (s, CH_3), 35.6 (CH); 36.3 (CH_2); 55.3 (OCH_3); 78.8 (q, C–OH, J = 30.7 Hz); 80.1 (C–CN); 113.4, 125.9, 126.9, 127.8, 128.5, 129.6, 130.3, 137.7, 141.8, 160.5 (4-$MeOC_6H_4$, 3-MeC_6H_4); 120.7 (CN); 123.8 (q, CF_3, J = 286.0 Hz); 154.5 (C=C–N).

Anal. calcd. for $C_{21}H_{19}F_3N_2O_2$: C, 64.94; H, 4.93. Found: C, 64.83; H, 4.84.

*3.2.1.9. 6-Hydroxy-2-(4-methoxyphenyl)-4-(3-methoxyphenyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2i**).* Yield 1070 mg (88%), light-yellow solid: m.p. 102–103 °C; IR (nujol): ν 1620 (C=C–N); 2210 (CN); 3310 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.84 (b.d.d, 1H, –CH_2–, J = 12.9 Hz, J = 12.7 Hz); 2.14 (d.d, 1H, –CH_2–, J = 12.9 Hz, J = 5.0 Hz); 3.77 (s, 3H, 3-$MeOC_6H_4$); 3.80 (s, 3H, 4-$MeOC_6H_4$); 3.84 (d.d, 1H, –CH–, J = 12.7 Hz, J = 5.0 Hz); 6.82 (d.d, 1H, 3-$MeOC_6H_4$, J = 7.8 Hz, J = 1.8 Hz); 6.90–6.98 (m, 2H, 3-$MeOC_6H_4$); 7.02 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz); 7.14 (b.s, 1H, NH); 7.29 (t, 1H, 3-$MeOC_6H_4$, J = 7.8 Hz); 7.51 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz); 7.88 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 35.4 (CH); 36.4 (CH_2); 55.0 (s, 3-$MeOC_6H_4$), 55.3 (s, 4-$MeOC_6H_4$); 78.8 (q, C–OH, J = 30.7 Hz); 80.0 (C–CN); 112.5, 113.4, 113.8, 120.2, 126.9, 129.7, 130.3, 143.5, 159.4, 160.5 (4-$MeOC_6H_4$, 3-MeC_6H_4); 120.8 (CN); 123.9 (q, CF_3, J = 286.0 Hz); 154.5 (C=C–N).

Anal. calcd. for $C_{21}H_{19}F_3N_2O_3$: C, 62.37; H, 4.74. Found: C, 62.40; H, 4.80.

*3.2.1.10. 6-Hydroxy-2-(4-methoxyphenyl)-4-(2-thienyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2j**).* Yield 1060 mg (93%), light-yellow solid: m.p. 141–142 °C; IR (nujol): ν 1615 (C=C–N), 2220 (CN), 3350 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.91 (b.d.d, 1H, –CH_2–, J = 12.9 Hz, J = 12.7 Hz); 2.27 (d.d, 1H, –CH_2–, J = 12.9 Hz, J = 4.9 Hz); 3.80 (s, 3H, 4-$MeOC_6H_4$); 4.22 (d.d, 1H, –CH–, J = 12.7 Hz, J = 4.9 Hz); 6.95–7.01 (m, 1H, C_4H_3S); 7.02 (d, 2H, 4-$MeOC_6H_4$, J = 8.4 Hz); 7.13 (d, 1H, C_4H_3S, J = 2.7 Hz); 7.22 (b.s, 1H, NH); 7.44 (d, 1H, C_4H_3S, J = 4.9 Hz); 7.47 (d, 2H, 4-$MeOC_6H_4$, J = 8.4 Hz); 7.98 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 31.6 (CH); 36.1 (CH_2); 55.3 (4-$MeOC_6H_4$), 78.8 (q, C–OH, J = 30.7 Hz); 80.5 (C–CN); 113.5, 126.0, 126.6, 126.9, 130.3, 144.8, 159.4, 160.6 (4-$MeOC_6H_4$, C_4H_3S); 120.3 (CN); 123.9 (q, CF_3, J = 286.0 Hz); 154.1 (C=C–N).

Anal. calcd. for $C_{18}H_{15}F_3N_2O_2S$: C, 56.84; H, 3.97. Found: C, 56.80; H, 4.26.

