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A Concise and Efficient Approach to 2,6-Disubstituted 4-Fluoropyrimidines from α-CF₃ Aryl Ketones

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Abstract Herein, a concise and efficient protocol to synthesize a series of 2,6-disubstituted 4-fluoropyrimidines as universal and useful building blocks in medicinal chemistry is reported. From readily accessible α-CF₃ aryl ketones and different amidine hydrochlorides, this method provides a very practical approach to this kind of compounds under mild conditions with good to excellent yields.

Key words fluoropyrimidine, α-CF₃ aryl ketone, metal-free, mild conditions

Fluorinated compounds have been widely applied in the fields of material science, medicinal chemistry, and agrochemicals.¹ For drug molecular design, pyrimidine is a distinctive scaffold² with important bioactivities as antibacterial,³ anticancer,⁴ and antiviral agents.⁵ Given the special properties of the fluorine atom, the introduction of fluorine into the pyrimidine moiety might significantly enhance its lipophilicity, binding selectivity, and metabolic stability.⁶

Fluorinated pyrimidine derivative flucytosine (Figure 1; A) was first synthesized in 1957. It was a breakthrough for drug research in systemic mycoses therapy.⁷ With further study of fluoropyrimidines, these compounds have been broadly applied in marketed drugs and agrochemicals such as voriconazole⁸ (B), abemaciclib⁹ (C), fostamatinib¹⁰ (D), florasulam¹¹ (E), and fluoxastrobin¹² (F).

Furthermore, fluorine atoms were found to be highly reactive when attached to the 4- or 6-positions of pyrimidines, and they could be easily substituted by nucleophilic reagents. Thus, 4-fluoropyrimidines were also very useful building blocks for the construction of complex compounds. For instance, azidopyrimidines could be obtained by treating 4-fluoropyrimidines with sodium azide¹³ (Figure 2, a). Meanwhile, 4-fluoropyrimidines reacted with Grignard reagents to afford alkylated pyrimidines¹⁴ (Figure 2, b), and if reacted with amines, aminopyrimidines¹⁵ would be obtained (Figure 2, c). Additionally, pyrimidone could be constructed by nucleophilic substitution from 4-fluoropyrimidine followed by oxidation processes¹⁶ (Figure 2, d), and diaryl compounds could also be obtained via a nucleophilic substitution reaction¹⁷ (Figure 2, e). The substitution

![Figure 1 Examples of fluoropyrimidines in marketed drugs and agrochemicals](image-url)
reaction of 4-fluoropyrimidine with β-dicarbonyl compounds could produce optically active spiropyrrolidone compounds18 (Figure 2, f). For more interesting examples, by treating 4-fluoropyrimidine-5-carbonyl chloride with potassium 3-methoxy-3-oxopropanoate followed by condensation with dimethylamino ethyl acrylate and nucleophilic cyclization, heterocyclic-fused quinolones could be synthesized.19 In addition, macrocyclic compounds with a pyrimidine scaffold could be synthesized by S_NAr reaction on 4,6-dihalopyrimidine.20

Figure 2  Examples of the use of 4-fluoropyrimidines for the construction of complex compounds

However, there were only a few synthetic routes available to prepare 4-fluoropyrimidines. The general approach to 4-fluoropyrimidines was nucleophilic substitution of other halogen atoms with fluorine reagents.21 In 1985, Inouye first reported a one-pot synthesis of CF_3, OCF_3, and F substituted pyrimidines by using complex perfluorinated compounds with amidine hydrochlorides, but the substrate scope of the reaction was very narrow.22 In 2014, Sedenkova and co-workers developed a two-step method to synthesize 4-fluoropyrimidines from gem-bromofluorocyclopanes, but the total yields of the target compounds were relatively low.23 Furthermore, a few examples have been reported in recent years on the synthesis of 4-fluoropyrimidines catalyzed by expensive metal catalysts such as Ag24 or Pd25 salts.

α-CF_3 aryl ketones are very important and useful building blocks for synthesizing fluorinated compounds. As a continuation of our work,26 in this article, we proposed a convenient and efficient approach to synthesize 2,6-disubstituted 4-fluoropyrimidines from α-CF_3 aryl ketones and amidine hydrochlorides, with the target compounds being prepared with good to excellent yields.

