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Microwave-assisted synthesis of substituted fluoroazines using KF·2H$_2$O

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ABSTRACT

This Letter describes a new microwave-assisted fluorination of azines using hydrated potassium fluoride in untreated DMSO under atmospheric conditions. It is thought that microwave irradiation promotes desolvation of the fluorine anion leading to halide nucleophilic substitution.

Fluorinated azines are important organic compounds, with several examples showing biological activity.[1] Pyridines containing the ^{18}F isotope have been used in radiotherapy[2,1b] and positron emission tomography as imaging agents.[2e] They are often utilized as building blocks in the syntheses of biologically active compounds, including naturally occurring examples.[1,3] They are typically obtained via nucleophilic substitution reactions. As such, pyridines containing leaving groups (Hal, R_3N^+, SO_2R, and NO_2) at position 2 or 4 are often used as starting materials for the preparation of 2- or 4-fluoropyridines.[4] As hydration significantly reduces the nucleophilicity of the fluoride anion,[5] these reactions are normally conducted in dry aprotic solvents (DMSO, DMF, and THF) with the fluoride source introduced as a fine dry powder (due to its low solubility in these solvents). At the same time, reactions of 2- and 4-halogeno-pyridines with KF·2H$_2$O or reactions in aqueous solutions were shown to be very slow and incomplete. Although, considerable effort has gone into the development and optimization of anhydrous conditions for the preparation of fluorinated pyridines, to the best of our knowledge, there are no reports on these reactions in untreated solvents or in aqueous medium.

Recently we demonstrated a practical synthetic approach towards 3-cyano-2-fluoropyrines based on nucleophilic substitution of various leaving groups at the 2-position of the pyridine ring using 'spray-dried' KF or Bu_4NF in dry DMF and DMSO.[6] The developed protocols offered good to high yields of the fluorinated pyridines, however, they suffered from relatively harsh conditions, prolonged reaction times, and the necessity to use anhydrous solvents and reagents. As such, 3-cyano-2-fluoropyridines **3a–c** were obtained from pyridines **1a–c** by heating for eight hours at 140 °C (Table 1).[6]

As part of our research to develop mild and operationally simple synthetic methods for fluorinated azines that use mild inexpensive reagents[7] and untreated solvents, we were interested in the possibility of using microwave irradiation, which can often accelerate the rate of nucleophilic substitution.[4] Microwave irradiation can promote dehydration, desolvation, and dissociation processes.[8] Thus, we decided to investigate this nucleophilic substitution reaction of a series of substituted halogeno-azines under microwave irradiation using readily available KF·2H$_2$O in 'non-dry' dimethylsulfoxide. As starting materials for these reactions we decided to use halogeno-azines **1**, which are stable and easy to handle, yet can undergo a variety of transformations under very mild conditions, and are readily accessible from inexpensive, commercially available reagents.

2-Chloro-3-cyanopyridines **1a–e** were reacted with KF·2H$_2$O (**2**) in DMSO in a sealed vessel using a focused microwave synthesis system (CEM Discover BenchMate) under continuous stirring. The incubation time was 90 s with a fixed 300 W microwave irradiation power and a maximum temperature of 120 °C. Under these conditions the highest yields of the target compounds were achieved when the ratio of halogeno-azine to KF·2H$_2$O was 1:2 (Scheme 1). Product azines **3a–e** were purified on a silica gel column and were isolated in good to high yields (Table 1).[9]

Using the same conditions, thienopyrimidine **1f** gave fluorinated compound **3f** in a high 81% yield (Scheme 2, Table 1).

To demonstrate the general versatility of our method, we also used non-activated pyridines (without the cyano group) in our fluorination protocol. Halogeno-azines **1g**,**h** required slightly longer reaction times (2 min (T_{max} = 140 °C) for **3g** (67% yield) and 4 min (T_{max} = 180 °C) for **3h** (62% yield); the prolonged reaction times resulted in some decomposition of the final products.