*3.2.1.11. 6-Hydroxy-2-(4-nitrophenyl)-4-phenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2k**).* Yield 540 mg (46%), yellow solid: m.p. 187–188 °C; IR (nujol): ν 1350, 1530 (NO_2), 1620 (C=C–N), 2220 (CN), 3350 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.89 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.5 Hz); 2.18 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 4.8 Hz); 3.91 (d.d, 1H, –CH–, J = 12.5 Hz, J = 4.8 Hz); 7.15–7.50 (m, 6H, Ph, NH); 7.84 (d, 2H, 4-$NO_2C_6H_4$, J = 8.6 Hz); 8.29 (b.s, 1H, OH); 8.33 (d, 2H, 4-$NO_2C_6H_4$, J = 8.6 Hz).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 35.1 (CH); 36.2 (CH_2); 78.8 (q, C–OH, J = 31.5 Hz); 82.1 (C–CN); 119.8 (CN); 124.0 (q, CF_3, J = 286.9 Hz); 123.2, 127.2, 128.1, 128.6, 130.5, 140.9, 141.3, 148.2 (4-$NO_2C_6H_4$, Ph); 153.0 (C=C–N).

Anal. calcd. for $C_{19}H_{14}F_3N_3O_3$: C, 58.61; H, 3.62. Found: C, 58.73; H, 3.64.

*3.2.1.12. 6-Hydroxy-4-(4-methylphenyl)-2-(4-nitrophenyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2l**).* Yield 460 mg (38%), yellow solid: m.p. 114–115 °C; IR (nujol): ν 1360, 1530 (NO_2), 1590 (C=C–N), 2215 (CN), 3360 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.87 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.5 Hz); 2.18 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 4.8 Hz); 2.30 (s, 3H, CH_3); 3.86 (d.d, 1H, –CH–, J = 12.5 Hz, J = 4.8 Hz); 7.18 (d, 2H, 4-MeC_6H_5); 7.22–7.35 (m, 3H, 4-MeC_6H_5, NH); 7.82 (d, 2H, 4-$NO_2C_6H_4$, J = 8.6 Hz); 8.25 (b.s, 1H, OH); 8.32 (d, 2H, 4-$NO_2C_6H_4$, J = 8.6 Hz).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 20.6 (CH_3); 35.1 (CH); 35.8 (CH_2); 78.8 (q, C–OH, J = 31.5 Hz); 82.3 (C–CN); 119.8 (CN); 124.0 (q, CF_3, J = 286.0 Hz); 123.2, 127.9, 129.2, 130.5, 136.3, 138.2, 140.9, 148.2 (4-$NO_2C_6H_4$, 4-MeC_6H_4); 152.8 (C=C–N).

Anal. calcd. for $C_{20}H_{16}F_3N_3O_3$: C, 59.55; H, 4.00. Found: C, 59.30; H, 4.04.

*3.2.1.13. 6-Hydroxy-4-(3-methylphenyl)-2-(4-nitrophenyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2m**).* Yield 460 mg (38%), yellow solid: m.p. 158–159 °C; IR (nujol): ν 1360, 1530 (NO_2),1590 (C=C–N), 2215 (CN), 3360 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.88 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.5 Hz); 2.15 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 4.8 Hz); 2.32 (s, 3H, CH_3); 3.86 (d.d, 1H, –CH–, J = 12.5 Hz, J = 4.8 Hz); 7.05–7.31 (m, 5H, 3-MeC_6H_4, NH); 7.83 (d, 2H, 4-$NO_2C_6H_4$, J = 8.6 Hz); 8.25 (b.s, 1H, OH); 8.33 (d, 2H, 4-$NO_2C_6H_4$, J = 8.6 Hz).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 21.0 (CH_3); 35.2 (CH); 36.1 (CH_2); 78.8 (q, C–OH, J = 30.7 Hz); 82.2 (C–CN); 119.8 (CN); 124.0 (q, CF_3, J = 286.0 Hz); 123.2, 125.2, 127.9, 128.5, 128.6, 130.5, 137.8, 140.9, 141.2, 148.2 (4-$NO_2C_6H_4$, 3-MeC_6H_4); 152.9 (C=C–N).

Anal. calcd. for $C_{20}H_{16}F_3N_3O_3$: C, 59.55; H, 4.00. Found: C, 60.13; H, 4.20.

