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Synthesis of 3-cyano-2-fluoropyridines

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ABSTRACT

The synthesis of 3-cyano-2-fluoropyridines from readily available precursors was achieved via nucleophilic substitution of a leaving group in the 2-postion with KF or Bu_4NF in polar aprotic solvents such as DMF and DMSO. Ionic tetrahydrothiophenium fragment is the most effective leaving group, the methanesulfonyl moiety is a somewhat less effective, and Br- and Cl- are the least effective. Relatively mild conditions of the reaction between (2-pyridyl)-tetrahydrothiophenium salts and KF, as well as the convenience of one-step synthesis of these salts from 2(1H)-pyridinethiones, make these salts the compounds of choice for the preparation of ring-fluorinated pyridines.

1. Introduction

2-Fluoropyridines are an important class of fluoroheterocyclic compounds. They have found numerous applications in synthetic organic chemistry as valuable building blocks [1–3], as well as in medicinal chemistry as precursors of biologically active molecules, radiotracers and radiopharmaceuticals [1,4–7]. Although many different methods for the preparation of 2-fluoropyridines have been published in the literature, regioselective synthesis remains a challenging problem especially in the presence of other reactive substituents. The classic method of synthesis of 2-fluoropyridines entails diazotation of 2-aminopyridines in HF [8]. One of the best methods for preparation of 2-fluoropyridines is based on reactions of 2-halopyridines with KF, Bu_4NF, and other sources of the fluoride ion [9]. Direct fluorination of substituted pyridines [10] and base-induced rearrangement of N-fluoropyridinium salts [11] have been proposed for the preparation of 2-fluoropyridines. Electrophilic fluorination has also been employed to prepare 2-fluoropyridines; however, fluorination of pyridine with XeF_2 or XeF_6 has shown to yield a mixture of 2- and 3-fluropyridines and 2,6-difluoropyridine [9]. 5-Aryl-3,4-dimethoxycabonyl-2-fluoropyridines have been prepared by the reaction of difluromethylaziridinium salts with dimethyl acetylenedicarboxylate [12].

3-Cyano-2-fluoropyridines have been successfully used in preparation of compounds with diverse spectrum of biological activity. For example, these molecules have recently been proposed as kinase inhibitors (**A**) [13], potassium channel inhibitors (**B**) [14], and as acetylcholine receptor ligands (e.g., as a central nervous system active agent, **C**) [15] (Fig. 1). Other 3-cyano-2-fluoropyridine can potentially be used as promising agents for the positron emission tomography (PET) [16]. Additionally, it has previously been demonstrated that 3-cyanopyridines can be transformed into -amides, -carboxylic acids, and -esters [17–19]. Furthermore, it has been shown on numerous occasions that the 3-cyano group in pyridines easily participates in intramolecular nucleophilic addition reactions leading to fused heterocyclic systems [20–22].

2. Results and discussion

Polysubstituted 3-cyano-2-fluoropyridines are relatively difficult to prepare compounds due to the lack of convenient synthetic methods [9]. One of the goals of the current effort is to develop synthetic approaches for the preparation of these compounds from readily available starting materials. The general synthetic scheme includes nucleophilic substitution reactions of nucleofuge-containing pyridines employing commonly used sources of nucleophilic fluoride ion, KF and Bu_4NF (Scheme 1).

First, we investigated 2-chloro-3-cyanopyridines as precursors for the desired fluoropyridines. We found that 3-cyano-2-fluoropyridines **2a–c** can be prepared from corresponding 2-chloro-3-cyanopyridines **1a–c** in 52–86% yield upon heating with

