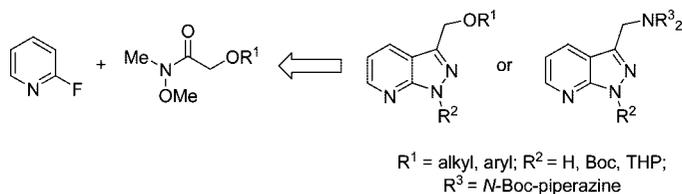# Expedient Synthesis of 3-Alkoxymethyl- and 3-Aminomethyl-Pyrazolo[3,4-*b*]pyridines

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R^1 = alkyl, aryl; R^2 = H, Boc, THP;
R^3 = *N*-Boc-piperazine

An effective strategy has been developed for the preparation of 3-alkoxymethyl-pyrazolo[3,4-*b*]pyridines, compounds that are currently not readily accessible by existing synthetic methods. Further manipulation of these compounds allows for access to 3-alkoxymethyl-pyrazolo[3,4-*b*]pyridines with a variety of substitution patterns as well as 3-aminomethyl-pyrazolo[3,4-*b*]pyridines.

1. Introduction

The pyrazolo[3,4-*b*]pyridine ring system (**1**) represents the core skeleton of a pharmaceutically important class of heterocyclic compounds possessing a broad range of biological activities. The synthesis of pyrazolo[3,4-*b*]pyridines of general type **1** has attracted a wealth of interest due to their structural analogy to purine bases, an important constituent of DNA and RNA nucleosides.[1] These compounds have been shown to be effective antimicrobial,[2] antiviral,[3] anti-inflammatory,[4] anxiolytic,[5] hypoglycemic[6] and antitumor agents[7] as well as serotonin reuptake inhibitors,[8] CCK agonists[9] and vasodilators.[10] To date, two distinct synthetic routes have been developed to

R_1 = COMe, COAr, CO_2Me, CN
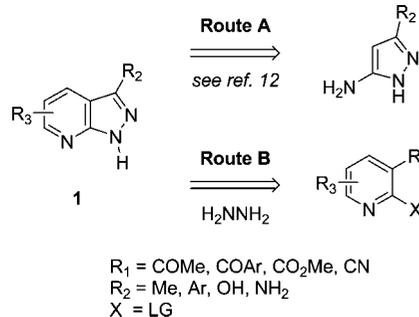R_2 = Me, Ar, OH, NH_2
X = LG

FIGURE 1. Synthetic routes to pyrazolo[3,4-*b*]pyridines.

access pyrazolo[3,4-*b*]pyridines of the general type **1** (Figure 1).[11] One involves appending the pyridine ring to a 5-aminopyrazole (Route A)[2,4a,5,7,10,12] while the other involves formation

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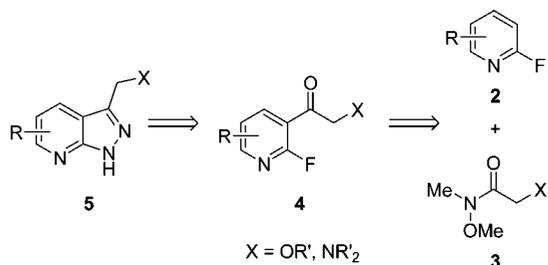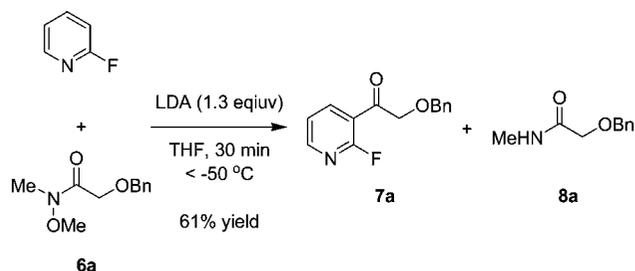
FIGURE 2. Proposed Synthesis of 3-substituted pyrazolo[3,4-*b*]pyridines.

SCHEME 1

SCHEME 2

of the pyrazole ring from a 3-acetyl,[3,4b,8,9,12a,13] 3-carboxy,[2] or 3-cyanopyridine[14] bearing a leaving group in the 2-position (Route B). While Route A is the most commonly employed protocol and offers a degree of flexibility in terms of substitution about the pyridine ring, harsh reaction conditions are often required for pyridine formation. Route A also requires an appropriately functionalized 5-aminopyrazole, placing additional synthetic steps in this route when the required 5-aminopyrazole is not commercially available. Route B has remained relatively unexplored and has been confined to pyrazoles containing a methyl-, aryl-, hydroxy- or an amino- group at the 3-position.