Initially, we attempted the synthesis of 2,6-disubstituted 4-fluoropyrimidine by employing 1-(4-benzyloxy)-3,3,3-trifluoropropan-1-one (1a), acetamidine hydrochloride (2a), and K_2CO_3 in methanol, under reflux conditions. However, none of the target compound was detected (Table 1, entry 1). By changing the solvent to aprotic DMF, we were delighted to obtain the desired product in 36% yield (entry 2). Based on this result, different bases were examined; the results showed that KHCO_3 (47% yield) was superior to other bases including K_2CO_3, Na_2CO_3, Cs_2CO_3, DBU, DIPEA, TEA and K_OAc (entries 2–9). Different aprotic solvents such as DMA, DMSO, MeCN, NMP, THF, and 1,4-dioxane were then screened (entries 10–15). When 1,4-dioxane was used as solvent, the yield increased to 55%. The yield improved further upon increasing the reaction temperature, but it decreased when the temperature exceeded 60 °C (entries 15–17). Finally, the use of KHCO_3 and 1,4-dioxane at 60 °C were established as the optimized reaction conditions for this protocol.

Under the optimized conditions, the substrate scope was explored. Different α-CF_3 aryl ketones reacted with acetamide hydrochloride to afford the products with moderate to excellent yields (50–93%; Scheme 1). The results showed that both para-substituted electron-donating and electron-withdrawing groups on the benzene ring of α-CF_3 phenyl ketones were well tolerated in these reactions, except for -OCH_3 (3b). Use of the ortho-substituted-CH_3 ketone (3d) decreased the yield, probably because of the steric effect. To our delight, 3,3,3-trifluoro-1-(thiophen-2-yl)propan-1-one also reacted with 2 with an acceptable yield of 43% (3m).

Table 1  Optimization of the Reaction Conditions a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%) b</th>
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<td>65</td>
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* Reaction conditions: 1a (0.30 mmol, 88 mg), 2a (0.33 mmol, 31 mg), base (0.90 mmol), solvent (3.0 mL) for 12 h.  
  a Isolated yield.

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The reactions of various amidine hydrochlorides and 1-(4-methylphenyl)-3,3,3-trifluoropropan-1-one (1f) were also investigated (Scheme 2), and the products were also obtained with good to excellent yields of 73–98%.

Interestingly, the N-heterocyclic amidine hydrochlorides gave the desired compounds with excellent yields (Scheme 2; 4n, 4o). Finally, to demonstrate the practical utility of this method, we employed 4-(3-chlorophenyl)-2-ethyl-6-fluoropyrimidine (5) as the substrate to synthesize a reported potent PED4 inhibitor 2-(4-((6-(3-chlorophenyl)-2-ethylpyrimidin-4-yl)amino)phenyl) acetamide (7) in a one-pot, two-step way with a combined yield of 18%.

Based on these results, we proposed a possible mechanism for this method below (Scheme 4). In the presence of KHCO₃, amidine hydrochloride first forms a free-base amidine, which undergoes a condensation reaction with the α-CF₃ aryl ketone to give intermediate [A]. The imine subsequently engages in nucleophilic substitution, leading to heterocyclic compound [B]. Hydrogen fluoride is then easily eliminated under KHCO₃ to give more stable aromatic compound as the target product [C].

In conclusion, it has been shown that synthesizing 2,6-disubstituted 4-fluoropyrimidines from α-CF₃ aryl ketones is a very convenient and efficient approach. This method tolerates a wide range of substrates, from different α-CF₃ aryl ketones to various amidine salts. The reaction

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conditions are mild and the protocol can be expanded to a diverse range of heterocyclic compounds that offer potential bioactive agents in medicinal chemistry.

