# Three-component synthesis of fluorinated pyrimidine carbonitrile derivatives under thermal aqueous conditions

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A series of new fluorine containing 4-amino-pyrimidine-5-carbonitrile derivatives has been synthesised from the three-component reaction of malononitrile, fluorinated aldehydes or ketone and *N*-unsubstituted amidines. The reaction occurs in water at reflux and is microwave assisted. This method provides a new route to produce fluorinated pyrimidine derivatives in good to excellent yields.

**Keywords:** fluorinated pyrimidine, malononitrile, fluorinated aldehydes, fluorinated ketones, *N*-unsubstituted amidines

Organic fluorine compounds have received significant attention in the materials and pharmaceutical sciences due to their unique physical and biological properties such as the increased membrane permeability, enhanced hydrophobic binding and stability against metabolic oxidation.[1] Among these compounds fluorinated pyrimidine derivatives are interesting compounds to study in connection with their biological activities.[2] The pyrimidine derivatives containing trifluoromethyl group are especially important, and attract increasing attention from various fields.[3] Nowadays, many trifluoromethylated molecules have been developed as well-known drugs such as prozac (antidepressant), diflucan (anti-fungal agent), casodex (anti-cancer agent) and desflurane (inhalation anesthetic).[4] Trifluoromethyl-containing Mosher's acid and its derivatives are widely used as chiral NMR resolution agents.[5]

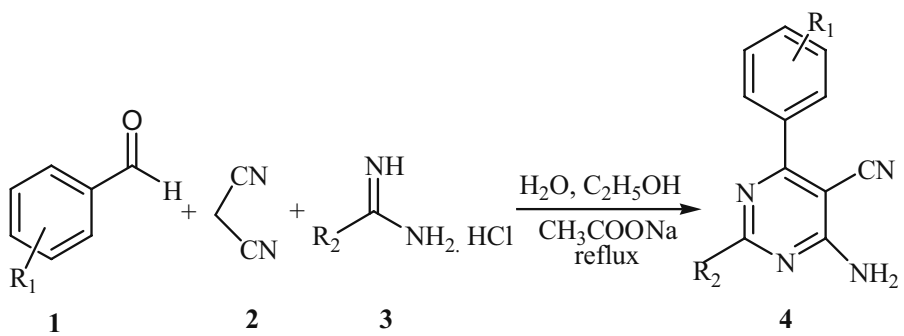
Although pyrimidine syntheses have long been established, the development of alternative and more efficient strategies has considerable relevance.[6] The increasing importance of pyrimidines and their derivatives as intermediates for the synthesis of biologically and industrially useful compounds prompted us to synthesise 4-aminopyrimidine-5-carbonitrile derivatives.[7] Peters *et al*.,[8,9] have reported the synthesis of 5-aminomethylpyrimidines with small substituents (Me, Cl, MeO, F and $CF_3$) in different positions at phenyl rings by reducing 5-cyanopyrimidines, which were obtained in a first step by the reaction of benzylamidines and arylidenemalononitriles under basic conditions.

Increasing attention for environmental protection has led to attempts to develop chemical process with maximum yield and minimum cost whilst using non-toxic reagents, solvents and catalysts. One tool used to combine economic aspects with the environmental ones is the multicomponent reaction (MCR) strategy; this process consists of two or more synthetic steps that are carried out without isolation of any intermediate thus reducing time, saving money, energy and raw materials.[10]

As part of program aimed at developing new selective and environmentally friendly methods for the synthesis of heterocyclic systems,[11-14] we synthesised fluorinated 4-aminopyrimidine-5-carbonitrile derivatives **4** from the three-component reaction of fluorinated aromatic aldehydes **1**, malononitrile **2** and amidines **3** in water at reflux and in the presence of sodium acetate in good yields Scheme 1.

In order to optimise the reaction conditions for preparing compounds **4**, the synthesis of 4-amino-2-phenyl-6-[4-(trifluoromethyl)phenyl]pyrimidine-5-carbonitrile **4a** was carried out under different reaction conditions. First we examined the three-component reaction of 4-trifluoromethylbenzaldehyde **1a**, malononitrile **2** and benzamidine hydrochloride **3a** in DMF at reflux in the presence of a catalytic amount of triethylamine. The reaction was too slow and the yield was low. For example, when the reaction time was extended to 16 h, compound **4a** was obtained in 25% yield, as compared to yield of 70% in 2 h under thermal aqueous conditions. The use of water as a solvent in organic chemistry has received increasing attention in the last decade. The enhanced reactivity and selectivity observed in some reactions were rationalised as a consequence of the hydrophobic effects and enforced hydrophobic interactions.[15-17] When the reaction was carried out in alcoholic solution good, yields were obtained due to the solubility of all the reagents in an alcohol solvent.