The highest yields were achieved for the 3-cyano-2-fluoropyridines **3a–e**, suggesting that the strong electron-withdrawing effect of the cyano group significantly accelerates the rate of the nucleophilic substitution. The identities and purities of compounds **3** were confirmed by mass spectrometry, and by ^{1}H, ^{13}C and ^{19}F NMR-spectroscopy.[9]

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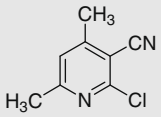
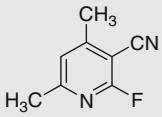
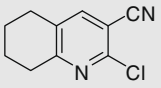
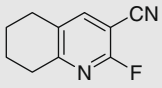
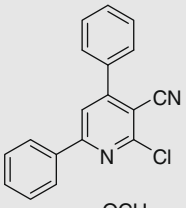
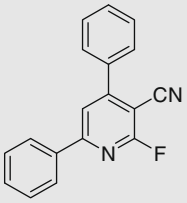
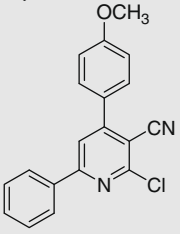
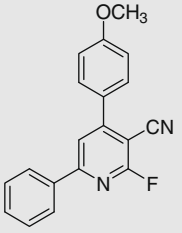
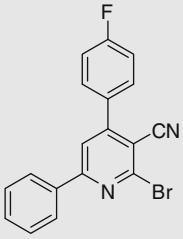
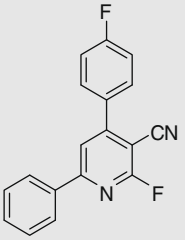
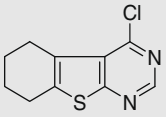
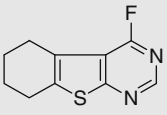
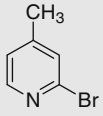
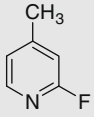
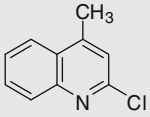
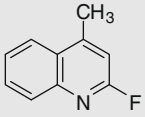
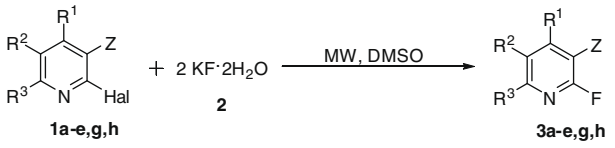
Table 1
Structures of starting materials **1** and yields of fluoroazines **3**

Starting material	Reaction product	Yield (%)	
		'Spray-dried' KF, anhydrous DMSO, 140 °C, 8 h[6]	$KF{\cdot}2H_2O$, DMSO, MW 300 W
1a 	**3a** 	75[6]	78[a]
1b 	**3b** 	52[6]	75[a]
1c 	**3c** 	86[6]	77[a]
1d 	**3d** 	–	75[a]
1e 	**3e** 	–	68[a]
1f 	**3f** 	–	81[a]
1g 	**3g** 	–	67[b]
1h 	**3h** 	–	62[c]

Reaction time—[a]90 s; [b]2 min; [c]4 min.

Taking into account that nucleophilic substitution reactions of azines **1** do not typically occur in untreated DMSO and $KF{\cdot}2H_2O$ under traditional heating, it is assumed that microwave irradiation promotes dissociation of KF and desolvation of the fluorine anion, which subsequently takes part in the nucleophilic substitution reaction, like 'spray-dried' KF in anhydrous DMSO (Fig. 1).

In conclusion, we have developed a simple and efficient method for the fluorination of halogen-substituted azines using $KF{\cdot}2H_2O$. The microwave-assisted reactions were conducted in untreated DMSO under atmospheric conditions to yield the fluorinated azines in moderate to high yields. To the best of our knowledge, this is the first example of nucleophilic fluorination conducted in aqueous solutions using untreated and inexpensive reagents. Considering the operational simplicity of this method, it may find a broad range of applications in the synthesis of fluorinated heterocycles. We are currently working on the development of similar protocols for other aromatic molecules and heterocycles.