Routes to pyrazolo[3,4-*b*]pyridines of general type **5** bearing more functionalized substituents have not appeared, presumably due to the lack of available methods for their synthesis (Figure 2). The preparation and utility of these structures could potentially lead to the discovery of more versatile pharmacophores. We reasoned that acylation of readily available 2-fluoropyridines **2** with a suitably functionalized electrophile **3** followed by cyclization in the presence of hydrazine would provide rapid access to the alkoxymethyl pyrazolo[3,4-*b*]pyridine ring system **5** in a manner analogous to that shown in Route B (Figure 1). Further manipulation would allow for the preparation of structurally intriguing synthetic targets. Herein, we describe a practical and highly efficient approach to 3-alkoxymethyl- and 3-aminomethyl substituted pyrazolo[3,4-*b*]pyridines.
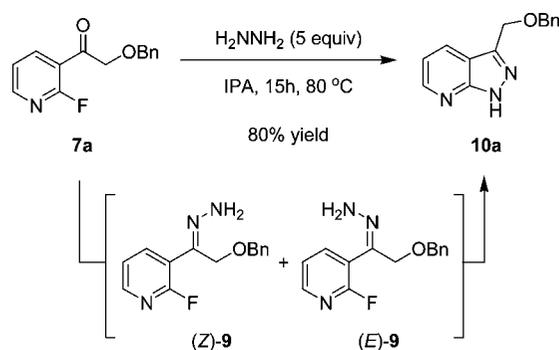
2. Results and Discussion

2.1. Synthesis of Pyrazolo[3,4-*b*]pyridines Derived from 2-Fluoropyridine. Our investigations began with the preparation of ketone **7a** (Scheme 1). Lithiation of 2-fluoropyridine (LDA, < −50 °C)[15] followed by reaction with Weinreb amide **6a**[16] gave **7a** in a low yield. Careful examination of the crude reaction

mixture revealed the formation of significant amounts of secondary amide **8a**.[17] Efforts to circumvent this problem by the use of the corresponding morpholine or dimethyl amide also gave poor yields of the desired ketone **7a**. After extensive optimization of the initial reaction parameters including solvent, temperature, and reagent charges, it was found that the use of 1.3 equiv of 2-fluoropyridine with 1.3 equiv of LDA followed by addition of **6a** while maintaining the internal temperature below −50 °C[18] provided **7a** in 61% yield. The mass balance of the reaction contained 2-fluoropyridine and amide **8a**, which were easily separated by chromatography.

With the desired α-benzyloxy ketone **7a** in hand, cyclization in the presence of hydrazine to form pyrazole **10a** was examined. Reaction of **7a** with an excess of 35 wt % hydrazine (5 equiv) at 80 °C in isopropanol (IPA) for 15 h resulted in the clean formation of 3-benzyloxymethyl pyrazolo[3,4-*b*]pyridine **10a** (Scheme 2). Monitoring the reaction by HPLC revealed the rapid formation of a mixture of the *E*- and *Z*-hydrazones **9** within 1 h, followed by slow ring closure to form the desired pyrazole **10a**. An excess of hydrazine was required to facilitate the pyrazole closure since the use of less than 5 equiv resulted in incomplete conversions, presumably due to the formation of azines, although they were not detected in the reaction mixture.[19] Upon completion of the reaction, the mixture was cooled to room temperature and diluted with water, allowing for direct crystallization of **10a** from the crude reaction mixture in 80% yield.

This reaction sequence proved to be general for accessing an array of functionalized 3-alkoxymethyl pyrazolo[3,4-*b*]pyridines (Table 1). In the preparation of the methyl-, 2-tetrahydropyranyl (THP), and *p*-methoxybenzyl (PMB) substituted pyrazolopyridines (**10b**−**d**), good to excellent yields were obtained in both the preparation of the ketones **7b**−**d** and corresponding pyrazoles **10b**−**d** (entries 1−3). The *p*-methoxyphenyl substituted pyrazole **10e** could also be prepared in comparable yield (entry 4). However, an interesting observation was made in the cyclization of phenoxy ketone **7f** to pyrazole **10f** (entry 5). Although the yield was comparable to that

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(15) (a) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49–64. (b) Gribble, G. W.; Sauliner, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137–4140.