Microwave-assisted solvent-free synthesis in organic reactions has been of growing interest as an efficient, economic and clean procedure ('green chemistry').[18] Based on our previous studies on the use of microwave irradiation method for carrying out carbon–carbon forming reactions,[19] the effects of solvent and base catalyst for preparing compounds **4a** and **4b** under different reaction conditions and microwave irradiation were investigated. First, reactions were carried out under solvent free microwave assisted in the presence of a catalytic amount of sodium acetate (method A) and without a catalyst (method B). Second, other reactions were performed




**1** **2** **3** **4**

**Scheme 1**

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**Table 1** Synthesis of **4a** and **4b** under different reaction conditions and microwave irradiation

| Compd. | $R_1$ | $R_2$ | Method | Solvent | Catalyst | Time/s | Yield/% |
|---|---|---|---|---|---|---|---|
| **4a** | 4-$CF_3$ | Ph | A | Solvent free | Sodium acetate | 300 | 65 |
| **4b** | 4-$CF_3$ | Me | A | Solvent free | Sodium acetate | 60 | 58 |
| **4a** | 4-$CF_3$ | Ph | B | Solvent free | Without catalyst | 600 | 45 |
| **4b** | 4-$CF_3$ | Me | B | Solvent free | Without catalyst | 480 | 50 |
| **4a** | 4-$CF_3$ | Ph | C | Toluene | Sodium acetate | 90 | 60 |
| **4b** | 4-$CF_3$ | Me | C | Toluene | Sodium acetate | 40 | 55 |
| **4a** | 4-$CF_3$ | Ph | D | Toluene | Triethylamine | 30 | 82 |
| **4b** | 4-$CF_3$ | Me | D | Toluene | Triethylamine | 50 | 75 |
| **4a** | 4-$CF_3$ | Ph | E | Water | Sodium acetate | 40 | 63 |
| **4b** | 4-$CF_3$ | Me | E | Water | Sodium acetate | 30 | 55 |

All reactions were carried out under 300W microwave irradiation.

in an organic solvent (toluene) in the presence of a catalytic amount of sodium acetate (method C) and triethylamine (method D). Finally: the three-component reaction was carried out in water and in the presence of a catalytic amount of sodium acetate (method E). Results of these methods are presented in Table 1.

As shown in Table 1 the yield of the reaction is markedly affected by the solvent and catalyst. Optimum results were obtained when reactions were treated in toluene and in the presence of a catalytic amount of triethylamine (method D).

The three-component reactions undergo the same reaction to give only one product under thermal aqueous conditions and microwave irradiation. The results of these reactions under thermal aqueous conditions and microwave irradiation are summarised in Table 2.

In connection with our ongoing project aiming at the development of new and highly efficient synthetic methods for various functional pyrimidine derivatives. The 2,2,2-trifluoro-1-phenylethanone **5** was mixed with benzamidine hydrochloride **3a** and malononitrile **2** in toluene and in the presence of a catalytic amount of triethylamine and the mixture was subjected to microwave irradiation for three minutes. The reaction afforded 4-amino-2,6-diphenyl-6-trifluoromethyl-1,6-dihydropyrimidine-5-carbonitrile **6** in 65% yields (Scheme 2) Attempts to perform this reaction under thermal conditions were mostly unsuccessful.

Structures **4a-h** and **6** were established on the basis of IR which showed the presence of CN in the region 2235–2238 $cm^{-1}$ and two sharp bands at 3500–3450 and 3390–3380 $cm^{-1}$ due to asymmetric and symmetric vibrations of $NH_2$ group. The $^1H$ and $^{19}F$ NMR, $^{13}C$ NMR and mass spectra are also in accordance with the proposed structures.

## Experimental

Melting points were determined on an Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. $^1H$ NMR, $^{19}F$ NMR and $^{13}C$ NMR spectra were determined on a Bruker DRX-300 Avance spectrometer at 300.13, 282.40 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionisation potential of 70 eV. Elemental analyses were performed using a Heracus CHN–O–rapid analyser.

*General procedure for the preparation of fluorinated 4-amino-pyrimidine-5-carbonitriles in water at reflux (Method I) and under microwave assisted(Method II)*

*Method I*: A mixture of the fluorinated aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), amidines hydrochloride (2 mmol) and sodium acetate (2 mmol) in $H_2O$ (40 ml) and ethanol (5 ml) was refluxed with stirring for the time reported in Table 2 (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). The product **4** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallised from ethanol.