*3.2.1.14. 6-Hydroxy-2-(4-nitrophenyl)-4-(2-thienyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**2n**).* Yield 480 mg (40%), yellow solid: m.p. 201–202 °C; IR (nujol): ν 1360, 1530 (NO_2), 1620 (C=C–N), 2220 (CN), 3380 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 1.97 (b.d.d, 1H, –CH_2–, J = 12.7 Hz, J = 12.4 Hz); 2.31 (d.d, 1H, –CH_2–, J = 12.7 Hz, J = 4.5 Hz); 2.32 (s, 3H, CH_3); 3.86 (d.d, 1H, –CH–, J = 12.4 Hz, J = 4.5 Hz); 6.96–7.06 (m, 1H, C_4H_3S); 7.15 (d,

1H, C_4H_3S, J = 9.6 Hz); 7.36 (b.s, 1H, NH); 7.45 (d, 1H, C_4H_3S, J = 4.3 Hz); 7.79 (d, 2H, 4-$NO_2C_6H_4$, J = 8.3 Hz); 8.32 (d, 2H, 4-$NO_2C_6H_4$, J = 8.3 Hz); 8.37 (b.s, 1H, OH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 31.5 (CH); 35.6 (CH_2); 78.8 (q, C–OH, J = 31.5 Hz); 82.5 (C–CN); 119.3 (CN); 123.9 (q, CF_3, J = 286.0 Hz); 123.3, 124.9, 126.2, 127.0, 130.5, 140.6, 143.9, 148.3 (4-$NO_2C_6H_4$, C_4H_3S); 152.5 (C=C–N).

Anal. calcd. for $C_{17}H_{12}F_3N_3O_3S$: C, 51.64; H, 3.06. Found: C, 51.72; H, 3.24.

3.2.2. Typical procedure for preparation of 1,4-dihydropyridines (**3**)

The solution of 2 mmol of α-hydroxytetrahydropyridine (**2**) and catalytic amount of p-TsOH in 20 ml of toluene was refluxed for several hours until complete of reaction (TLC monitoring, hexane–ethylacetate 3:1). The mixture was diluted with methylene chloride (1:1) and the solution was passed through thin silica gel layer and evaporated to result the product as light solid.

*3.2.2.1. 2,4-Diphenyl-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3a**).* Yield 523 mg (76%), white solid: m.p. 143–144 °C; IR (nujol): ν 2200 (CN), 3220 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 4.58 (d, 1H, –CH–, J = 3.2 Hz); 5.51 (d, 1H, –C=CH–, J = 4.4 Hz); 7.28–7.39 (m, 3H, Ph); 7.39–7.46 (m, 2H, Ph); 7.47–7.57 (m, 5H, Ph); 9.68 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 40.3 (CH); 80.3 (C–CN); 106.0 (q, C=C–CF_3, J = 4.3 Hz); 120.3 (CN); 120.5 (q, CF_3, J = 272.3 Hz); 126.1 (q, C=C–CF_3, J = 33.7 Hz); 127.5, 127.6, 128.5, 128.6, 129.0, 130.5, 133.0, 144.7 (Ph, Ph); 150.6 (C=C–N).

Anal. calcd. for $C_{19}H_{13}F_3N_2$: C, 69.93; H, 4.02. Found: C, 69.70; H, 3.84.

*3.2.2.2. 4-(4-Methylphenyl)-2-phenyl-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3b**).* Yield 670 mg (99%), white solid: m.p. 120–121 °C; IR (nujol): ν 2200 (CN), 3260 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 2.31 (s, 3H, –Me); 4.52 (d, 1H, –CH–, J = 3.5 Hz); 5.47 (d, 1H, –C=CH–, J = 4.5 Hz); 7.19–7.29 (m, 4H, Ph, 4-MeC_6H_4); 7.46–7.57 (m, 5H, Ph, 4-MeC_6H_4); 9.64 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 20.6 (CH_3); 39.9 (CH); 80.6 (C–CN); 106.1 (q, C=C–CF_3, J = 4.4 Hz); 120.3 (CN); 120.5 (q, CF_3, J = 272.3 Hz); 126.1 (q, C=C–CF_3, J = 34.4 Hz); 127.4, 128.4, 128.5, 129.5, 130.4, 133.0, 136.7, 141.9 (Ph, 4-MeC_6H_4); 150.3 (C=C–N).

Anal. calcd. for $C_{20}H_{15}F_3N_2$: C, 70.58; H, 4.44. Found: C, 70.24; H, 4.20.