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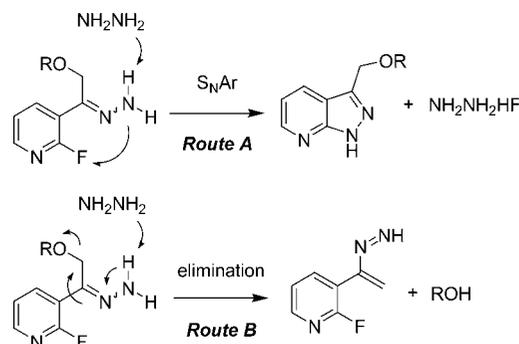
TABLE 1. Synthesis of Pyrazolo[3,4-b]pyridines

a.) LDA, THF, 30 min, -70 °C. b.) H$_2$NNH$_2$, IPA, 15h, 80 °C.

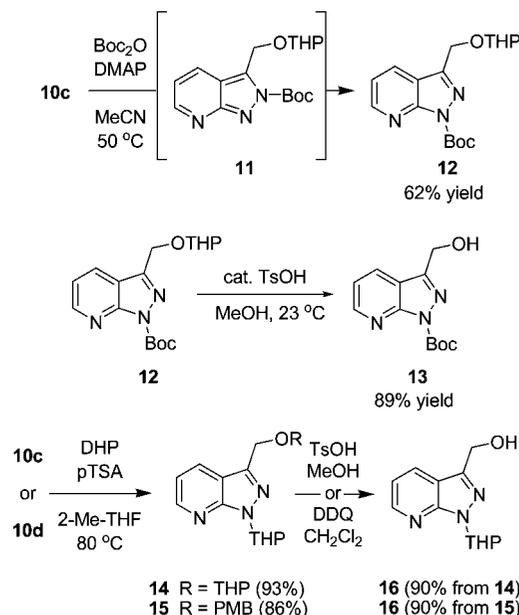| entry	amide (R)	step 1 yield (%)	step 2 yield (%)	ROH (%)	pK$_a$(H$_2$O)
1	Me (6b)	66 (7b)	90 (10b)	ND	15.54[20]
2	THP (6c)	65 (7c)	74 (10c)	ND	13.34[21]
3	PMB (6d)[22]	74 (7d)	81 (10d)	ND	14.43[21]
4	p-MeOC$_6$H$_4$- (6e)	69 (7e)	91 (10e)	ND	10.50[23]
5	C$_6$H$_5$- (6f)[24]	71 (7f)	89 (10f)	5%	9.99[25]
6	p-ClOC$_6$H$_4$- (6g)	73 (7g)	48 (10g)	45%	9.37[25]
7	3,4-Cl$_2$−C$_6$H$_3$- (6h)	27 (7h)	0 (10h)	>99%	8.56[26]

observed for **10e**, a small amount of phenol (<5%) was detected in the crude NMR. There was no detectable amount of *p*-methoxyphenol observed by either HPLC or crude NMR in the cyclization of ketone **7e** to pyrazole **10e**. In order to further probe this observation, the *p*-chlorophenyl substituted ketone **7g** was prepared and subjected to pyrazole formation (entry 6). Treatment of **7g** under the identical reaction conditions gave the desired pyrazole **10g** in only 48% isolated yield. The mass balance of the reaction was *p*-chlorophenol. When the 3,4-dichlorophenoxy substituted ketone **7h** was subjected to the same reaction conditions, none of the desired pyrazole **10h** was formed and the only observed product was 3,4-dichlorophenol (entry 7). The fate of the pyridine-containing fragment could not be determined due to extensive decomposition.

The dramatic split between productive cyclization and phenol elimination in entries 4−7 of Table 1 seemed to track with the electronic nature of the phenol. A mechanism which rationalizes this trend can be proposed that considers the reactivity of the intermediate hydrazones in this series (Scheme 3). Once formed, the hydrazone intermediate can either undergo productive cyclization by attack of the terminal hydrazone nitrogen on the pyridyl fluoride (Route A) or it can undergo elimination of the oxygen containing moiety to form a vinyl azine (Route B).[27] A survey of the literature shows that similar processes leading to

(20) See http://research.chem.psu.edu/brpgroup/pKa_compilation.pdf, pKa Data Compiled by R. Williams, p 10.

