Simple approach to the synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine analogues

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R_1 = aliphatic amine, cycloalkyl amine, benzyl amine and heteroaryl amine

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ABSTRACT

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A simple method for the synthesis of novel 3-fluoro pyrazolo[1,5-a]pyrimidine analogues has been developed starting from fluoro acetonitrile and benzoyl chloride. The desired compounds are synthesized from a 3-amino-4-fluoro pyrazole intermediate. The versatility of the approach was demonstrated by the synthesis of a small library of pyrazolo[1,5-a]pyrimidine.

Keywords:

Pyrazolo[1,5-a]pyrimidine

Pyrazole

Heterocycle

Cyclization

Pyrazolo[1,5-a]pyrimidine¹ analogues have been extensively studied as kinase inhibitors and several compounds have been found active such as the B-Raf kinase inhibitor² **1** or the cyclin dependent kinase inhibitor **2**³ (Figure 1).

In addition, this core has shown inhibitory activity towards other kinases such as Pim. The substitution pattern and the kind of decoration explored, allowed selectivity towards particular kinases. It has been demonstrated that the pyrazolo[1,5-a]pyrimidine scaffold itself interacts with the hinge region of the ATP binding site.⁴

Figure 1. Kinase inhibitors based on pyrazolo[1,5-a]pyrimidine.

In view of previous literature⁵ describing this structure as potential scaffold to develop kinase inhibitor, the synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine was considered. This synthesis fits in our ongoing interest⁶ to explore new heterocycles for drug design project.

Herein, we describe the synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine starting from 3-amino-4-fluoro pyrazole. One of the most common methods for the synthesis of fluorinated pyrazolo[1,5-a]pyrimidine is the fluorination of the scaffold directly by electrophilic fluorination,⁷ using a reagent like 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) also known as Selectfluor **3**⁸ (Scheme 1).

Scheme 1. Electrophilic fluorination of the 7-chloro pyrazolo[1,5-a]pyrimidine.

However, such fluorination method is generally low yielding and has never worked in the case of the 7-chloro pyrazolo[1,5-a]pyrimidine in our hands, in contrast to other halogenations such as iodination.⁹ An alternative procedure was envisioned to avoid this problem i.e. the introduction of the fluorine at an earlier stage. In fact, the synthesis of an intermediate containing a fluorine could be of value for the development of a simple approach to the synthesis of pyrazolo[1,5-a]pyrimidine derivatives and other related heterocycles.

The synthetic scheme started with the synthesis of the 3-amino-4-fluoro pyrazole derivative¹⁰ **6** by using fluoro acetonitrile **4** as the starting material. An acylation reaction was performed at low temperature with LiHMDS as the base to afford

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the intermediate α -fluoro- β -ketonitrile **5** which was used without further purification in the next step.

The hydrazinolysis of **5** in ethanol to obtain the 3-amino-4-fluoro pyrazole **6** is straightforward. The formation¹¹ of the 3-fluoro pyrazolo[1,5-a]pyrimidine scaffold was realized by condensation of **6** with diethyl ethoxymethylenemalonate in acetic acid at 100°C for 10h to afford the pyrazolo[1,5-a]pyrimidine **7** in good yield, which after saponification with sodium hydroxide gave **8**. A final decarboxylation with Dowtherm A at 230°C for 5h, led to the desired intermediate **9**^{12, 13} (Scheme 2).

Intermediate **9** was treated in refluxing phosphorus oxychloride to give the chlorinated derivative **10** which was subjected to nucleophilic substitution with different amines to obtain compound **11**¹⁴ (Scheme 3). The versatility of this approach was demonstrated by the synthesis of a small-size library as shown in table 1.

The amines used during the last step varied from aliphatic amines, cycloalkyl amines, benzyl amines to heteroaryl amines. The 3-amino-4-fluoro pyrazole **6** has also been condensed with (hetero)aryl dimethylamino propenone **13** (obtained from acetophenone derivatives **12**) in refluxing acetic acid to obtain 3-fluoro-7-(hetero)aryl-2-phenyl-pyrazolo[1,5-a]pyrimidine derivatives **14**¹⁵ (Scheme 4).

Table 1. Synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine derivatives **11** and **14**.

Entry	Product	Yield (%)
a	 11a	70
b	 11b	63
c	 11c	65
d	 11d	60
e	 11e	58
f	 11f	68
g	 11g	58
h	 11h	55
i	 14a	50
j	 14b	42

Scheme 4. Synthesis of 3-fluoro-7-(hetero)aryl-2-phenyl pyrazolo[1,5-a]pyrimidine derivatives.

In conclusion, we have elaborated a simple approach for the synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine derivatives by introducing the fluorine at an earlier stage of the synthesis instead of using a direct electrophilic fluorination on the pyrazolo[1,5-a]pyrimidine. The method could be employed to the development of a small-size library of “drug-like” compounds with different amines. In a first screening assay, compound **11h** showed 71% of inhibition at 10 μ M towards the TGF- β receptor II. The further biological evaluation of the fluorinated pyrazolo[1,5-a]pyrimidines obtained in these experiments is ongoing.