*3.2.2.3. 4-(3-Methylphenyl)-2-phenyl-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3c**).* Yield 670 mg (99%), white solid: m.p. 92–93 °C; IR (nujol): ν 2200 (CN); 3230 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 2.33 (s, 3H, –Me); 4.53 (d, 1H, –CH–, J = 4.7 Hz); 5.48 (d. 1H, –C=CH–, J = 4.9 Hz); 7.11–7.18 (m, 3H, 3-MeC_6H_4); 7.32 (t, 1H, 3-MeC_6H_4, J = 7.6 Hz); 7.46–7.57 (m, 5H, Ph); 9.66 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 21.1 (CH_3); 40.1 (CH); 80.4 (C–CN); 106.1 (q, C=C–CF_3, J = 3.7 Hz); 120.3 (CN); 120.5 (q, CF_3, J = 272.3 Hz); 126.0 (q, C=C–CF_3, J = 36.6 Hz); 124.8, 126.2, 128.5, 128.6, 128.9, 129.4, 130.4, 133.0, 138.1 (Ph, 3-MeC_6H_4); 150.3 (C=C–N).

Anal. calcd. for $C_{20}H_{15}F_3N_2$: C 70.58, H 4.44. Found, %C, 70.36; H, 4.32.

*3.2.2.4. 4-(3-Methoxyphenyl)-2-phenyl-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3d**).* Yield 700 mg (98%), white solid: m.p. 82–83 °C; IR (nujol): ν 2200 (CN), 3250 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 3.77 (s, 3H, –OMe); 4.55 (d, 1H, –CH–, J = 3.7 Hz); 5.51 (d, 1H, –C=CH–, J = 4.7 Hz); 6.86–6.92 (m, 1H, 3-$MeOC_6H_4$); 6.95 (d, 1H, 3-$MeOC_6H_4$, J = 7.2 Hz); 7.33–7.39 (m, 1H, 3-$MeOC_6H_4$); 7.46–7.56 (m, 5H, Ph); 9.66 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 55.0 (OCH_3); 40.2 (CH); 80.4 (C-CN); 106.1 (q, C=C-CF_3, J = 4.4 Hz); 120.3 (CN); 120.5 (q, CF_3, J = 272.3 Hz); 126.0 (q, C=C–CF_3, J = 36.6 Hz); 124.8, 126.2, 128.4, 128.5, 128.9, 129.3, 130.4, 133.0, 146.3, 159.7 (Ph, 3-$MeOC_6H_4$); 150.3 (C=C–N).

Anal. calcd. for $C_{20}H_{15}F_3N_2O$: C, 67.41; H, 4.24; Found: C, 67.02; H, 4.13.

*3.2.2.5. 2-Phenyl-4-(2-thienyl)-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3e**).* Yield 630 mg (95%), white solid: m.p. 105–106 °C; IR (nujol): ν 2190 (CN), 3270 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 4.90 (d, 1H, –CH–, J = 4.5 Hz); 5.61 (d, 1H, –C=CH–, J = 4.5 Hz); 6.99–7.08 (m, 2H, Ph); 7.44–7.69 (m, 6H, Ph, 2-Th); 9.86 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 35.3 (CH); 80.6 (C–CN); 105.5 (q, C=C–CF_3, J = 4.4 Hz); 120.1 (CN); 120.5 (q, CF_3, J = 275.5 Hz); 124.2, 126.1, 127.3, 128.5, 128.6, 129.3, 130.5, 132.7 (Ph, 2-Th); 126.2 (q, C=C–CF_3, J = 34.4 Hz); 150.1 (C=C–N).

Anal. calcd. for $C_{17}H_{11}F_3N_2S$: C, 61.44; H, 3.34. Found: C, 61.09; H, 3.16.

*3.2.2.6. 2-(4-Methoxyphenyl)-4-phenyl-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3f**).* Yield 585 mg (85%), white solid: m.p. 106–107 °C; IR (nujol): ν 2220 (CN), 3260 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 3.8 (s, 3H, OMe); 4.54 (d, 1H, –CH–, J = 4.5 Hz); 5.61 (d, 1H, –C=CH–, J = 4.5 Hz); 7.04 (d, 2H, 4-$MeOC_6H_4$, J = 8.8 Hz); 7.15 (d, 2H, Ph, J = 8.8); 7.27–7.37 (m, 3H, Ph); 7.48 (d, 2H, 4-$MeOC_6H_4$, J = 8.8 Hz); 9.58 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO–d_6): δ 40.3 (CH); 55.3 (–OMe); 79.5 (C–CN); 106.0 (q, C=C–CF_3, J = 4.4 Hz); 120.7 (CN); 114.0 (4-$MeOC_6H_4$); 120.8 (q, CF_3, J = 275.2 Hz); 125.0 (4-$MeOC_6H_4$); 125.8 (q, C=C–CF_3, J = 34.4 Hz); 127.5, 128.9, 129.1, 135.3 (Ph); 144.8 (4-$MeOC_6H_4$); 150.2 (C=C–N); 160.9 (4-$MeOC_6H_4$).

