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An efficient access to 3,6-disubstituted 1*H*-pyrazolo[3,4-*b*]pyridines via a one-pot double S_NAr reaction and pyrazole formation

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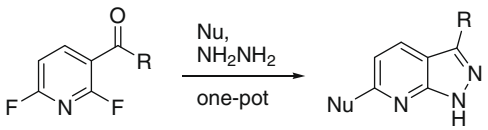
ABSTRACT

A general and efficient synthetic method for the synthesis of biologically important series of 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines was discovered. 2,6-Difluoropyridine was deprotonated using 1.1 equiv of *n*-BuLi in THF at <−60 °C, followed by quenching with a variety of Weinreb amides to generate 2,6-Difluoro-3-ketopyridines in high yields. A mild tandem reaction sequence of selective nucleophilic substitution of the 6-fluoride with a variety of nucleophiles, followed by hydrazine substitution of the 2-fluoride and pyrazole formation in a one-pot fashion afforded a series of 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines in moderate to good yields.

Substituted pyrazolo[3,4-*b*]pyridines represent an important class of heterocycles due to their well-documented biological activity.[1] We were particularly interested in the synthesis of 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines due to their potent antiviral activity on the inhibition of non-nucleoside reverse transcriptase.[2] Despite continuing interest in these heterocycles, to date a few published methods for the synthesis of this class of 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines required harsh conditions and a four-step sequence starting from commercially available 2,6-difluoropyridine in low overall yield.[3] In our search for a practical and mild synthesis of 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines, we reasoned that the desired compounds could be assembled in a one-pot protocol from 2,6-difluoro-3-ketopyridines via a selective double S_NAr reaction followed by pyrazole formation (Scheme 1). Herein, we report our efforts to accomplish the described set of chemical transformations.

The first step was to generate lithiated 2,6-difluoropyridine and to convert the 3-lithiated species into a variety of 2,6-difluoro-3-ketopyridines. It is well known that *ortho* lithiation of 2-fluoropyridine and 2,6-difluoropyridine can be performed using either LDA,[4] or LiTMP.[5] Stronger bases such as *n*-BuLi are known to add to the pyridine ring, even at very low temperature.[6] However, given the cost benefit and convenience of using *n*-BuLi alone, it was worth re-examining the deprotonation of 2,6-difluoropyridine with *n*-BuLi. Thus, to a THF solution of 2,6-difluoropyridine was slowly added 1.1 equiv of 1.6 M *n*-BuLi in hexane through a syringe pump while maintaining an internal temperature below −60 °C. After the addition was complete, the reaction mixture was stirred at −78 °C for 0.5 h resulting in the formation of an orange slurry of the lithiate. Precooled (−55 °C) solution of the Weinreb amide **1a**[7] was quickly added to the lithiated 2,6-difluoropyridine slurry through a cannula. The reaction mixture was then stirred at −60 °C for 1 h. To our delight, the desired product 2,6-difluoro-3-benzothiophenoyl-pyridine **2a** was isolated in 93% yield (Table 1, entry 1).[8] Inspired by this successful transformation, the 3-lithiated-2,6-difluoropyridine intermediate was trapped with a variety of aromatic Weinreb amides **1b–j**, including those with a simple phenyl ring (entry 2), halogen-substituted aromatic rings (entries 1, 3, 6, and 9), electron rich aromatics (entries 4, 7, and 8), an electron deficient aromatic (entry 5), and a furanyl group (entry 10) to produce the corresponding 2,6-difluoro-3-ketopyridines **2a–j** in good to excellent yields. The 3-lithiated-2,6-difluoropyridine also reacted with an aliphatic Weinreb amide (entry 11) to generate the corresponding 2,6-difluoro-3-acetoxypyridine in a moderate yield without further optimization.



Scheme 1.