All reagents were purchased from commercial suppliers and used without further purification. The progress of all of the reactions was monitored by thin layer chromatography with standard TLC silica gel plates, and the developed plates were visualized under UV light. All of the compounds were purified by column chromatography. Chromatography was performed on silica gel (200–300 mesh). Nuclear magnetic resonance spectra were recorded on a Bruker Avance III 600/500/600 NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ). Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Tetramethylsilane (TMS) was used as internal standard (1H NMR: TMS at 0.00 ppm; CHCl3 at 7.26 ppm, DMSO at 2.50 ppm; 13C NMR: CDCl3 at 77.16 ppm). High-resolution mass spectra (HRMS) were recorded at 0.00 ppm; CHCl3 at 7.26 ppm, DMSO at 2.50 ppm; 13C NMR: CDCl3 at 77.16 ppm). Reaction time: 24 h.

Yield: 0.067 g (0.27 mmol, 91%); yellow oil; Rf = 0.20 (PE/EtOAc, 60:1).
1H NMR (400 MHz, CDCl3): δ = 8.02–7.96 (m, 2 H), 7.53 (d, J = 8.6 Hz, 2 H), 7.10 (s, 1 H), 2.75 (s, 3 H), 1.36 (s, 9 H).
13C NMR (101 MHz, CDCl3): δ C = 170.8 (d, J = 142.2 Hz), 169.2 (d, J = 7.5 Hz), 162.3, 128.9, 128.5 (d, J = 5.1 Hz), 114.3, 97.8 (d, J = 30.9 Hz), 55.4, 25.9.
19F NMR (471 MHz, CDCl3): δ = –62.10.

4-Fluro-2-methyl-6-(o-tolyl)pyrimidine (3e)

Yield: 0.036 g (0.18 mmol, 60%); colorless oil; Rf = 0.20 (PE/EtOAc, 60:1).
1H NMR (500 MHz, CDCl3): δ = 7.42 (dd, J = 7.8, 1.5 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.33–7.28 (m, 2 H), 6.87 (d, J = 1.4 Hz, 1 H), 2.76 (s, 3 H), 2.42 (s, 3 H).
13C NMR (126 MHz, CDCl3): δ C = 172.0 (d, J = 7.1 Hz), 170.0 (d, J = 259.8 Hz), 169.1 (d, J = 5.6 Hz), 137.3 (d, J = 4.5 Hz), 136.1, 131.3, 129.9, 129.5, 126.3, 103.4 (d, J = 29.8 Hz), 26.0, 20.4.
19F NMR (471 MHz, CDCl3): δ = –61.08.

4-Fluro-2-methyl-6-(p-tolyl)pyrimidine (3e)

Yield: 0.050 g (0.25 mmol, 82%); colorless oil; Rf = 0.20 (PE/EtOAc, 60:1).
1H NMR (400 MHz, CDCl3): δ = 7.89 (d, J = 2.2 Hz, 1 H), 7.83 (d, J = 7.6 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.12 (s, 1 H), 2.76 (s, 3 H), 2.46 (s, 3 H).
13C NMR (126 MHz, CDCl3): δ C = 170.8 (d, J = 250.2 Hz), 169.5 (d, J = 13.8 Hz), 169.2 (d, J = 7.4 Hz), 138.9, 136.1 (d, J = 4.9 Hz), 132.3, 129.0, 128.1, 124.6, 99.2 (d, J = 30.7 Hz), 26.0, 21.6.
19F NMR (376 MHz, CDCl3): δ = –61.46.

4-Fluro-2-methyl-6-(p-tolyl)pyrimidine (3f)

Yield: 0.055 g (0.27 mmol, 90%); yellow solid; mp 35–36 °C; Rf = 0.20 (PE/EtOAc, 60:1).
1H NMR (400 MHz, CDCl3): δ = 7.97 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.09 (s, 1 H), 2.74 (s, 3 H), 2.43 (s, 3 H).
13C NMR (101 MHz, CDCl3): δ = 170.8 (d, J = 249.9 Hz), 169.4 (d, J = 13.8 Hz), 168.8 (d, J = 7.2 Hz), 142.0, 133.3 (d, J = 4.9 Hz), 129.8, 127.3, 98.7 (d, J = 31.0 Hz), 26.0, 21.6.
19F NMR (471 MHz, CDCl3): δ = –61.77.
**4-Fluoro-2-methyl-6-(thiophen-2-yl)pyrimidine (3m)**

Yield: 0.056 g (0.26 mmol, 86%); white solid; mp 216–218 °C; Reaction time: 48 h.