Anal. calcd. for $C_{20}H_{15}F_3N_2O$: C, 67.41; H, 4.24. Found: C, 67.12; H, 4.17.

*3.2.2.7. 2-(4-Methoxyphenyl)-4-(4-methylphenyl)-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3g**).* Yield 670 mg (91%), white solid: m.p. 128–129 °C; IR (nujol): ν 2190 (CN), 3270 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 2.30 (s, 3H, –Me); 3.80 (s, 3H, –OMe); 4.49 (d, 1H, –CH–, J = 4.5 Hz); 5.46 (d. 1H, –C=CH–, J = 4.5 Hz); 7.05 (d, 2H, 4-$MeOC_6H_4$, J = 8.5 Hz); 7.23 (b.s., 4H, 4-MeC_6H_4); 7.48 (d, 2H, 4-$MeOC_6H_4$, J = 8.5 Hz); 9.56 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 20.6 (–Me); 40.0 (CH); 55.3 (–OMe); 79.8 (C–CN); 106.1 (q, C=C–CF_3, J = 4.4 Hz); 120.7 (CN); 113.8 (4-$MeOC_6H_4$); 120.5 (q, CF_3, J = 272.3 Hz); 125.0 (4-$MeOC_6H_4$); 126.0 (q, C=C–CF_3, J = 34.4 Hz); 127.7 (4-MeC_6H_4); 129.5 (4-MeC_6H_4); 136.6 (4-MeC_6H_4); 137.7 (4-MeC_6H_4); 144.8 (4-$MeOC_6H_4$); 150.0 (C=C–N); 160.9 (4-$MeOC_6H_4$).

Anal. calcd. for $C_{21}H_{17}F_3N_2O$: C, 68.10; H, 4.63. Found: C, 67.97; H, 4.46.

*3.2.2.8. 2-(4-Methoxyphenyl)-4-(3-methylphenyl)-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3h**).* Yield 670 mg (91%), white solid: m.p. 153–154 °C; IR (nujol): ν 2200 (CN), 3250 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 2.33 (s, 3H, –Me); 3.81 (s, 3H, –OMe); 4.50 (d, 1H, –CH–, J = 4.5 Hz); 5.48 (d. 1H, –C=CH–, J = 4.5 Hz); 7.05 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz); 7.10–7.20 (m, 3H, 3-MeC_6H_4); 7.32 (t, 1H, 3-MeC_6H_4, J = 7.7 Hz); 7.49 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz); 9.57 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 21.1 (–Me); 40.3 (CH); 55.4 (–OMe); 79.6 (C–CN); 106.1 (q, C=C–CF_3, J = 4.4 Hz); 113.8 (4-$MeOC_6H_4$); 120.4 (q, CF_3, J = 272.3 Hz); 120.7 (CN); 124.8, 128.0, 128.1, 128.9, 130.2, 138.1 (3-MeC_6H_4); 125.0 (4-$MeOC_6H_4$); 125.9 (q, C=C–CF_3, J = 34.4 Hz); 144.8 (4-$MeOC_6H_4$); 150.2 (C=C–N); 160.9 (4-$MeOC_6H_4$).

Anal. calcd. for $C_{21}H_{17}F_3N_2O$: C, 68.10; H, 4.63. Found: C, 67.93; H, 4.41.

*3.2.2.9. 4-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (**3i**).* Yield 670 mg (91%), white solid: m.p. 105–106 °C; IR (nujol): ν 2200 (CN), 3250 (–NH);

^{1}H NMR (400 MHz, Me_2SO-d_6): δ 3.76 (s, 3H, –OMe); 3.81 (s, 3H, –OMe); 4.51 (d, 1H, –CH–, J = 4.5 Hz); 5.51 (d. 1H, –C=CH–, J = 4.5 Hz); 6.85–6.91 (m, 2H, 3-$MeOC_6H_4$); 6.93 (d, 1H, 3-$MeOC_6H_4$, J = 7.7 Hz); 7.05 (d, 2H, 4-MeOPh, J = 8.8 Hz); 7.35 (d, 1H, 3-$MeOC_6H_4$, J = 7.7 Hz); 7.48 (d, 2H, 4-MeOPh, J = 8.8 Hz); 9.58 (b.s., 1H, NH).