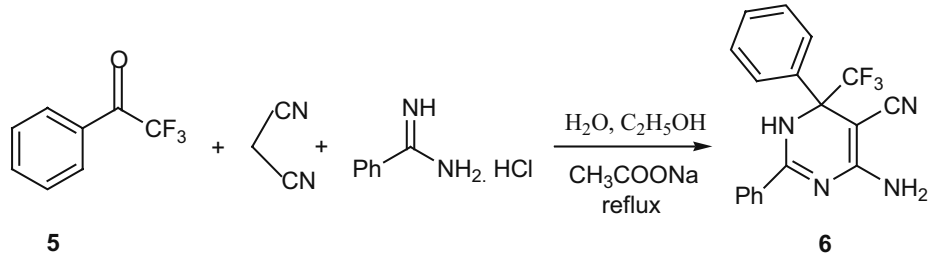
*Method II*: A mixture of fluorinated aldehyde **1** (2 mmol), malononitrile **2** (2 mmol) and amidine hydrochloride **3** (2 mmol) in toluene (5 ml) containing triethylamine (3–4 drops) was placed in a 15 ml high pressure glass tube and placed in a 250 ml beaker. After microwave irradiation at 300 W in the microwave oven for the period of time shown in Table 1, the reaction mixture was allowed to cool to ambient temperature. The product was purified according to the sample method I. We used method D to obtain the best results.

*4-Amino-2-phenyl-6-[4-(trifluoromethyl)phenyl]-pyrimidine-5-carbonitrile* **(4a)**: Yellow crystals; m.p. 231–233°C; $\nu_{max}$ (KBr) 3478,

**Table 2** Synthesis of **4a-h** under microwave irradiation and thermal conditions

| Yield/% | Time/s | Yield/% | Time/h | $R_2$ | $R_1$ | Compd no. |
|---|---|---|---|---|---|---|
| 82 | 30 | 70 | 2 | Ph | 4-$CF_3$ | **4a** |
| 75 | 50 | 60 | 5 | Me | 4-$CF_3$ | **4b** |
| 77 | 35 | 72 | 4 | $NH_2$ | 4-$CF_3$ | **4c** |
| 78 | 45 | 66 | 4 | Ph | 4-F | **4d** |
| 75 | 40 | 63 | 4 | $NH_2$ | 4-F | **4e** |
| 75 | 40 | 80 | 3 | Ph | 3-F | **4f** |
| 75 | 45 | 60 | 5 | Me | 3-F | **4g** |
| 79 | 35 | 68 | 4 | $NH_2$ | 3-F | **4h** |

All reactions were carried out under 300W microwave irradiation.




**5** **6**

**Scheme 2**

3329($NH_2$), 2237(CN), 1641(C=N), 1542(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.51–8.40(m, Ar and $NH_2$), $\delta_C$ (75 MHz, DMSO-$d_6$) 85.47($C_5$), 116.44(CN), 125.86(q, $^3J_{=C-F}$ 3.75 Hz), 128.01(q, $^1J_{C-F}$ 270.75 Hz, $CF_3$),128.91, 129.96, 131.70(q, $^2J_{=C-F}$ 32.25 Hz), 132.06, 136.84, 140.90, 164.66, 164.92, 167.33; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) -61.28; MS, *m/z* (%) 340($M^+$, 90), 237(100), 210(20), 145(23), 104(55), 77(34), 51(20); Anal. Calcd. for $C_{18}H_{11}F_3N_4$: C, 63.5; H, 3.3; N, 16.5. Found: C, 63.4; H, 3.2; N, 16.4%.

*4-Amino-2-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine-5-carbonitrile* **(4b)**: Light yellow crystals; m.p. 234–236°C; $\nu_{max}$ (KBr) 3379, 3329, 3156($NH_2$), 2985($CH_3$), 2212(CN), 1666(C=N), 1542(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 2.46(3H, s, $CH_3$), 7.89–8.03(6H, m, Ar and $NH_2$); $\delta_C$ (75 MHz, DMSO-$d_6$) 26.43($CH_3$), 116.35(CN), 125.85(q, $^3J_{=C-F}$ 3.75 Hz), 128.02(q, $^1J_{C-F}$ 272.55 Hz, $CF_3$), 129.88, 131.07(q, $^2J_{=C-F}$ 31.80 Hz), 140.76, 164.55, 167.17, 169.89; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) -61.22, MS, *m/z* (%) 278($M^+$, 87), 259(15), 237(100), 210(15), 145(25), 66(25), 42(62); Anal. Calcd. for $C_{13}H_9F_3N_4$: C, 56.1; H, 3.3; N, 20.1. Found: C, 56.05; H, 3.2; N, 20.0%.