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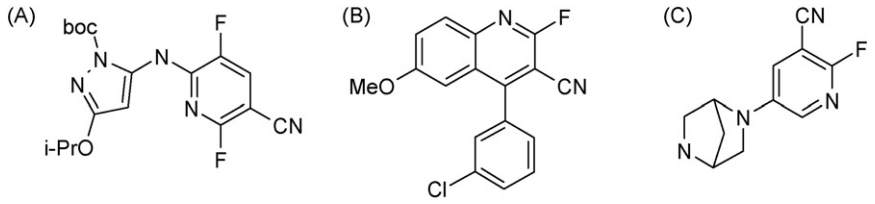
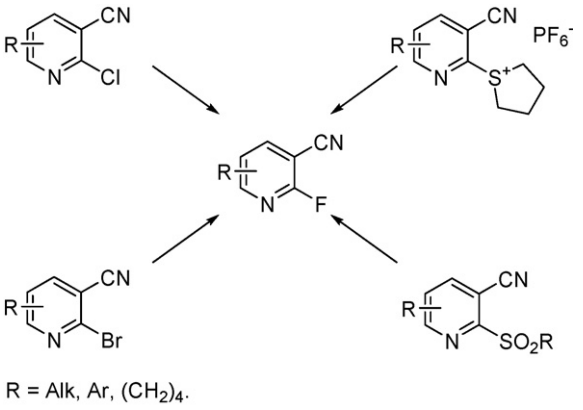


Fig. 1. Biologically active 3-cyano-2-fluoropyridines.



Scheme 1.

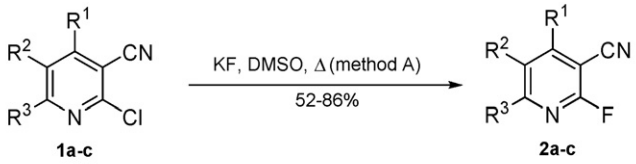
excess of KF in DMSO at 120–140 °C (Method A, Scheme 2). The limiting step of this approach is the synthesis of the starting materials, 2-chloro-3-cyanopyridines, which can be prepared from 3-cyanopyridin-2(1H)-ones in moderate yields (40–62%) [9].

Substituted 2-bromopyridines can also be used for the synthesis of corresponding 2-fluoropyridines. Contrary to 2-chloro-3-cyanopyridines, 2-bromo-3-cyanopyridines can be easily prepared in one step from acyclic reagents. For example, 2-bromo-3-cyanopyridines **3a**–**c** were prepared in up to 98% yields via bromination of corresponding 2-aryl-3-aroyl-1,1-dicyanopropanes in acetic acid [23,24]. We found that heating of these 2-bromo-3-cyanopyridines **3a**–**c** with excess KF in DMF resulted in formation of 2-fluoropyridines **2b**,**d**,**e** in 62–76% yield (Method B, Scheme 3). The use of more organic-soluble Bu_4NF in these reactions improved the yield by 11–28% (2-fluoropyridines **2b**,**d**; Method C, Scheme 3).

We also investigated the utility of readily available 3-cyanopyridine-2(1H)-thiones [25–27] as starting materials for the synthesis of Biologically active 3-cyano-2-fluoropyridines. These compounds were first converted into 3-cyano-2-methanesulphonylpyridines **4** by a previously published protocol [28]. The methanesulfonyl group in **4** was then successfully replaced with fluorine using excess KF in DMF at 120–125 °C. This method gives 3-cyano-2-fluoropyridines **2b**,**f** in good yields (72 and 75%, Method D, Scheme 4).

In addition, we examined a possibility of conversion of 3-cyanopyridine-2(1H)-thiones into 3-cyano-2-fluoropyridines via intermediate tetrahydrothiophenium salts **6** (Method E, Scheme 5). Tetrahydrothiophene has previously been shown as an excellent leaving group in the intramolecular addition-elimination reaction [29], and we have envisioned that it will act as a good nucleofuge in nucleophilic fluorination reactions. The tetrahydrothiophenium salts **6a**,**b** were prepared according to the known procedure [30] from corresponding pyridinethiones **5a**,**b**, 1,4-dibrombutane and KPF_6 in 53–67% yields. Reaction of **6** with excess KF in DMF in relatively mild conditions (70–75 °C) gave corresponding 3-cyano-2-fluoropyridines **2** in 65–70% yields (Method E, Scheme 5).