^{13}C NMR (100 MHz, Me_2SO-d_6): δ 40.3 (CH); 55.0 (–OMe); 55.4 (–OMe); 79.4 (C–CN); 106.1 (q, C=C–CF_3, J = 4.4 Hz); 112.5, 113.4, 125.0, 146.4, 150.3, 159.7 (3-$MeOC_6H_4$); 113.8 (4-$MeOC_6H_4$); 120.4 (q, CF_3, J = 272.3 Hz); 120.7 (CN); 125.0 (4-$MeOC_6H_4$); 125.9 (q, C=C–CF_3, J = 34.4 Hz); 146.4 (4-$MeOC_6H_4$); 150.2 (C=C–N); 160.9 (4-$MeOC_6H_4$).

Anal. calcd. for $C_{21}H_{17}F_3N_2O_2$: C, 65.28; H, 4.43. Found: C, 64.97; H, 4.28.

*3.2.2.10. 2-(4-Methoxyphenyl)-6-(trifluoromethyl)nicotinonitrile (**5**).* Yield 510 mg (92%), white solid: m.p. 91–92 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H, OCH_3); 7.04 (d, 2H, 4-$MeOC_6H_4$, J = 8.8 Hz); 7.65 (d, 1H, H–C=C–CF_3, J = 8.1 Hz); 8.02 (d, 2H, 4-$MeOC_6H_4$, J = 8.8 Hz); 8.20 (d, 1H, H–C=C–CN, J = 8.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4 (OCH_3); 109.0 (C–CN); 114.3, 128.1, 130.7, 160.5 (4-$MeOC_6H_4$); 117.0 (CN); 117.2 (d, H–C=C–CF_3, 2.2 Hz); 120.9 (q, CF_3, J = 275.2 Hz); 143.9 (H–C=C–CN); 150.5 (q, C=C–CF_3, J = 35.9 Hz); 162.0 (4-$MeOC_6H_4$–C–N).

Anal. calcd. for $C_{14}H_9F_3N_2O_2$: C, 60.44; H, 3.26. Found: C, 60.17; H, 3.12.

*3.2.3. Typical procedure for preparation of CF_3-pyridines (**4**)*

To a solution of 0.5 mmol of 1,4-dihydropyridine (**3**) in 3 ml of anhydrous methylene chloride 0.5 mmol of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added. The mixture immediately warmed up and 2,3-dichloro-5,6-dicyanohydroquinone precipitated. Solvent was evaporated and the residue was taken up in hexanes–ethylacetate mixture (15:1) and passed through thin silica gel layer. The solvent was evaporated to result the product as light solid.

*3.2.3.1. 2,4-Diphenyl-6-(trifluoromethyl)nicotinonitrile (**4a**).* Yield 150 mg (93%), white solid: m.p. 140–141 °C; IR (nujol): ν 2245 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.61 (m, 6H, Ph); 7.63–7.69 (m, 2H, C–H, Ph); 7.96–8.03 (m, 2H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): 108.8 (C–CN) 116.3 (CN); 118.9 (q, H–C=C–CF_3, J = 2.9 Hz); 120.8 (q, CF_3, J = 275.2 Hz); 128.6, 128.7, 129.2, 129.4, 130.7, 130.8, 135.3, 136.3 (2 Ph); 150.0 (q, C=C–CF_3, J = 35.9 Hz); 157.0 (Ph–C); 163.0 (Ph–C–N).

Anal. calcd. for $C_{19}H_{11}F_3N_2$: C, 70.37; H, 3.42. Found: C, 70.28; H, 3.21.

*3.2.3.2. 4-(3-Methylphenyl)-2-phenyl-6-(trifluoromethyl)nicotinonitrile (**4b**).* Yield 160 mg (95%), white solid: m.p. 123–124 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.42 (m, 1H, 3-MeC_6H_4); 7.43–7.51 (m, 3H, 3-MeC_6H_4); 7.53–7.60 (m, 3H, Ph); 7.75 (s, 1H, C–H); 7.94–8.04 (m, 2H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): 21.4 (CH_3); 108.8 (C–CN); 116.3 (CN); 118.8 (q, H–C=C–CF_3, J = 2.9 Hz); 120.8 (q, CF_3, J = 275.2 Hz); 125.8, 128.7, 129.1, 129.2, 129.4, 130.8, 131.4, 135.3, 136.4 (3-MeC_6H_4, Ph); 149.9 (q, C=C–CF_3, J = 35.1 Hz); 157.2 (3-MeC_6H_4–C); 163.0 (Ph–C–N).

Anal. calcd. for $C_{20}H_{13}F_3N_2$: C, 71.00; H, 3.87. Found: C, 70.78; H, 3.80.

