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A facile method for the synthesis of substituted pyrazolo[3,4-*c*]pyridines

Sharad K. Verma *, Louis V. LaFrance

Medicinal Chemistry, Oncology Research and Development, GlaxoSmithKline, 1250 S. Collegeville Road, Collegeville, PA 19426, United States

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ABSTRACT

Methods for a facile high-yielding synthesis of substituted pyrazolo[3,4-*c*]pyridines from 2-bromo-5-fluoropyridine are described, along with a brief mechanistic discussion for the key cyclization step. The methods utilize inexpensive commercially available starting materials and unlike previous methods, are more suitable for SAR work and scale-up.

1. Introduction

The pyrazolo[3,4-*c*]pyridine group is present in compounds of biological interest. For example, modified 4-deaza analogs of formycins have been investigated as potential nucleoside antibiotics,[1,2] and compound **1** was recently reported as a potent anti-cancer agent (Figure 1).[3] However, despite the value of the pyrazolo-[3,4-*c*]pyridine group, an efficient, high-yielding synthesis is still required. The standard method entails application of the Huisgen indazole synthesis to functionalized pyridines, as first reported by Chapman and Hurst.[4] Unfortunately, this method is not optimal for structure–activity relationship (SAR) work due to poor versatility, scalability, and low overall yields. A very creative approach was recently reported by Heller, wherein the pyrazolo[3,4-*c*]pyridine scaffold could be prepared in good to moderate yields via Ni/Zn (or Pd) catalyzed annulation of alkynes with tert-butyl 4-iodopyrazolocarboximines.[5] However, this method is not totally regioselective, involves expensive catalysts, and scalability has not been established.

As part of a medicinal chemistry research program, we required a robust synthesis of the pyrazolo[3,4-*c*]pyridine group. Herein we report a practical, high yielding, and scalable method for the preparation of this group from inexpensive commercially available starting materials.

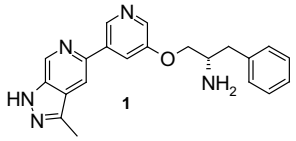
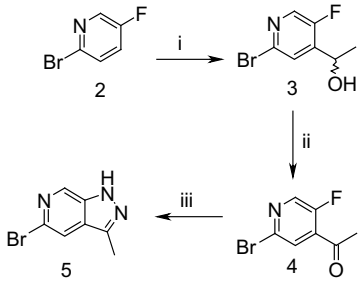


Figure 1.

The reaction of 2-fluoro-acetophenones with hydrazine has been reported for the preparation of indazoles.[6]. Based on this precedent, we reasoned that the pyrazolo[3,4-*c*]pyridine scaffold should be accessible from an appropriately functionalized fluoro-acetylpyridine, which in turn might be prepared from the corresponding fluoropyridine. To this end, commercially available 2-bromo-5-fluoropyridine **2** was treated with LDA according to the method of Queguiner, to effect a chemo- and regioselective lithiation reaction (Scheme 1).[7] Quenching the intermediate lithio species with acetaldehyde furnished substituted pyridine alcohol **3** in 86% yield.[8] Oxidation of alcohol **3** yielded the desired 2-bromo-5-fluoro-acetylpyridine **4** in 88% yield.[9,10] Reaction of **4** with a slight excess of hydrazine in ethylene glycol furnished compound **5** in 99% yield. The product obtained following workup was of sufficiently high purity such that no additional purification was required. The bromo group of this product provides a handle for diversification, thereby making the core amenable for SAR work.

This method was further extended to the synthesis of the 3-substituted pyrazolo[3,4-*c*]pyridines **6–8**. In each case, treatment of the anion of **2** with the appropriate aldehyde followed by oxidation led to ketone products suitable for reaction with hydrazine in ethlyene glycol (i.e., Scheme 1, step iii).[11] The reactions involving



Scheme 1. Reaction conditions: (i) (1) LDA, THF, −78 °C to 0 °C, 4 h; (2) acetaldehyde, warm to rt, 86%; (ii) MnO_2, $CHCl_3$, 95 °C, 2.5 h (sealed flask), 88%; (iii) anhyd hydrazine, ethylene glycol, 165 °C, 3.5 h (sealed flask), 99%.