**4-Fluoro-2-methyl-6-(4-fluorophenyl)pyrimidine (3k)**

Yield: 0.055 g (0.27 mmol, 89%); white solid; mp 107–108 °C; Reaction time: 24 h.

**4-Fluoro-6-(4-fluorophenyl)-2-methylpyrimidine (3j)**

Yield: 0.051 g (0.21 mmol, 71%); colorless oil; mp 123–124 °C; Reaction time: 48 h.

**4-(3,4-Dimethyl-2-propenyl)-6-fluoro-2-methylpyrimidine (3k)**

Yield: 0.065 g (0.28 mmol, 93%); yellow solid; mp 174–176 °C; Reaction time: 24 h.

**4-(4-Fluoro-2-methyl-6-(p-toly1)pyrimidine (4a)**

Yield: 0.056 g (0.26 mmol, 86%); white solid; mp 216–218 °C; Reaction time: 24 h.

**4-(4-Fluoro-2-methyl-6-(thiophen-2-yl)pyrimidine (3m)**

Yield: 0.025 g (0.13 mmol, 43%); colorless oil; Reaction time: 48 h.

**4-(4-Fluoro-2-methyl-6-(3,5-dimethylphenyl)pyrimidine (3l)**

Yield: 0.053 g (0.23 mmol, 81%); white solid; mp 78–80 °C; Reaction time: 24 h.
1H NMR (400 MHz, CDCl 3): δ = 7.96 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.02 (d, J = 0.9 Hz, 1 H), 2.43 (s, 3 H), 2.27 (td, J = 8.2, 4.2 Hz, 1 H), 1.27–1.21 (m, 2 H), 1.11 (dq, J = 7.4, 3.8 Hz, 2 H).

13C NMR (126 MHz, CDCl 3): δ = 173.6 (d, J = 13.9 Hz), 171.0 (d, J = 249.3 Hz), 168.3 (d, J = 7.3 Hz), 141.8, 133.5 (d, J = 5.1 Hz), 129.7, 127.3, 98.0 (d, J = 31.7 Hz), 21.5, 18.4, 11.2.

19F NMR (471 MHz, CDCl 3): δ = −62.35.


2-Cyclobutyl-4-fluoro-6-(p-tolyl)pyrimidine (4c)

Reaction time: 48 h.

Yield: 0.065 g (0.27 mmol, 90%); yellow solid; mp 50–51 °C; Rf = 0.30 (PE/EtOAc, 60:1).

1H NMR (400 MHz, CDCl 3): δ = 8.03–7.98 (m, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.08 (d, J = 0.9 Hz, 1 H), 3.87–3.77 (m, 1 H), 2.53 (pd, J = 9.2, 2.4 Hz, 2 H), 2.44 (s, 3 H), 2.49–2.34 (m, 2 H), 2.09 (dp, J = 11.0, 8.9 Hz, 1 H), 2.03–1.92 (m, 1 H).

13C NMR (101 MHz, CDCl 3): δ = 174.4 (d, J = 12.9 Hz), 171.1 (d, J = 249.9 Hz), 168.4 (d, J = 7.3 Hz), 141.9, 133.5 (d, J = 5.2 Hz), 129.7, 127.3, 98.5 (d, J = 31.1 Hz), 42.9, 27.6, 21.5, 18.3.

19F NMR (471 MHz, CDCl 3): δ = −61.81.


2-(Diethoxymethyl)-4-fluoro-6-(p-tolyl)pyrimidine (4d)

Yield: 0.065 g (0.23 mmol, 75%); yellow solid; Rf = 0.2 (PE/EtOAc, 60:1).

1H NMR (400 MHz, CDCl 3): δ = 8.02 (d, J = 8.1 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.24 (s, 1 H), 5.57 (s, 1 H), 3.87 (dq, J = 9.5, 7.0 Hz), 3.75 (dq, J = 9.8, 7.1 Hz, 2 H), 2.44 (s, 3 H), 1.30 (t, J = 7.0 Hz, 6 H).

13C NMR (126 MHz, CDCl 3): δ = 171.4 (d, J = 253.0 Hz), 169.1 (d, J = 7.3 Hz), 166.9 (d, J = 12.4 Hz), 142.3, 132.9 (d, J = 4.5 Hz), 129.8, 127.5, 101.9, 101.0 (d, J = 30.9 Hz), 62.9, 21.6, 15.3.