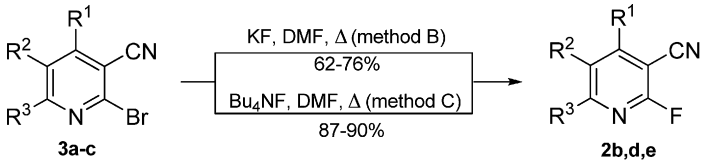
The structures of all reported compounds were elucidated by means of infrared (IR) and multi-NMR (^1H, ^{13}C and ^{19}F) spectroscopy, mass spectrometry (MS), and confirmed by elemental analysis. The presence of C≡N in fluoropyridines **2** was confirmed by the characteristic absorption band at 2228–2236 cm^{-1} in IR spectra. This band is shifted ~10 cm^{-1} compared to the corresponding 2-bromo-3-cyanopyridines (2218–2226 cm^{-1}) [24,31]. This difference can be attributed to the presence of a



1a-c **2a-c**

1,**2**: R^1 R^3 CH_3, R^2 H (**a**); R^1 R^3 C_6H_5, R^2 H (**b**); R^1 H, R^2-R^3 $(CH_2)_4$ (**c**).

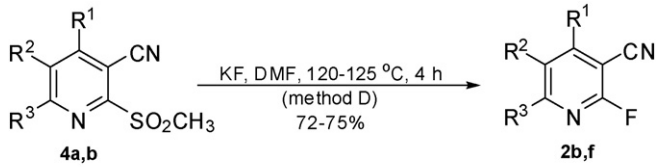
Scheme 2.



3a-c **2b,d,e**

$R^1 = R^3 = C_6H_5$, R^2 = H (**2b**, **3a**); R^1 = 4-CH_3-C_6H_4, R^2 = H, $R^3 = C_6H_5$ (**2d**, **3b**); R^1 = 4-Cl-C_6H_4, R^2 = H, $R^3 = C_6H_5$ (**2e**, **3c**).

Scheme 3.



$R^1 = R^3 = C_6H_5$, $R^2 = H$ (**2b**, **4a**);
$R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = H$, $R^3 = C_6H_5$ (**2f**, **4b**).

Scheme 4.

strong electronegative fluorine atom next to the cyano group. The same effect is observed in NMR ^{13}C spectra where the signal of C2 is shifted downfield (δ 157.4–158.4) for compounds **2b**,**d**–**g**, and even further downfield (δ 162.3–164.2) for compounds **2a**,**c**, which do not have aryl π-donors. The signal of fluorine atom in ^{19}F NMR of 2-fluoropyridines **2** is in the range of −52.2 to −66.4 ppm.

Based on the observed yields and reaction conditions (time and temperature), it appears that the substitution reaction is the most difficult in the case of 2-halopyridines and is much easier in the case of tetrahydrothiophenium salts, with methanesulphonyl derivatives being somewhere in between (Table 1). Observations of the relative reactivity of these four leaving groups towards the fluoride anion are in general agreement with the existing body of theoretical and experimental data related to nucleophilic substitution reactions at the 2-position of the pyridine ring [9]. A specific high reactivity of sulfonium salts compared to covalent compounds can be attributed to Columb interactions between the fluoride anion and cationic substrates [32]. This assumption is further supported by the fact that the only known-to-date enzymatic fluorination reaction also entails reaction of the fluoride anion and a sulfonium salt [33].