(21) Calculated using ACD/Labs extension for *CS ChemDraw (v 8.0)*; Advanced Chemistry Development, Inc.: Toronto, Canada; http://www.acdlabs.com.

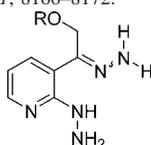(22) Tius, M. A.; Busch-Petersen, J. *Synlett* **1997**, 531–532.

(23) Barlin, G. B.; Perrin, D. D. *Chem. Soc. Rev.* **1966**, *20*, 75–101.

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(27) While not observed, the intermediacy of hydrazone hydrazide can not be completely ruled out. For a discussion on the cyclization of hydrazone hydrazides to indazoles, see: (a) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, M. R. *J. Org. Chem.* **2006**, *71*, 8166–8172.

SCHEME 3

SCHEME 4

the formation of vinyl azines and nitroso compounds are known for α-substituted hydrazones and oximes, respectively.[28] The electronic nature of the alkoxy moiety governs which pathway (Route A or Route B) is the preferred mode of reactivity. In the case of ketones such as **7a−f**, the elimination of an aliphatic alcohol or electron rich phenol (pK$_a$ > 10) is disfavored and good yields of the desired pyrazoles are obtained via Route A. In contrast, the elimination of more acidic phenols, such as *p*-chlorophenol (pK$_a$ = 9.38),[25] via Route B is facile in the reactions of ketones such as **7 g−h**.

In order to provide access to pyrazolo[3,4-b]pyridines containing electron deficient ethers at the 3-position, our attention turned to further manipulation of the 3-alkoxymethyl group for late stage introduction of an electron deficient group, such as those contained in **10g** or **10h**. Therefore, an appropriate oxygen protecting group was sought which would be stable to the conditions of the pyrazole formation. We elected to protect the pyrazole nitrogen in order to avoid undesirable side reactions (Scheme 4).[9] *N*-Protection of *O*-THP-protected pyrazole **10c** with di-*tert*-butyl dicarbonate (Boc anhydride) was conducted in MeCN at 50 °C in the presence of catalytic DMAP.[9] Monitoring the reaction by HPLC revealed initial formation of

(28) (a) Tsuji, T.; Kosower, E. M. *J. Am. Chem. Soc.* **1969**, *91*, 3375. (b) Gilchrist, T. L.; Hughes, D.; Stretch, W.; Chrystal, E. J. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2505–2509. (c) Collins, P. M.; Hurford, J. R.; Overend, W. G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2163–2177.

SCHEME 5

SCHEME 6
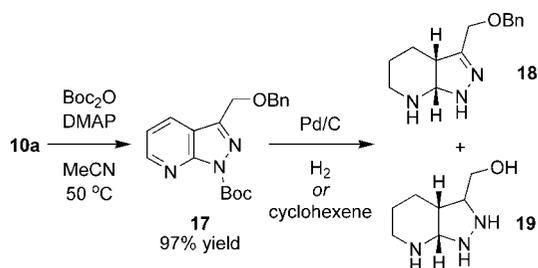
a mixture of the N_1- and N_2-Boc-protected pyrazoles **11** and **12**. Heating this mixture for several hours led to the exclusive formation of pyrazole **12**. Selective deprotection of the *O*-THP group was accomplished by simply stirring **12** in methanol with catalytic *p*-toluene sulfonic acid to give the 3-hydroxymethyl pyrazole **13** in 89% yield. Alternatively, *N*-THP protection could be performed on either pyrazoles **10c** or **10d** by reaction with dihydropyran (DHP) in the presence of catalytic TsOH in 2-Me-THF at 80 °C for several hours giving **14** and **15** as the sole products in 93% and 86% yields, respectively. In the case of **14**, selective *O*-deprotection was observed when allowed to react in MeOH in the presence of catalytic TsOH to provide **16** in 90% yield. The highly selective deprotection of **14** clearly shows the lability of the *O*-THP group when compared to the *N*-THP group. An alternative route to alcohol **16** involves removal of the PMB ether with DDQ.[29]