*3.2.3.3. 4-(4-Methylphenyl)-2-phenyl-6-(trifluoromethyl)nicotinonitrile (**4c**).* Yield 160 mg (95%), white solid: m.p. 143–144 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H, CH_3); 7.39 (d, 2H, 4-MeC_6H_4, J = 7.8 Hz) 7.53–7.61 (m, 5H, 4-MeC_6H_4, Ph); 7.75 (s, 1H, C–H); 7.97–8.01 (m, 2H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 (CH_3); 108.6 (C–CN); 116.5 (CN); 118.7 (q, H–C=C–CF_3, J = 2.9 Hz); 120.8 (q, CF_3, J = 275.2 Hz); 128.5, 128.6, 128.7, 129.4, 129.9, 130.7, 132.4, 136.4, 141.2 (4-MeC_6H_4, Ph); 149.8 (q, C=C–CF_3, J = 35.1 Hz); 157.0 (4-MeC_6H_4–C); 163.1 (Ph–C–N).

Anal. calcd. for $C_{20}H_{13}F_3N_2$: C, 71.00; H, 3.87. Found: C, 69.92; H, 3.77.

*3.2.3.4. 4-(3-Methoxyphenyl)-2-phenyl-6-(trifluoromethyl)nicotinonitrile (**4d**).* Yield 175 mg (99%), white solid, m.p. 103–104 °C; IR (nujol): ν 2240 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d.d, 1H, 3-$MeOC_6H_4$, J = 8.2 Hz, J = 1.8 Hz); 7.16 (t, 1H, 3-$MeOC_6H_4$, J = 1.8 Hz); 7.22 (d, 1H, 3-$MeOC_6H_4$, J = 8.2 Hz); 7.48 (t, 1H, 3-$MeOC_6H_4$, J = 8.0 Hz); 7.53–7.60 (m, 3H, Ph); 7.75 (s, 1H, C–H); 7.94–8.03 (m, 2H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5 (OCH_3); 108.8 (C–CN); 114.2, 116.4, 120.9, 128.7, 129.4, 130.4, 130.8, 136.3, 136.5, 160.0 (3-$MeOC_6H_4$, Ph); 116.3 (CN); 118.8 (q, H–C=C–CF_3, J = 2.9 Hz); 120.7 (q, CF_3, J = 275.9 Hz); 149.9 (q, C=C–CF_3, J = 35.1 Hz); 156.9 (3-$MeOC_6H_4$–C); 163.0 (Ph–C–N).

Anal. calcd. for $C_{20}H_{13}F_3N_2O$: C, 67.79; H, 3.70. Found: C, 67.74; H, 3.75.

*3.2.3.5. 2-Phenyl-4-(2-thienyl)-6-(trifluoromethyl)nicotinonitrile (**4e**).* Yield 160 mg (97%), white solid: m.p. 107–108 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H, OCH_3); 7.39 (d.d, 1H, 2-Th, J = 5.0 Hz; J = 4.0 Hz); 7.53–7.58 (m, 3H, Ph); 7.66 (d.d, 1H, 2-Th, J = 5.0 Hz; J = 1.0 Hz); 7.83 (s, 1H, C–H); 7.91–7.96 (m, 2H, Ph); 8.00 (d.d, 1H, 2-Th, J = 4.0 Hz; J = 1.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 106.4 (C–CN); 116.9 (CN); 118.7 (q, H–C=C–CF_3, J = 2.5 Hz); 120.3 (q, CF_3, J = 275.2 Hz); 128.7, 129.1, 129.4, 130.8 (b), 136.2, 136.3, 148.4 (2-Th, Ph); 150.1 (q, C=C–CF_3, J = 35.1 Hz); 156.5 (2-Th–C); 164.0 (Ph–C–N).

Anal. calcd. for $C_{17}H_{19}F_3N_2S$: C, 61.81; H, 2.75. Found: C, 62.06; H, 2.57.

*3.2.3.6. 2-(4-Methoxyphenyl)-4-phenyl-6-(trifluoromethyl)nicotinonitrile (**4f**).* Yield 170 mg (96%), white solid: m.p. 121–122 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, 2H, 4-$MeOC_6H_4$, J = 7.6 Hz); 7.48–7.76 (m, 6H, Ph, C–H); 8.01 (d, 2H, 4-$MeOC_6H_4$, J = 7.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4 (OCH_3); 107.9 (C–CN); 114.1, 128.6, 128.7, 129.2, 130.6, 131.1, 135.4, 161.8 (4-$MeOC_6H_4$, Ph); 116.7 (CN); 118.1 (b, H–C=C–CF_3); 120.7 (q, CF_3, J = 275.2 Hz); 149.8 (q, C=C–CF_3, J = 35.1 Hz); 157.0 (Ph–C); 162.4 (4-$MeOC_6H_4$–C–N).