* Corresponding author. Tel.: +1 610 917 7948.
E-mail address: sharad.k.verma@gsk.com (S. K. Verma).

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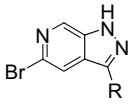
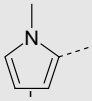
Table 1



Compd	Structure (R=)	% Yield[a]	% Yield from **2**
5	$-CH_3$	99	75
6[b]		60	48
7[b]		90	77
8[b]		86	78
9		0	0[c]

[a] Isolated yield using sealed flask conditions.
[b] For workup and isolation of **6**–**8**, see Ref. 12.
[c] See Ref. 11.

hydrazine in ethylene glycol proceeded in typically good yields, and products were obtained from **2** in good overall yields (Table 1).[12] However, the hydrazine-mediated cyclization reaction was not successful for the synthesis of **9** (R = furan) from its corresponding ketone precursor. For this example, multiple products were observed by both TLC and LC/MS.[13] Only a trace amount of a mass ion consistent with **9** was observed by LC/MS, and this product was not isolated. The exact reasons for this observation are unknown. This result would suggest that the scope of the hydrazine-mediated cyclization reaction has some limitation.

Although the cyclization of **4** to **5** proceeds to completion in 3.5 h on heating in a sealed flask, it can also be conducted under standard reflux conditions, albeit with a significantly longer reaction time. For example, heating **4** with hydrazine-dihydrochloride in ethylene glycol for 60 h under standard reflux conditions, gave **5** in 65% yield.[14] These conditions were applied to a successful scale-up campaign for the synthesis of over 250 g compound **5** from **2**. We recommend using the standard reflux conditions for larger scale reactions (>20 g).

We propose that the conversion of the functionalized pyridines to pyrazolo[3,4-*c*]pyridine**s** proceeds by way of an intermediary hydrazone, which then undergoes in situ cyclization to furnish the desired pyrazolo[3,4-*c*]pyridine scaffold (Fig. 2). This sequence of events is based on observations made during careful reaction monitoring by LC/MS. Early in the reaction, we observed a gradual increase in an intermediate which had a mass ion consistent with the proposed hydrazone, with concominant decrease in the starting material. Subsequently, we observed a decrease in the putative hydrazone intermediate, with a concominant increase in the mass of the desired product.

In summary, we have described a robust, high-yielding route to substituted pyrazolo[3,4-*c*]pyridines. The method starts from inexpensive, commercially available starting materials, allows for convenient incorporation of diversity at the 3-position, and is suitable for scale-up, as illustrated by the preparation of over 250 g of compound **5**. Although some limitations have already been identified, we believe the desirable features of this methodology more than compensate, and will facilitate the further use of the pyrazole[3,4-*c*]pyridine group in drug discovery efforts.

2. Representative procedure (compound 5)

2.1. 1-(2-Bromo-5-fluoro-4-pyridinyl)ethanol (3)

To a 1000 mL 3-neck flask was added THF (200 mL) with cooling to −20 °C, followed by dropwise addition of *n*-BuLi (20.0 mL, 50 mmol, 2.5 M in hexanes). After stirring for 5 min, diisopropylamine (7.0 mL, 50 mmol) was added dropwise via syringe, and the mixture stirred with warming to 0 °C for 1 h. The contents were cooled to −78 °C and a 20 mL THF solution of 2-bromo-5-fluoropyridine (8.80 g, 50 mmol) was added via addition funnel. After stirring at −78 °C for 4 h, acetaldehyde (3.1 mL, 55 mmol) was added dropwise via syringe. The contents were removed from the cold bath and stirred with warming to room temperature overnight. The mixture was diluted with H_2O (150 mL), and vigorously stirred for 5 min. The contents were extracted with ethyl ether (3 × 150 mL), the combined organic layers dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was passed through a short silica column (eluent: 3:1 hexanes/EtOAc) to afford the title compound as a white solid (9.5 g, 86%). ^{1}H NMR: (CD_3OD-d_4) δ8.21 (d, *J* = 3 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 5.06–5.11 (m, 1H), 1.45–1.47 (d, *J* = 8 Hz, 3H); LC/MS (MH+) = 219.8, 221.9.