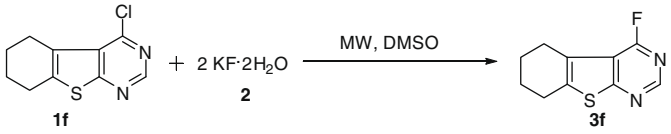


1a-e,g,h 3a-e,g,h

1: Hal = Br (**e,g**); Cl (**a-d, f, h**).

1, 3: Z = CN, R^1= R^3 = CH_3 , R^2 = H (**a**); Z = CN, R^1 = H, R^2 - R^3 = $(CH_2)_4$ (**b**); Z = CN, R^1= R^3 = C_6H_5 , R^2 = H (**c**); Z = CN, R^1 = 4-CH_3O-C_6H_4, R^2 = H, R^3 = C_6H_5 (**d**); Z = CN, R^1 = 4-F-C_6H_4, R^2 = H, R^3 = C_6H_5 (**e**); Z = R^2 = R^3 = H, R^1 = CH_3 (**g**); Z = H, R^1 = CH_3, R^2-R^3 = $(CH{=}CH)_2$ (**h**).

Scheme 1. Microwave-assisted synthesis of 2-fluoropyridines **3**.



1f 3f

Scheme 2. Synthesis of substituted fluorothienopyridine **3f**.

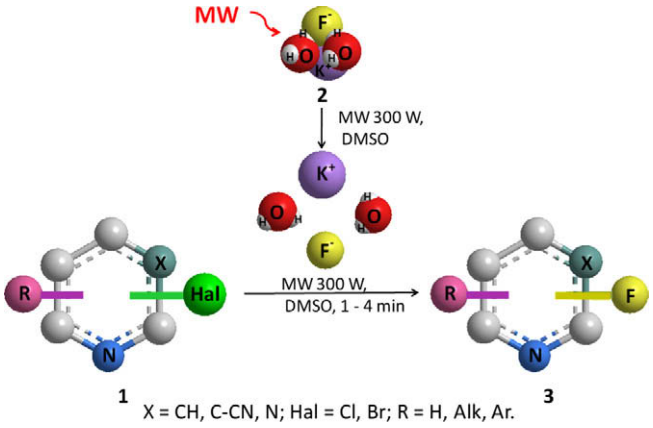


Figure 1. Desolvation of the F^- anion under microwave irradiation.