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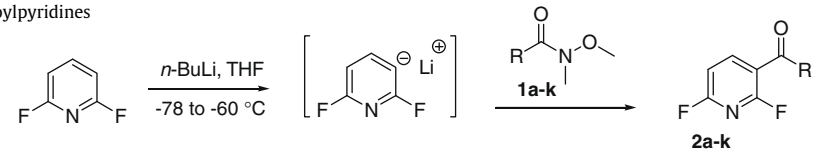
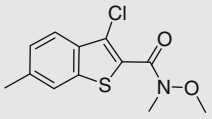
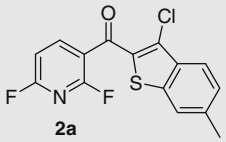
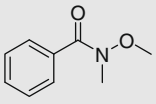
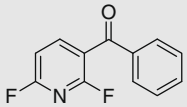
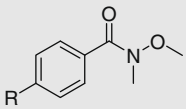
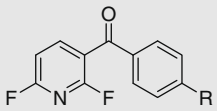
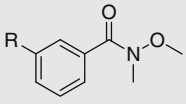
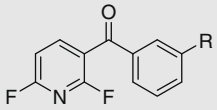
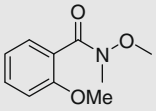
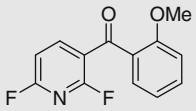
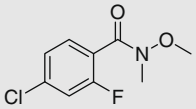
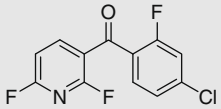
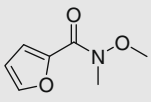
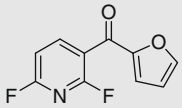
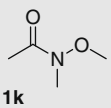
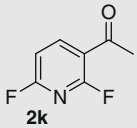
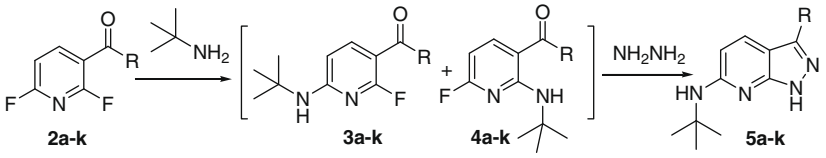
Table 1
Preparation of 2,6-difluoro-3-benzoylpyridines

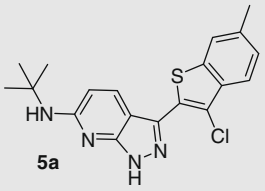
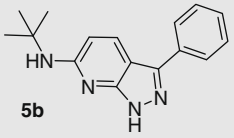
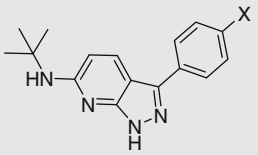
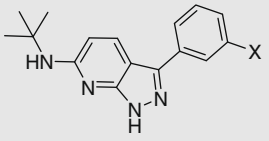
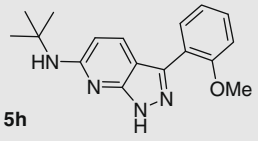
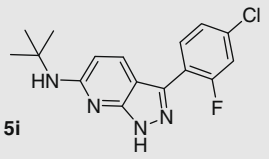
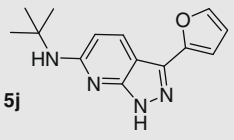
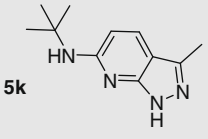


Entries	Substrates (**1a**–**k**)	Products (**2a**–**k**)	Isolated yields (%)
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	93
3			92
4			97
5			96
6			98
7			92
8	 **1h**	 **2h**	93
9	 **1i**	 **2i**	70
10	 **1j**	 **2j**	83
11	 **1k**	 **2k**	50