2.2. 1-(2-Bromo-5-fluoro-4-pyridinyl)ethanone (4)

To a 350 mL sealed flask was dissolved 1-(2-bromo-5-fluoro-4-pyridinyl)ethanol (9.4 g, 42.3 mmol) in 60 mL dry $CHCl_3$. Added next to the stirring solution was manganese(IV)oxide (14.7 g, 169 mmol). The vigorously stirring contents were sealed and heated at 95 °C for 2.5 h. After cooling to room temperature, the black heterogenous mixture was vacuum filtered through a pad of Celite, and the filter pad washed with CH_2Cl_2 (10 mL). The yellow colored filtrate was concentrated in vacuo to a yellow oil, which was purified by silica gel column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the final product as a pale yellow oil (8.2 g, 88%) ^{1}H NMR: (DMSO-d_6) δ 8.66, 7.92 (d, *J* = 8 Hz, 1H), 2.62 (s, 3H); LC/MS (MH+) = 217.9, 219.8. *Note*: Di-methyl ketal is observed if CD_3OD is used as NMR solvent.

2.3. 5-Bromo-3-methyl-1*H*-pyrazolo[3,4-*c*]pyridine (5)

To a 150 mL sealed flask containing 50 mL dry ethylene glycol was dissolved 1-(2-bromo-5-fluoro-4-pyridinyl)ethanone (8.2 g, 37.6 mmol). Added next was anhydrous hydrazine (1.24 mL, 39.5 mmol) dropwise via syringe. The stirring light yellow mixture was sealed, and heated at 165 °C. After 3.5 h, the orange-tan reaction mixture was removed from heating. After cooling to room temperature, the contents were poured onto a stirring mixture of 300 g ice/water (1:1), wherein solid precipitation occurred. After

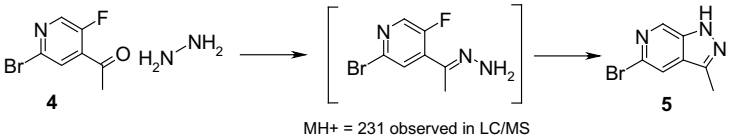


Figure 2.

stirring for 10 min, the off-white precipitate was collected. This solid was dried in vacuo and collected as an off-white solid (7.9 g, 99%). ^{1}H NMR: (CD_3OD-d_4) δ 8.74 (s, 1H), 7.98 (s, 1H), 2.58 (s, 3H); LC/MS (MH+) = 211.7, 213.7.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.013.

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8. The regiochemistry of **3** was verified by 2D NMR.
9. Attempts to treat the lithiated pyridine of **2** with acetyl chloride instead of acetaldehyde to directly access **4** were unsuccessful, giving only complex mixtures.
10. When conducting oxidations on larger scale (>20 g), IBX in refluxing EtOAc (24 h) was found to be a superior choice of oxidizing condition.
11. The lithiation-trapping-oxidation sequence leading to the synthesis of the ketone precursors of **6**–**9** proceeded in >90% yield for each step. The oxidation reactions were conducted using Dess–Martin reagent.
12. For the synthesis of products **6**–**8** via hydrazine-mediated cyclization in ethylene glycol, the following workup procedure was used for product isolation: after equilibration to room temperature, reaction mixtures were diluted with 200 mL saturated aqueous NH_4Cl, and extracted with 1:9 THF/EtOAc (2 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrates concentrated in vacuo. The products were dried in a vacuum oven at 45 °C for 24 h to afford the respective products as tan solids. The lower yield of product **6** is attributed to its poor solubility in the extraction solvent.
13. For the attempted synthesis of **9**, the reaction mixture turned nearly black during heating. TLC analysis of the reaction mixture showed streaking, and LC/MS analysis indicated several product peaks.
14. Hydrazine dihydrochloride was used as an alternative to anhydrous hydrazine for the larger scale reactions.