3. Conclusions

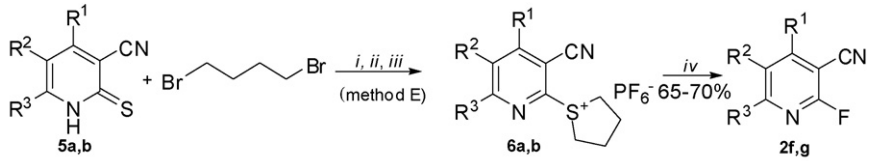
We have developed a practical synthetic approach towards 3-cyano-2-fluoropyrines based on nucleophilic substitution of various leaving groups at the 2-postion of the pyridine ring using KF or Bu_4NF in DMF and DMSO at elevated temperatures. The developed protocols offer a simple and efficient way to make 3-cyano-2-fluoropyridines from available 2-substituted-3-cyanopyridines. The 3-cyano group in these 2-fluoropyridines can potentially be further modified, providing an efficient route to various fluoroheterocyclic systems [17–19]. We continue to explore the use of 2-substituted-3-cyanopyridines in the synthesis of 3-cyano-2-fluoropyridines and their subsequent synthetic transformations.

4. Experimental

^1H NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz). ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (50.32 MHz). ^{19}F NMR spectra were recorded on a Bruker AC-200 spectrometer (188.31 MHz). Chemical shifts of ^1H were measured (ppm) relative to Me_4Si as the internal standard, ^{13}C – relative to DMSO-d_6, and ^{19}F – relative to $CFCl_3$. IR-spectra were recorded on a PerkinElmer 467 spectrophotometer in KBr pellets. MS spectra were recorded on a Varian MAT-CH-6 instrument (EI, 70 eV). Thin-layer chromatography (TLC) was performed on Silufol UV-254 silica gel (hexane–acetone 5:3). "Spray-dried" KF (Aldrich) and 1 M solution of Bu_4NF in THF (5% H_2O, Acros) were used in all reactions.

4.1. 3-Cyano-2-fluoropyridines 2a–c. Method A

A mixture of 0.05 mol of 3-cyano-2-chloropyridine **1a**–**c** and 8.7 g (0.15 mol) of KF in 30 ml of anhydrous DMSO was heated at



i - K_2CO_3, DMF, 45-50 °C, 3 h; *ii* - KPF_6; *iii* - CH_3COCH_3, Et_2O; *iv* - KF, DMF, 70-75 °C, 4 h

5a, **6a**, **2f**: $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = H$, $R^3 = C_6H_5$;
5b, **6b**, **2g**: $R^1 = C_6H_5$, $R^2 = H$, $R^3 = 4\text{-}F\text{-}C_6H_4$.

Scheme 5.

Table 1
Fluorination reaction yields and conditions for the methods **A** (–Cl, KF), **B** (–Br, KF), **C** (–Br, Bu_4NF), **D** (–SO_2Me, KF) and **E** (–$S^+(CH_2)_4$, KF).

2-Fluoropyridine	R^1	R^2	R^3	Starting material	Yield (%)	F^- source	Leaving group	Method	Reaction conditions
2a	CH_3	H	CH_3	**1a**	75	KF	Cl	A	DMSO, 140 °C, 8 h
2b	C_6H_5	H	C_6H_5	**1b**	86	KF	Cl	A	DMSO, 140 °C, 8 h
				3a	62	KF	Br	B	DMF, 135 °C, 14 h
				3a	90	Bu_4NF	Br	C	DMF, 110 °C, 10 h
				4a	72	KF	SO_2Me	D	DMF, 125 °C, 4 h
2c		H	$(CH_2)_4$	**1c**	52	KF	Cl	A	DMSO, 140°C, 8 h
2d	4–CH_3–C_6H_4	H	C_6H_5	**3b**	76	KF	Br	B	DMF, 135 °C, 14 h
				3b	87	Bu_4NF	Br	C	DMF, 110 °C, 10 h
2e	4–Cl–C_6H_4	H	C_6H_5	**3c**	68	KF	Br	B	DMF, 135 °C, 14 h
2f	4–OCH_3–C_6H_4	H	C_6H_5	**4b**	75	KF	SO_2Me	D	DMF, 125 °C, 4 h
				6a	65	KF	$S^+(CH_2)_4$	E	DMF, 75 °C, 4 h
2g	C_6H_5	H	4–F–C_6H_4	**6b**	70	KF	$S^+(CH_2)_4$	E	DMF, 75 °C, 4 h

120–140 °C with stirring for 7–8 h. The reaction mixture was cooled to room temperature, poured into crushed ice (200 g), and extracted with $CHCl_3$ (3 × 50 ml). The organic extract was washed with water, dried over Na_2SO_4, and filtered through a short layer of silica gel. The organic solvent was evaporated; the residue was taken up in boiling n-hexane (50 ml), filtered through a paper filter, and placed in a refrigerator (5 °C) overnight. The precipitate was collected by filtration and dried.