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- Representative procedure for 6:** A 1M solution of LiHMDS in THF (29.4 mL, 29.4 mmol, 2.0 equiv) was added dropwise to a solution of benzoyl chloride (1.7 mL, 14.68 mmol, 1.0 equiv) and fluoroacetonitrile **4** (0.82 mL, 14.68 mmol, 1.0 equiv) in dry THF (15 mL) cooled to -78 °C under nitrogen. The mixture was allowed to reach room temperature after 5h of reaction and quenched with a saturated solution of ammonium chloride. The mixture was concentrated under reduced pressure to afford the desired α -fluoro- β -ketonitrile **5** in a form pure enough for the next step. Hydrazine hydrate (64% in water) (1.4 mL, 29.4 mmol, 2.0 equiv) was added to a solution of the α -fluoro- β -ketonitrile **5** (14.68 mmol) in ethanol (20 mL), and the reaction was heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with water. The organic phase was concentrated to give a crude product, flash column chromatography on silica gel (ethyl acetate/hexane 90:10) afforded the desired product **6** as a beige powder (1.3 g, 50%); mp 115-118°C; ¹H NMR (500 MHz, DMSO-d₆): δ 11.92 (br. s, 1H), 7.66 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 4.77 (br. s, 2H); ¹³C NMR (125 MHz, DMSO-d₆): δ 143.3, 135.9, 134.3, 129.0, 127.9, 126.2, 124.7. ¹⁹F NMR (470 MHz, DMSO-d₆): δ -186.5. HRMS calcd for C₉H₈FN₃ (M+H)⁺: 178.0775, found: 178.0778.
- Representative procedure for 9:** To the carboxylic acid **8** (1 g, 3.66 mmol) was added Dowtherm A (10 mL). The suspension was heated to 230 °C for 5h. The reaction mixture was cooled to room temperature, then diluted with hexanes (30 mL), stirred vigorously, filtered, and dried to obtain the desired product **9** as a light brown powder (0.68 g, 82%); mp 205-208°C; ¹H NMR (500 MHz, DMSO-d₆): δ 7.97 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 5.9 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 5.48 (d, J = 5.9 Hz, 1H); ¹³C NMR (125 MHz, DMSO-d₆): δ 157.2, 148.0, 136.9, 131.8, 131.7, 128.8, 128.3, 126.5, 92.8. HRMS calcd for C₁₂H₈FN₃O (M+H)⁺: 230.0724, found: 230.0725.
- Representative procedure for 11a:** To a solution of **10** (100 mg, 0.4 mmol, 1.0 equiv) in ethanol (10 mL) was added a solution of 70% ethylamine (70% in water) (48 μ L, 0.6 mmol, 1.5 equiv), followed by triethylamine (83 μ L, 0.6 mmol, 1.5 equiv) at room temperature. The reaction mixture was refluxed for 16h and after completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature. Dichloromethane was added and the organic phase was then washed two times with a saturated solution of NaHCO₃, and one time with brine. It was then dried over Na₂SO₄, and concentrated in vacuo. Flash column chromatography on silica gel (ethyl acetate/hexane 75:25) afforded the desired product **11a** as a white powder (72 mg, 70%); mp 212-216°C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.16 (d, J = 5.3 Hz, 1H), 8.13 (t, J = 5.8 Hz, 1H), 8.04 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.5 Hz, 1H), 6.22 (d, J = 5.3 Hz, 1H), 3.48 (m, 2H), 1.26 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-d₆): δ 149.8, 146.0, 138.7, 136.9, 135.1, 133.5, 130.6, 129.1, 126.7, 85.5, 36.6, 14.2. HRMS calcd for C₁₄H₁₃FN₄ (M+H)⁺: 257.1197, found: 257.1195.
- Representative procedure for 14b:** To a solution of 3-amino-4-fluoropyrazole **6** (150 mg, 0.85 mmol, 1 equiv) in acetic acid (5 mL) at room temperature was added 2-thienyl dimethylamino propenone (170 mg, 0.94 mmol, 1.1 equiv). The mixture was refluxed for 16h. The suspension was filtered warm, then washed several times with ethanol and dried to obtain the desired product **14b** as a yellow powder (105 mg, 42%); mp 233-237°C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.61 (d, J = 4.6 Hz, 1H), 8.59 (d, J = 3.8 Hz, 1H), 8.18 (d, J = 5.0 Hz, 1H), 8.13 (d, J = 7.7 Hz, 2H), 7.82 (d, J = 4.6 Hz, 1H), 7.62 (t, J = 7.7 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 4.8 Hz, 1H); ¹³C NMR (125 MHz, DMSO-d₆): δ 149.0, 139.2, 138.6, 136.2, 135.0, 134.2, 132.5, 130.0, 129.6, 129.3, 129.2, 127.8, 126.6, 104.6. HRMS calcd for C₁₆H₁₀FN₃S (M+H)⁺: 296.0652, found: 296.0659.

Graphical abstract- Simple approach to the synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine analogues.

Figure 1. Kinase inhibitors based on pyrazolo[1,5-a]pyrimidine.

Scheme 1. Electrophilic fluorination of the 7-chloro pyrazolo[1,5-a]pyrimidine.

Scheme 2. Synthesis of 3-fluoro-7-hydroxy-2-phenyl pyrazolo[1,5-a]pyrimidine.

Scheme 3. Synthesis of 3-fluoro pyrazolo[1,5-a]pyrimidine derivatives.

Scheme 4. Synthesis of 3-fluoro-7-(hetero)aryl-2-phenyl pyrazolo[1,5-a]pyrimidine derivatives.