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9. *General procedure for the synthesis fluoroazines* **3**: Chloro- or bromoazines **1** (2 mmol) and KF·$2H_2O$ (**2**) (0.4 g, 4 mmol) were mixed together in DMSO (4 mL) in a 10-mL Pyrex glass sample holder (CEM). The reaction was carried out in a closed vessel using a focused microwave synthesis system (CEM Discover BenchMate) under continuous stirring. The incubation time was 1.5–4 min with a fixed microwave irradiation power of 300 W and a maximum temperature of 120–180 °C. After completion, the reaction mixture was cooled, poured into water (50 ml), extracted with chloroform, and purified by column chromatography on silica gel (eluent: $CHCl_3$–hexane, 3:2) (Table 1). Physical data of representative compounds: *3-Cyano-2-fluoro-4-(4-methoxyphenyl)-6-phenylpyridine* (**3d**): Yield: 75%; mp 193 °C (from $CHCl_3$–MeOH, 1:1). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 3.88 (s, 3H, CH_3O); 7.19 (d, 2H, C_6H_4, ^3J = 8.3 Hz); 7.56–8.25 (m, 3H, C_6H_5); 7.84 (d, 2H, C_6H_4, ^3J = 8.3 Hz); 8.19 (s, 1H, C^5H); 8.23–8.26 (m, 2H, C_6H_5). ^{13}C NMR (50 MHz, DMSO-d_6), δ: 55.52; 96.28; 113.72 (CN); 114.51; 118.06; 126.82; 127.63; 129.12; 130.52; 131.31; 135.47; 157.44; 157.90; 161.32; 163.17 (d, $^1J_{CF}$ = 239.9 Hz). ^{19}F NMR (188 MHz, DMSO-d_6), δ: -61.4. MS (EI, 70 eV) *m/z*: 304 $[M]^+$ (100). *3-Cyano-2-fluoro-4-(4-fluorophenyl)-6-phenylpyridine* (**3e**): Yield: 68%; mp 192 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.49 (m, 2H, C_6H_4); 7.58 (m, 3H, C_6H_5); 7.91 (m, 2H, C_6H_4); 8.24 (m, 3H, C^5H, C_6H_5). ^{13}C NMR (50 MHz, DMSO-d_6), δ: 96.33; 113.20 (CN); 116.04; 118.50; 127.82; 129.09; 131.27; 131.39; 131.45; 135.29; 153.91; 158.52; 159.20 (d, $^1J_{CF}$ = 247.0 Hz); 163.60 ($^1J_{CF}$ = 242.7 Hz). ^{19}F NMR (282 MHz, DMSO-d_6), δ: −62.95, −110.88. MS (EI, 70 eV) *m/z*: 292 $[M]^+$ (100). *4-Fluoro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine* (**3f**): Yield: 81%; mp 87 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.84 (m, 4H, CH_2CH_2); 2.86 (m, 4H, CH_2, CH_2); 8.73 (s, 1H, C^2H).). ^{13}C NMR (50 MHz, DMSO-d_6), δ: 21.47; 22.24; 24.50; 24.96; 117.51; 125.55; 138.34; 152.12; 159.83; 167.59 ($^1J_{CF}$ = 269.7 Hz). ^{19}F NMR (188 MHz, DMSO-d_6), δ: −64.43. MS (EI, 70 eV) *m/z*: 208 $[M]^+$ (57), 180 (100). *4-Methyl-2-fluoropyridine* (**3g**)**:** Yield: 67%; oil (eluent: toluene–hexane, 1:1). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.35 (s, 3H, CH_3); 6.97 (s, 1H, C^3H), 7.15 (m, 1H, C^5H), 8.08 (d, 1H, C^6H, J = 5.14 Hz). ^{13}C NMR (50 MHz, DMSO-d_6), δ: 20.25 (CH_3); 109.53 (d, C^3H, J = 37.59 Hz), 122.86 (d, C^5H, J = 4.42 Hz), 146.93 (d, C^4H, J = 15.48 Hz), 153.50 (d, C^6H, J = 8.85 Hz), 163.87 (d, C^2H, $^1J_{CF}$ = 244.43 Hz). ^{19}F NMR (282 MHz, DMSO-d_6), δ: -71.08. MS (EI, 70 eV) *m/z*: 111 $[M]^+$ (100). *4-Methyl-2-fluoroquinoline* (**3h**)**:** Yield: 62%; oil (eluent: toluene–hexane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.61 (s, 3H, CH_3); 7.15 (s, 1H, C^3H), 7.51 (dd, 1H, C^7H, J = 8.06 Hz, J = 7.25 Hz), 7.67 (dd, 1H, C^6H, J = 8.06 Hz, J = 7.25 Hz), 7.88 (d, 1H, C^5H, J = 8.06 Hz), 7.98 (d, 1H, C^8H, J = 8.06 Hz), ^{13}C NMR (75 MHz, $CDCl_3$), δ: 18.79, 109.8, 123.80, 125.92, 126.74, 128.67, 130.15, 150.93, 161.17 (d, C^2H, $^1J_{CF}$ = 256.18 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −63.80. MS (EI, 70 eV) *m/z*: 161 $[M]^+$ (69), 143 (100).