Anal. calcd. for $C_{20}H_{13}F_3N_2O$: C, 67.79; H, 3.70. Found: C, 67.57; H, 3.93.

*3.2.3.7. 2-(4-Methoxyphenyl)-4-(4-methylphenyl)-6-(trifluoromethyl)nicotinonitrile (**4g**).* Yield 170 mg (92%), white solid: m.p. 142–143 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 7.05 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz); 7.37 (d, 2H, 4-MeC_6H_4, J = 7.6 Hz); 7.56 (d, 2H, 4-MeC_6H_4, J = 7.6 Hz); 7.67 (s, 1H, C–H); 8.00 (d, 2H, 4-$MeOC_6H_4$, J = 8.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3); 55.4 (OCH_3); 107.8 (C–CN); 114.2, 118.0, 128.6, 129.9, 131.1, 132.6, 141.1, 161.7 (4-$MeOC_6H_4$, 4-MeC_6H_4); 116.9 (CN); 118.0 (q, H–C=C–CF_3, J = 2.9 Hz); 120.9 (q, CF_3, J = 275.9 Hz); 149.8 (q, J = 35.1 Hz, C=C–CF_3); 157.1 (4-MeC_6H_4–C); 162.8 (4-$MeOC_6H_4$–C–N).

Anal. calcd. for $C_{21}H_{15}F_3N_2O$: C, 68.47; H, 4.10. Found: C, 68.09; H, 4.29.

*3.2.3.8. 2-(4-Methoxyphenyl)-4-(3-methylphenyl)-6-(trifluoromethyl)nicotinonitrile (**4h**).* Yield 180 mg (99%), white solid: m.p. 156–157 °C; IR (nujol): ν 2235 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 7.05 (d, 2H, 4-$MeOC_6H_4$, J = 9.1 Hz); 7.35–7.40 (m, 1H, 3-MeC_6H_4,); 7.42–7.47 (m, 3H, 3-MeC_6H_4,); 7.67 (s, 1H, C–H); 8.00 (d, 2H, 4-$MeOC_6H_4$, J = 9.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3); 55.4 (OCH_3); 108.0 (C–CN); 114.1, 118.0, 128.6, 129.9, 131.1, 132.6, 135.4, 139.0, 141.1, 161.8 (4-$MeOC_6H_4$, 3-MeC_6H_4); 116.8 (CN); 118.0 (q, H–C=C–CF_3, J = 2.4Hz); 120.9 (q, CF_3, J = 275.9 Hz); 149.8 (q, C=C–CF_3, J = 35.1 Hz,); 157.2 (3-MeC_6H_4–C); 162.4 (4-$MeOC_6H_4$–C–N).

Anal. calcd. for $C_{21}H_{15}F_3N_2O$: C, 68.47; H, 4.10. Found: C, 68.17; H, 4.33.

*3.2.3.9. 2-(4-Methoxyphenyl)-4-(3-methoxyphenyl)-6-(trifluoromethyl)nicotinonitrile (**4i**).* Yield 180 mg (99%), white solid: m.p. 120–121 °C; IR (nujol): ν 2240 (CN);

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 6H, OCH_3, OCH_3); 7.05 (d, 2H, 4-$MeOC_6H_4$, J = 9.1 Hz); 7.07–7.11 (m, 1H, 3-$MeOC_6H_4$,); 7.15 (t, 1H, 3-MeC_6H_4, J = 1.8 Hz); 7.18–7.22 (m, 1H, 3-$MeOC_6H_4$); 7.47 (t, 1H, 3-MeC_6H_4, J = 7.8 Hz); 7.68 (s, 1H, CH); 8.00 (d, 2H, 4-$MeOC_6H_4$, J = 9.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4 (OCH_3); 55.5 (OCH_3); 108.0 (C–CN); 114.1, 116.2, 120.8, 128.7, 130.3, 131.1, 136.7, 159.9, 161.8 (4-$MeOC_6H_4$, 3-$MeOC_6H_4$); 116.7 (CN); 118.0 (b, H–C=C–CF_3); 120.9 (q, CF_3, J = 275.9 Hz); 149.9 (q, C=C–CF_3, J = 35.9 Hz); 156.9 (3-$MeOC_6H_4$–C); 162.4 (4-$MeOC_6H_4$–C–N).

Anal. calcd. for $C_{21}H_{15}F_3N_2O_2$: C, 65.62; H, 3.93. Found: C, 65.48; H, 3.98.

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