19F NMR (471 MHz, CDCl 3): δ = −60.05.


2-(Phenoxy)methyl-4-fluoro-6-(p-tolyl)pyrimidine (4e)

Reaction time: 24 h.

Yield: 0.071 g (0.24 mmol, 81%); white solid; mp 55–56 °C; Rf = 0.25 (PE/EtOAc, 60:1).

1H NMR (400 MHz, CDCl 3): δ = 7.97 (d, J = 8.2 Hz, 2 H), 7.35–7.25 (m, 4 H), 7.21 (s, 1 H), 7.08–7.00 (m, 2 H), 7.01–6.94 (m, 1 H), 5.31 (s, 2 H), 2.43 (s, 3 H).

13C NMR (126 MHz, CDCl 3): δ = 171.4 (d, J = 252.6 Hz), 169.2 (d, J = 7.6 Hz), 167.1 (d, J = 13.2 Hz), 158.5, 142.4, 132.8 (d, J = 4.9 Hz), 129.9, 129.5, 127.4, 121.3, 115.1, 100.2 (d, J = 30.6 Hz), 70.3, 21.6.

19F NMR (471 MHz, CDCl 3): δ = −60.32.


4-Fluoro-2,6-di-p-tolylpyrimidine (4f)

Reaction time: 48 h.

Yield: 0.071 g (0.22 mmol, 73%); white solid; mp 90–92 °C; Rf = 0.20 (PE/EtOAc, 80:1).

1H NMR (400 MHz, CDCl 3): δ = 8.60–8.51 (m, 2 H), 8.16–8.08 (m, 2 H), 7.52 (dd, J = 5.2, 2.0 Hz, 3 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.18 (s, 1 H), 2.46 (s, 3 H).

13C NMR (126 MHz, CDCl 3): δ = 171.4 (d, J = 249.2 Hz), 168.7 (d, J = 7.3 Hz), 165.4 (d, J = 14.0 Hz), 142.1, 136.6, 133.4 (d, J = 5.1 Hz), 131.5, 129.8, 128.7, 127.4, 99.1 (d, J = 31.7 Hz), 21.6.

19F NMR (471 MHz, CDCl 3): δ = −61.15.


2-(4-Bromophenyl)-4-fluoro-6-(p-tolyl)pyrimidine (4j)

Yield: 0.099 g (0.29 mmol, 98%); yellow solid; mp 132–133 °C; Rf = 0.20 (PE/EtOAc, 100:1).
4-Fluoro-2-(4-fluorophenyl)-6-(p-toly)pyrimidine (4k)

Yield: 0.069 g (0.24 mmol, 81%); white solid; mp 98–100 °C; \( R_f = 0.20 \) (PE/EtOAc 100:1).

\[ \text{HRMS (ESI): } [M + H]^+ \text{ calcd for C}_{15}H_{12}FN_4: 267.1041; \text{ found: 267.1041.} \]

4-Fluoro-6-(p-toly)-2,2'-bipyrimidine (4o)

Yield: 0.067 g (0.25 mmol, 84%); yellow solid; mp 85–88 °C; \( R_f = 0.15 \) (PE/EtOAc 100:1).

\[ \text{HRMS (ESI): } [M + H]^+ \text{ calcd for C}_{15}H_{12}FN_4O: 357.0942; \text{ found: 357.0942.} \]

Synthesis of 2-[(3-Chlorophenyl)-2-ethyl-6-fluoropyrimidine (0.207 g, 0.8 mmol) reacted with 4-(2-amino)-4H-1,3-benzo[d]imidazole (0.207 g, 2.0 mmol) dissolved in EtOH (20 mL) and the mixture was extracted with CHCl₃ (3 x 20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum by rotary evaporation. The resulting residue was purified by column chromatography (silica gel, CH₂Cl₂/MeOH 7:3) to give the product.

Yield: 0.100 g (0.27 mmol, 31%); yellow solid; mp 85–88 °C; \( R_f = 0.15 \) (CH₂Cl₂/MeOH, 5:1).

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Supporting Information

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