With the desired 2,6-difluoro-3-substituted-benzoyl-pyridines in hand, a one-pot synthesis of 3,6-substituted-1*H*-pyrazolo[3,4-*b*]pyridines was examined (Table 2). Selective replacement of the 6-fluorine with nucleophiles, followed by displacement of the 2-fluoride by hydrazine and then closure of the pyrazole ring would lead to the desired products. Our initial studies began with selective substitution of compound **2a** with *tert*-butylamine.[9] Acceleration of S_NAr reactions by using aprotic solvents is well known. Thus, treatment of compound **2a** with *tert*-butylamine in *N,N*-dimethylacetoamide (DMAc) at 0–5 °C afforded a clean reaction to a mixture of 6-*tert*-butylamino-2-fluoro-3-benzothiophenoyl-pyridine **3a** and 2-*tert*-butylamino-6-fluoro-3-benzothiophenoyl-pyridine **4a** in a 4:1 ratio, as determined by ^{1}H NMR spectroscopy. A similar outcome was observed when the reaction was run in DMF, NMP, and DMSO. In a reversal of selectivity, **4a** was the major product when the reaction was performed in EtOAc, MTBE, and THF. A highly selective formation of **4a** was found in toluene (**4a**:**3a** = 16.7:1). A lower ratio of **3a**:**4a** was obtained when

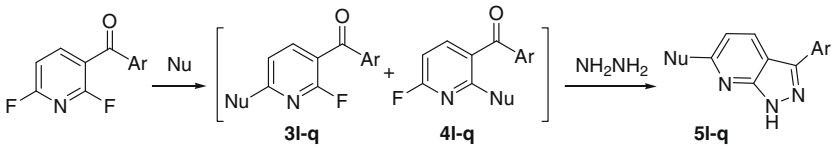
Table 2
Synthesis of 6-*tert*-butylamino-1*H*-pyrazolo[3,4-*b*]pyridines via a one-pot double S_NAr reaction/pyrazole formation

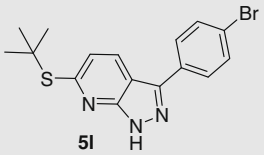
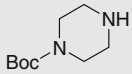
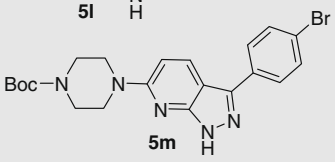
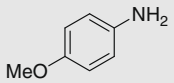
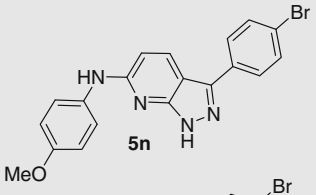
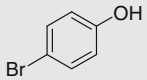
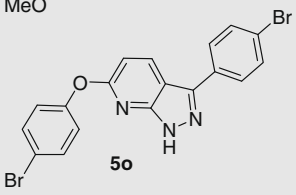
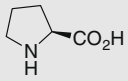
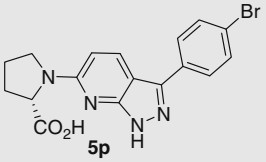
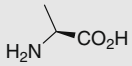
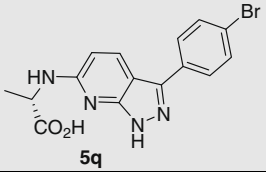


Entries	Substrates	**3a–k**/**4a–k** Ratio	Products (**5a–k**)	Isolated yields (%)
1	**2a**	4.0:1	 **5a**	77
2	**2b**	2.0:1	 **5b**	67
3	**2c**	2.3:1		70
4	**2d**	1.1:1		51
5	**2e**	4.1:1		80
6	**2f**	2.9:1		73
7	**2g**	2.0:1		61
8	**2h**	3.2:1	 **5h**	75
9	**2i**	5.3:1	 **5i**	84
10	**2j**	2.0:1	 **5j**	65
11	**2k**	8.6:1	 **5k**	69

the reaction was run at higher temperature. A rationale for this solvent dependence can be tentatively proposed based on hydrogen-bonding effects. In non-polar solvents (e.g., toluene), hydrogen-bonding between the carbonyl group and the incoming amine nucleophile can direct the substitution reaction to the more sterically hindered C-2 site. In polar solvents (e.g., DMAc) this interaction is disfavored due to preferential hydrogen-bonding between the amine and the solvent, which in turn generates an effectively

Table 3
Synthesis of 3, 6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines via a one-pot double S_NAr reaction/pyrazole formation



Entries	Nu	**3c**/**4c** ratio	Products	Isolated yields (%)
1		19:1	 **5l**	91
2		3.2:1	 **5m**	75
3		1.5:1	 **5n**	59
4		20:1	 **5o**	84
5		1.2:1	 **5p**	43
6		1.7:1	 **5q**	55

larger solvated nucleophile, factors which together lead to selective substitution at the less hindered C-6 position.