*4.2. 3-Cyano-4,6-dimethyl-2-fluoropyridine (**2a**)*

Yield 5.62 g (75%), m.p. 85 °C (hexane). IR, ν, cm^{-1}: 2232 (C≡N). ^1H NMR (DMSO-d_6): δ 2.47 (s, 3H); 2.52 (s, 3H); 7.36 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 19.63 (CH_3), 23.74 (CH_3), 112.65, 122.85, 149.57, 157.05, 161.75, 164.24. ^{19}F NMR (DMSO-d_6): δ −63.93; *m*/*z*: 150 $[M]^+$ (100). Found (%): C, 64.02; H, 4.76; N, 18.57. $C_8H_7FN_2$ calculated (%): C, 63.99; H, 4.70; N, 18.66.

*4.3. 3-Cyano-4,6-diphenyl-2-fluoropyridine (**2b**)*

Yield 11.78 g (86%), m.p. 143 °C. IR, ν, cm^{-1}: 2228 (C≡N). ^1H NMR (DMSO-d_6): δ 7.62 (m, 5H); 7.64 (m, 5H); 8.35 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 118.35, 127.58, 128.67, 128.73, 128.97, 129.09, 129.21, 130.52, 130.73, 131.40, 131.47, 134.68, 135.23, 157.92. ^{19}F NMR (DMSO-d_6): δ −52.29; *m*/*z*: 274 $[M]^+$ (100). Found (%): C, 78.79; H, 4.05; N, 10.23. $C_{18}H_{11}FN_2$ calculated (%): C, 78.82; H, 4.04; N, 10.21.

*4.4. 3-Cyano-2-fluoro-5,6-tetramethylenepyridine (**2c**)*

Yield 4.58 g (52%), m.p. 45 °C (hexane). IR, ν, cm^{-1}: 2236 (C≡N). ^1H NMR (DMSO-d_6): δ 1.78–1.96 (m, 4H); 2.79 (m, 2H); 2.94 (m, 2H); 7.72 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 20.18, 27.53, 32,43, 112.98, 130.64, 144.16, 157.47, 161.91, 162.32. ^{19}F NMR (DMSO-d_6): δ −66.41; *m*/*z*: 176 $[M]^+$ (100). Found (%): C, 68.13; H, 5.17; N, 15.92. $C_{10}H_9FN_2$ calculated (%): C, 68.17; H, 5.15; N, 15.90.

*4.5. 3-Cyano-2-fluoropyridines **2b**,**d**,**e**. Method B*

A mixture of 0.01 mol of 3-cyano-2-bromopyridine **3a**–**c** and 1.7 g (0.03 mol) of KF in 15 ml of anhydrous DMF was heated at 130–135 °C with stirring for 14 h. The reaction mixture was cooled to room temperature and poured into crushed ice (200 g). The precipitate was filtered and recrystallized from $CHCl_3$/MeOH (1:2).

*4.6. 3-Cyano-4,6-diphenyl-2-fluoropyridine (**2b**)*

Yield 1.70 g (62%).