Interestingly, attempts to prepare **13** from the *O*-benzyl protected pyrazole **10a** by catalytic hydrogenation of the benzyl group of **17** were completely unsuccessful (Scheme 5). Protection of **10a** with Boc anhydride under identical conditions used in the preparation of **12** gave **17** in 97% yield. Catalytic hydrogenation (EtOH, Pd/C, balloon pressure of H$_2$, 8 h) provided a complex mixture of products from which the partially and fully reduced piperidines **18** and **19** were identified.[30] Similarly, transfer hydrogenation (cyclohexene, EtOAc, Pd/C, reflux) gave similar results. The presence of **18** suggests that reduction of the pyridine ring is faster than removal of the benzyl group.

With **13** and **16** in hand, our attention turned to activation of the alcohol and displacement with an appropriately substituted nucleophile (Scheme 6). For example, treatment of **13** with MsCl in the presence of NEt$_3$ in 2-Me-THF at 0 °C gave the corresponding mesylate. After filtration of the precipitated ammonium salts, the crude mesylate was concentrated and redissolved in *N,N*-dimethylacetamide (DMAc) and added to a mixture of KI (1.7 equiv), CsF (5.0 equiv) and 3,4-dichlorophenol in DMAc. After 18 h at 23 °C, **20** was obtained in 82% isolated yield. Although the direct formation of **10h** was not possible (Table 1, entry 7) the alkylation of **13** via mesylation and reaction with 3,4-dichlorophenol represents a viable alternative entry to these pyrazolopyridines bearing electron withdrawing groups. The use of anhydrous CsF as the base was found to be critical for the success of the reaction. Other bases resulted in cleavage of the Boc group and the formation of dimeric and polymeric products. The use of KI as a promoter, which converts the mesylate into a more reactive iodide as determined by HPLC, led to increased reaction rates and yields. Although the reaction
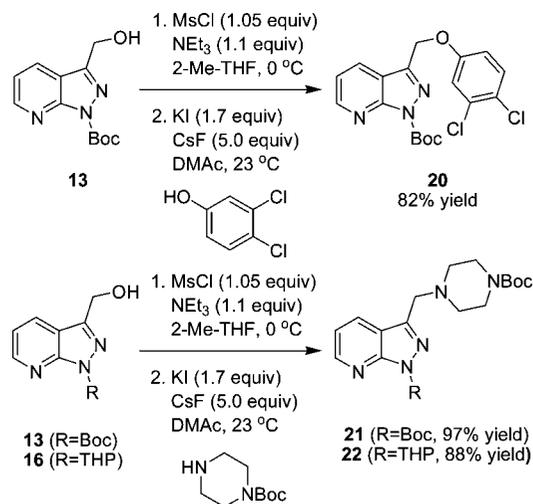
TABLE 2. Synthesis of 6-Chloro-pyrazolo[3,4-*b*]pyridines

a.) LDA, THF, -70 °C, 30 min. b.) H$_2$NNH$_2$, IPA.
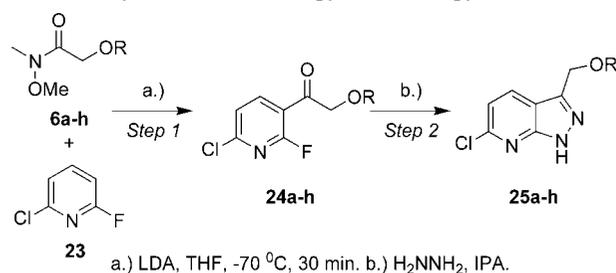
entry	amide (R)	step 1 yield (%)	step 2 yield (%)
1	Bn (**6a**)[31]	73 (**24a**)	90 (**25a**)
2	*p*-MeOC$_6$H$_4$- (**6e**)	31 (**24e**)	97 (**25e**)
3	C$_6$H$_5$- (**6f**)[32]	42 (**24f**)	96 (**25f**)
4	*p*-ClOC$_6$H$_4$- (**6g**)	34 (**24g**)	81 (**25g**)
5	3,4-Cl$_2$−C$_6$H$_3$- (**6h**)	38 (**24h**)	52 (**25h**)

proceeded in the absence of KI, significantly lower isolated yields resulted. Via the corresponding mesylate, alcohols **13** and **16** also underwent efficient displacement with *N*-Boc piperazine to give **21** and **22**, demonstrating the utility of this procedure for the preparation of 3-aminomethyl-pyrazolo[3,4-*b*]pyridines.