Employing the above protocol, a variety of 2,6-difluoro-3-keto-pyridines **2b**–**k** could be selectively converted to 6-*tert*-butylamino-2-fluoro-3-keto-pyridines **3a**–**k**. Functional groups such as bromo, chloro, fluoro, methoxy, nitro, furanyl, and benzothiophenyl were well tolerated under the reaction conditions. Interestingly, besides the solvent effects discussed above, both the electronic and steric properties significantly affected the regioselectivity of the initial displacement. An electron-donating group at the *para*-position (entry 4, X = OMe) decreased the ratio of **3d** and **4d**, wherein electron-withdrawing substituents (entries 1, 5, and 9) favored formation of 6-substituted intermediates (**3a**, **3e**, **3i**) over the 2-substituted intermediates (**4a**, **4e**, **4i**). Substitution at the *ortho*-position with electron-donating functional groups (entry 8) and electron-withdrawing groups (entries 1 and 9) significantly increased the percentage of desired intermediates (**3a**, **3h**, and **3i**), presumably due to steric effects.

After full conversion of the starting materials **2a**–**k** to the intermediates **3a**–**k** and **4a**–**k**, hydrazine monohydrate[10] was slowly added to the reaction mixture at 0–5 °C, and then warmed to room temperature to afford 6-*tert*-butylamino-3-aryl-1*H*-pyrazolo[3,4-*b*]pyridines **5a**–**k** in 51–84% overall yield as a one-pot procedure starting from **2a**–**k** (Table 2).[11] The second SNAr substitution of the 2-fluorine by hydrazine and the pyrazole formation were achieved in very mild conditions (0 °C to rt) in nearly quantitative yields by HPLC analysis.

To further demonstrate the utility of this one-pot protocol, selective substitution of the 6-fluorine of 2,6-difluoro-3-substitutedbenzoyl-pyridines was investigated using different nucleophiles followed by hydrazine substitution of the 2-fluorine and pyrazole formation. As shown in the Table 3, reaction of compound **2c** with *tert*-butyl thiol (entry 1) or phenol (entry 4) afforded excellent regioselective substitution of the 6-fluorine, giving a high overall yield for the one-pot transformation. Reaction with a secondary amine (entry 2) or an aniline (entry 3) also proceeded

smoothly. Addition of amino acids (entries 5 and 6) also proved efficient, generating the corresponding pyrazoles in moderate yields.[12]

In summary, the 2,6-difluoro-3-ketopyridines were generated in high yields through a cost-effective and convenient protocol involving deprotonation of 2,6-difluoropyridine using *n*-butyllithium, followed by quenching with a variety of Weinreb amides. A series of 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines could then be efficiently prepared from the 2,6-difluoro-3-ketopyridines in moderate to good yields by a tandem reaction sequence of selective nucleophilic substitution of the 6-fluoride, followed by hydrazine substitution of the 2-fluoride and pyrazole formation in a one-pot fashion at very mild conditions (0 °C to room temperature). This process could be performed with a variety of nitrogen-, oxygen- and sulfur-containing nucleophiles. The high chemo- and regioselectivities observed in these reactions, the high yields after multiple bond forming steps, and mild reaction conditions employed make this process broadly applicable to the synthesis of the 3,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines both in academy and industry.