*4.7. 3-Cyano-2-fluoro-4-(4-methylphenyl)-6-phenypyridine (**2d**)*

Yield 2.19 g (76%), m.p. 214–215 °C ($CHCl_3$/MeOH). IR, ν, cm^{-1}: 2228 (C≡N). ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H); 7.42 (d, 2H, *J* = 8.7 Hz); 7.57 (m, 3H); 7.73 (d, 2H, *J* = 8.7 Hz); 8.12 (s, 1H); 8.18 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 21.50 (CH_3), 118.84, 128.82, 129.32, 129.73, 129.93, 130.22, 133.73, 135, 137.52, 140.01, 158.07. ^{19}F NMR (DMSO-d_6): δ −61.30; *m*/*z*: 288 $[M]^+$ (100). Found (%): C, 79.04; H, 4.60; N, 9.77. $C_{19}H_{13}FN_2$ calculated (%): C, 79.15; H, 4.54; N, 9.72.

*4.8. 3-Cyano-2-fluoro-4-(4-chlorophenyl)-6-phenypyridine (**2e**)*

Yield 2.09 g (68%), m.p. 198–199 °C ($CHCl_3$/MeOH). IR, ν, cm^{-1}: 2236 (C≡N). ^1H NMR (DMSO-d_6): δ 7.54–7.56 (m, 3H); 7.70 (d, 2H, *J* = 8.5 Hz); 7.85 (d, 2H, *J* = 8.5 Hz); 8.22–8.24 (m, 3H). ^{13}C NMR (DMSO-d_6): δ 113.31, 118.45, 127.70, 129.16, 131.49, 135.71, 158.42. ^{19}F NMR (DMSO-d_6): δ −61.17; *m*/*z*: 308 $[M]^+$ (100). Found (%): C, 70.10; H, 3.29; N, 8.94. $C_{18}H_{10}ClFN_2$ calculated (%): C, 70.02; H, 3.26; N, 9.07.

*4.9. 3-Cyano-2-fluoropyridines **2b**,**d**. Method C*

A mixture of 0.01 mol of 3-cyano-2-bromopyridine **3a**,**b**, 15 ml (0.015 mol) of a 1 M solution of Bu_4NF in THF, and 15 ml of anhydrous DMF was heated at 105–110 °C with stirring for 10 h. The reaction mixture was cooled to room temperature and poured into crushed ice (200 g). The precipitate was filtered and recrystallized from $CHCl_3$/MeOH (1:2).

*4.10. 3-Cyano-4,6-diphenyl-2-fluoropyridine (**2b**)*

Yield 2.47 g (90%).

*4.11. 3-Cyano-2-fluoro-4-(4-methylphenyl)-6-phenypyridine (**2d**)*

Yield 2.51 g (87%).

*4.12. 3-Cyano-2-fluoropyridines **2b**,**f**. Method D*

A mixture of 0.01 mol of 3-cyano-2-methanesulphonylpyridine **4a**,**b** and 1.16 g (0.02 mol) of KF in 20 ml of anhydrous DMF was heated at 120–125 °C with stirring for 4 h. The reaction mixture was cooled to room temperature and poured into crushed ice (200 g), and the precipitate was filtered and recrystallized from $CHCl_3$/MeOH (1:2).

*4.13. 3-Cyano-4,6-diphenyl-2-fluoropyridine (**2b**)*

Yield 1.97 g (72%).

*4.14. 3-Cyano-2-fluoro-4-(4-methoxylphenyl)-6-phenypyridine (**2f**)*

Yield 2.28 g (75%), m.p. 193 °C ($CHCl_3$/MeOH). IR, ν, cm^{-1}: 2228 (C≡N). ^1H NMR (DMSO-d_6): δ 3.88 (s, 3H); 7.19 (d, 2H, *J* = 8.3 Hz); 7.56–8.25 (m, 5H); 7.84 (d, 2H, *J* = 8.3 Hz); 8.18 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 55.52, 114.51, 118.09, 126.93, 127.63, 129.12, 130.52, 131.31, 135.47, 157.42. ^{19}F NMR (DMSO-d_6): δ −61.40; *m*/*z*: 304 $[M]^+$ (100). Found (%): C, 75.03; H, 4.30; N, 9.24. $C_{19}H_{13}FN_2O$ calculated (%): C, 74.99; H, 4.31; N, 9.21.