*2,4-Diamino-6-[4-(trifluoromethyl)phenyl]pyrimidine-5-carbonitrile* **(4c)**: Yellow crystals; m.p. 239–241°C(dec.); $\nu_{max}$ (KBr) 3429, 3379, 3156($2NH_2$), 2212(CN), 1691, 1617(C=N), 1542(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.24(4H, broad, $NH_2$), 7.89–7.93(4H, m, Ar); $\delta_C$ (75 MHz, DMSO-$d_6$) 76.74($C_5$), 118.01(CN), 125.66(q, $^3J_{=C-F}$ 3.75 Hz), 126.57(q, $^1J_{C-F}$ 270.58 Hz, $CF_3$), 129.53, 130.68(q, $^2J_{=C-F}$ 31.72 Hz), 141.47, 163.44, 165.27, 168.68; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) -61.20; MS, *m/z* (%) 279($M^+$, 100), 260(15), 237(50), 210(17), 145(20), 69(25), 43(55); Anal. Calcd. for $C_{12}H_8F_3N_5$ C, 51.6; H, 2.9; N, 25.1. Found: C, 51.4; H, 2.8; N, 25.0%.

*4-Amino-6-(4-fluorophenyl)-2-phenyl-pyrimidine-5-carbonitrile* **(4d)**: White crystals; m.p. 222°C; $\nu_{max}$ (KBr) 3478, 3354($NH_2$), 2212(CN), 1641, 1611(C=N), 1567(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.43–8.39 (m, Ar and $NH_2$); $\delta_C$ (75 MHz, DMSO-$d_6$) 84.75($C_5$), 116.19(d, $^2J_{=C-F}$ 21.75 Hz), 116.84(CN), 128.89, 129.01, 131.67(d, $^3J_{=C-F}$ 8.25 Hz), 132.11, 133.47, 136.90, 164.12(d, $^1J_{=C-F}$ 248.25 Hz), 164.45, 165.03, 167.48; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) -109.40; MS, *m/z* (%) 290($M^+$, 100), 187(90), 160(20), 104(45), 77(25), 51(18); Anal. Calcd. for $C_{17}H_{11}FN_4$ C, 70.3; H, 3.8; N, 19.3. Found: C, 70.05; H, 3.7; N, 19.15%.

*2,4-Diamino-6-(4-fluorophenyl)pyrimidine-5-carbonitrile* **(4e)**: Yellow crystals; m.p. 239–241°C(dec.); $\nu_{max}$ (KBr) 3453, 3354, 3230($2NH_2$), 2212(CN), 1666, 1641(C=N), 1551(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 6.63–7.46 (m, Ar and $NH_2$); $\delta_C$ (75 MHz, DMSO-$d_6$) 80.89($C_5$), 115.90(d, $^2J_{=C-F}$ 21.75 Hz), 116.98(CN), 131.37(d, $^3J_{=C-F}$ 9.00 Hz), 132.63, 158.47, 159.13, 163.10(d, $^1J_{=C-F}$ 245.25 Hz), 163.11; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) -111.83; MS, *m/z* (%) 290($M^+$, 23), 187(18), 140(20), 123(25), 95(22), 59(38), 43(100); Anal. Calcd. for $C_{11}H_8FN_5$ C, 57.6; H, 3.5; N 30.55. Found: C, 57.5; H, 3.45; N, 30.4.%.

*4-Amino-6-(3-fluorophenyl)-2-phenyl-pyrimidine-5-carbonitrile* **(4f)**: White crystals; m.p. 195–197°C; $\nu_{max}$ (KBr) 3478, 3354, 3230($NH_2$), 2212(CN), 1641(C=N), 1542(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.43–7.84(7H, m, Ar), 8.04(2H, broad, $NH_2$), 8.39(2H, d, Ar); $\delta_C$ (75 MHz, DMSO-$d_6$) 85.16($C_5$), 115.92(d, $^2J_{=C-F}$ 22.25 Hz), 116.62(CN), 118.25(d, $^2J_{=C-F}$ 21.00 Hz), 125.28, 128.93, 129.01, 131.15(d, $^3J_{=C-F}$ 7.50 Hz), 132.12, 136.85, 139.27(d, $^3J_{=C-F}$ 7.50 Hz), 162.34(d, $^1J_{=C-F}$ 243.00 Hz), 164.97, 167.18, 167.22; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) –112.39; MS, *m/z* (%) 290($M^+$, 75), 187(100), 160(20), 104(30), 77(25), 51(15); Anal. Calcd. for $C_{17}H_{11}FN_4$ C, 70.3; H, 3.8; N, 19.3. Found: C, 70.5; H, 3.7; N, 19.4%.