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8. General procedure for the preparation of 2,6-difluoro-3-ketopyridines **2**. To a 250 mL three-necked round-bottomed flask, equipped with an overhead stirrer, thermocouple, and nitrogen inlet, was charged 2,6-difluoropyridine (20.0 mmol), and dry THF (28 mL). The solution was cooled to about −70 °C. *n*-butyllithium (2.5 M) in hexane solution (22.0 mmol) was slowly added through a syringe pump at <−60 °C over 0.5 h. After complete addition of the butyllithium, the resulting mixture was stirred at −65 °C for 1 h. Weinreb's amide **1a**–**k** (20.0 mmol) in THF (10 mL) solution, which was pre-cooled to −55 °C, was quickly charged through a cannula without stopping. The resulting reaction mixture was stirred at −60 °C for 1 h to go to completion. The reaction mixture was reversely quenched to a solution of 5 N HCl/THF (2:1, 25 mL) at −15 to −5 °C. The mixture was extracted by MTBE (30 mL). After phase separation, the organic layer was washed with water (20 mL), and concentrated. The resulting solid was recrystallized from MTBE/heptane to afford desired 2,6-difluoro-3-ketopyridines **2**. Selected example **2a** was isolated as a colorless crystalline solid, mp 99.2–100.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (m, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.00 (dd, J = 8.0, 4.0 Hz, 1H), 2.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.0 (d, J = 4 Hz), 162.9 (dd, J = 252 Hz, 14 Hz), 158.6 (dd, J = 252, 15 Hz), 145.6 (dd, J = 9, 3 Hz), 145.5, 140.0, 135.0, 134.0, 127.9, 126.5, 124.0, 122.6, 119.4 (dd, J = 27, 6 Hz), 106.9 (dd, J = 35, 6 Hz), 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −61.5 (d, J = 9 Hz), −64.5 (d, J = 9 Hz). HRMS (ESI) calculated for $C_{15}H_8ClF_2NOS$ $(M+H)^+$ 324.0062, found 324.0046.
9. Methylamine substitution of 2,6-difluoropyridine-3-carboxylic esters gave a mixture of methyl 2-fluoro-6-methylaminopyridine-3-carboxylate and methyl-6-fluoro-2-methylaminopyridine-3-carboxylate in a ratio of 1.8:1–1:3 depending on the solvent used. Please see: (a) Hirokawa, Y.; Horikawa, T.; Kato, S. *Chem. Pharm. Bull.* **2000**, *48*, 1847; (b) Hirokawa, Y.; Yoshida, N.; Kato, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1551; (c) Hirokawa, Y.; Fujiwara, I.; Suzuki, K.; Harada, H.; Yoshikawa, T.; Yoshida, N.; Kato, S. *J. Med. Chem.* **2003**, *46*, 702.
10. 35 wt% of hydrazine aqueous also worked well.
11. The 6-*N*-*tert*-butyl group of 6-*tert*-butylamino-3-substituted-1*H*-pyrazolo[3,4-*b*]pyridines **5a**–**k** could be easily removed to generate the corresponding 6-amino-3-substituted-1*H*-pyrazolo[3,4-*b*]pyridines by TFA treatment. Please see: Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554.
12. General procedure for the preparation of 3,6-disubstituted-1*H*-Pyrazolo[3,4-*b*]pyridines **5**. To a solution of 2,6-difluoro-3-ketopyridine (3.00 mmol) in DMAc (5 mL) was slowly added nucleophile (9.00 mmol) at 0–5 °C (exothermic), and stirred at the same temperature for 0.5–3 h. Then, hydrazine monohydrate (12.0 mmol) was slowly added at 0–5 °C (exothermic). After complete addition, the reaction mixture was stirred at 0–5 °C for 1 h, and at rt for 1–5 h. The reaction mixture was cooled to 0 °C, and adjusted to pH 5 by 5 N sulfuric acid at <20 °C. Water (10 mL) and EtOAc (10 mL) were charged, respectively. After phase separation, the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 10:1, 5:1) to afford desired product 3,6-dibstituted-1*H*-pyrazolo[3,4-*b*]pyridines **5**. Selected example **5a** was isolated as an off-white crystalline solid, m.p. 203.8–203.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.95 (br s, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.62 (s, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 6.31 (d, J = 8.0 Hz, 1 H), 4.79 (s, 1 H), 2.50 (s, 3 H), 1.53 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 152.8, 137.9, 137.7, 135.8, 135.4, 131.5, 128.7, 126.7, 122.2, 121.8, 117.5, 108.1, 105.7, 51.7, 29.2, 21.6.