*4.15. Tetrahydrothiophenium salts **6a**,**b***

A solution of 0.03 M of 2(1H)-pyridinethione **5a**,**b** in 15 ml of anhydrous DMF; 6.2 g (0.045 mol) K_2CO_3; and 13 g (0.06 mol) of 1,4-dibrombutane was heated at 45–50 °C for 3 h. After that, excess 1,4-dibrombutane and most of the solvent were removed under reduced pressure. The residue was treated with 200 ml of acetone and 9.2 g (0.05 mol) of KPF_6. The resulting mixture was stirred at 20 °C for 2 h. Most of the solvent was evaporated, and the residue was treated with 100 ml of Et_2O. The mixture was refrigerated overnight, and the precipitate was collected by filtration and washed with water (3 × 20 ml), EtOH (2 × 20 ml), and Et_2O (3 × 20 ml).

*4.16. [3-Cyano-4-(4-methoxyphenyl)-6-phenylpyrid-2-yl]-tetrahydrothiophenium hexafluorophosphate (**6a**)*

Yield 8.4 g (54%), m.p. 197–199 °C (acetone/Et_2O). ^1H NMR (DMSO-d_6): δ 2.23 (m, 4H), 3.77 (m, 2H), 3.89 (m, 2H), 3.94 (s, 3H), 7.24 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 2H, *J* = 8.4 Hz), 7.54–8.26 (m, 5H),

8.26 (s, 1H). Found (%): C, 52.99; H, 3.83; N, 5.07. $C_{23}H_{21}F_6N_2OSP$ calculated (%): C, 53.28; H, 4.08; N, 5.40.

4.17. [3-Cyano-4-(4-fluorophenyl)-6-phenylpyrid-2-yl]-tetrahydrothiophenium hexafluorophosphate (**6b**)

Yield 7.8 g (51%), m.p. 181–183 °C (acetone/Et_2O). ^{1}H NMR (DMSO-d_6): δ 2.26 (m, 4H), 3.82 (m, 2H), 3.94 (m, 2H), 7.38 (m, 2H), 7.74–8.36 (m, 7H), 8.28 (s, 1H). Found (%): C, 52.47; H, 3.72; N, 5.32. $C_{22}H_{18}F_7N_2SP$ calculated (%): C, 52.18; H, 3.58; N, 5.53.

4.18. 3-Cyano-2-fluoropyridines **2f,g**. Method E

A mixture of 0.01 mol of tetrahydrothiophenium salt **6a**,**b** and 0.87 g (0.015 mol) of KF in 20 ml of anhydrous DMF was heated at 70–75 °C with stirring for 4 h, following which the reaction mixture was cooled to room temperature and poured into crushed ice (200 g). The precipitate was filtered and recrystallized from $CHCl_3$/MeOH (1:2).

4.19. 3-Cyano-2-fluoro-4-(4-methoxylphenyl)-6-phenypyridine (**2f**)

Yield 1.98 g (65%).

4.20. 3-Cyano-2-fluoro-6-(4-fluorophenyl)-4-phenypyridine (**2g**)

Yield 2.04 g (70%), m.p. 211 °C ($CHCl_3$/MeOH). IR, ν, cm^{-1}: 2228 (C≡N). ^{1}H NMR (DMSO-d_6): δ 7.27–7.41 (m, 2H); 7.57–7.69 (m, 3H); 7.79–7.92 (m, 2H); 8.14–8.34 (m, 2H), 8.23 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 113.8, 114.9, 116.8, 118.2, 119.4, 129.2, 130.07, 131.02, 132.05, 135.12, 157.85. ^{19}F NMR (DMSO-d_6): δ −58.41, −105.13; *m*/*z*: 292 $[M]^+$ (100). Found (%): C, 74.00; H, 3.47; N, 9.65. $C_{18}H_{10}F_2N_2$ calculated (%): C, 73.97; H, 3.45; N, 9.58.

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