*4-Amino-6-(3-fluorophenyl)-2-methyl-pyrimidine-5-carbonitrile* **(4g)**: Yellow crystals; m.p. 234–236°C(dec.); $\nu_{max}$ (KBr) 3379, 3329, 3156($NH_2$), 2212(CN), 1666(C=N), 1542(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 2.44(3H, s, $CH_3$), 7.36–7.68(4H, m, Ar), 7.85(2H, broad, $NH_2$); $\delta_C$ (75 MHz, DMSO-$d_6$) 26.40($CH_3$), 84.35($C_5$), 115.73(d, $^2J_{=C-F}$ 23.25 Hz), 116.48(CN), 118.03(d, $^2J_{=C-F}$ 21.00 Hz), 125.10(d, $^4J_{=C-F}$ 2.25 Hz), 131.02(d, $^3J_{=C-F}$ 8.25 Hz), 139.08(d, $^3J_{=C-F}$ 7.50 Hz), 162.24(d, $^1J_{=C-F}$ 243.22 Hz), 164.65, 166.90(d, $^4J_{=C-F}$ 2.25 Hz), 169.79; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) –112.23; MS, *m/z* (%) 229($M^{+1}$, 85), 228($M^{+1}$,75), 187(100), 160(30), 95(15), 66(18), 42(45); Anal. Calcd. for $C_{12}H_9FN_4$ C, 63.15; H, 4.0; N, 24.55. Found: C, 63.0; H, 3.8; N, 24.35%.

*2,4-Diamino-6-(3-fluorophenyl)pyrimidine-5-carbonitrile* **(4h)**: Yellow crystals; m.p. 236–238°C(dec.); $\nu_{max}$ (KBr) 3429, 3379, 3156($2NH_2$), 2212(CN), 1691, 1617(C=N), 1567(Ar) $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.20(4H, broad, $NH_2$), 7.26–7.62(4H, m, Ar); $\delta_C$ (75 MHz, DMSO-$d_6$) 115.40(d, $^2J_{=C-F}$ 23.25 Hz), 117.57(d, $^2J_{=C-F}$ 20.25 Hz), 118.13(CN), 124.78, 130.84(d, $^3J_{=C-F}$ 8.25 Hz), 139.80(d, $^3J_{=C-F}$ 7.50 Hz), 162.16(d, $^1J_{=C-F}$ 242.55 Hz), 163.39, 165.39, 168.44; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) –112.89; MS, *m/z* (%) 229($M^+$,100), 187(50), 95(15), 60(20), 43(68); Anal. Calcd. for $C_{11}H_8FN_5$ C, 57.6; H, 3.5; N, 30.55. Found: C, 57.6; H, 3.5; N, 30.4%.

*4-Amino-2,6-diphenyl-6-trifluoromethyl-1,6-dihydro-pyrimidine-5-carbonitrile* **(6)**: Green crystals; m.p. 235–237°C(dec.); $\nu_{max}$ (KBr) 3478(NH), 3304, 3180($NH_2$), 2212(CN), 1641(C=N), 1542(Ar) $cm^{-1}$. $\delta_H$ (300 MHz, DMSO-$d_6$) 6.42–7.89(10H, m, Ar), 9.57(1H, broad, NH), 10.01(2H, broad, $NH_2$); $\delta_C$ (75 MHz, DMSO-$d_6$) 65.65(q, $^2J_{C-F}$ 26.17 Hz), 79.32(q, $^3J_{C-F}$ 8.55 Hz, $C_5$), 120.26(CN), 125.52(q, $^1J_{C-F}$ 258.37 Hz, $CF_3$), 127.25, 127.36, 128.56, 128.72(q, $^3J_{C-F}$ 6.75 Hz), 129.19, 132.07, 132.37, 133.09, 141.70, 150.60, 153.46; $\delta_F$ (282 MHz, DMSO-$d_6$, internal standard $CFCl_3$) –60.87; MS, *m/z* (%) 343(M + 1, 65), 273(100), 104(40), 77(35), 51(25); Anal. Calcd. for $C_{18}H_{13}F_3N_4$ requires C, 63.2; H, 3.8; N, 16.4. Found: C, 62.7; H, 3.5; N, 16.0%.

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