2.2. Synthesis of Pyrazolo[3,4-*b*]pyridines Derived from 2-Chloro-6-fluoropyridine. Having examined the scope of this method with respect to the 3-substituent on the pyrazole ring, the scope of the reaction with respect to the pyridine ring was explored. The use of 2-chloro-6-fluoro pyridine **23** would provide a handle for functionalization of the pyrazolo[3,4-*b*]pyridine at the 6-position. Initial experiments using the conditions described above for lithiation and acylation of 2-fluoropyridine gave highly regioselective lithiation *ortho* to the 2-fluorine, a result consistent with the known directing abilities of different halogen substituents on aromatic rings. Moderate to good yields could be obtained in the cases of the benzyloxy-substituted ketone **24a** as well as the phenoxy-substituted ketones **24e−h** (Table 2). The lower yields obtained in the acylations of 2-chloro-6-fluoropyridine result from an increased amount of demethoxylation of the Weinreb amide when compared to the acylation of 2-fluoropyridine.

Upon treatment of a solution of ketone **24a** in IPA at room temperature with 5 equiv of 35 wt % hydrazine, a rapid

(29) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.

(30) Compounds **18** and **19** were identified by careful NMR analysis of the crude reaction mixture and were not isolated or separated from one another.

(31) Tius, M. A.; Busch-Petersen, J. *Synlett* **1997**, 531–532.

(32) Hiyama, T.; Reddy, G. B.; Minami, T.; Hanamoto, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 350–363.
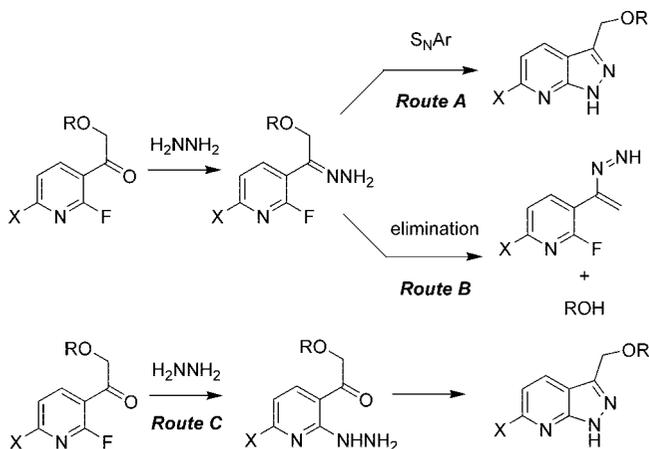
SCHEME 7

SCHEME 8

SCHEME 9
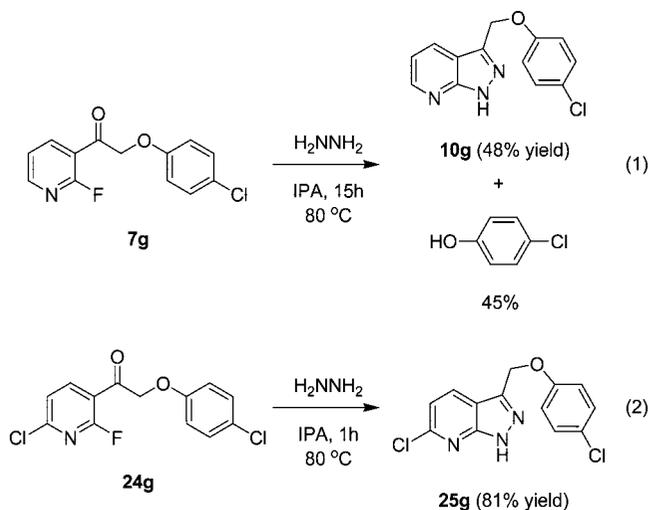
exotherm to 71 °C was observed and complete conversion to **25a** occurred in less than 30 min (Table 2, entry 1). Compound **25a** could be isolated in 90% yield by direct crystallization from the crude reaction mixture by dilution with water. This result stands in stark contrast to the prolonged reaction times required for the cyclization of **7a** to **10a** (15 h, see Scheme 2). Treatment of the phenoxy ketones **24e–h** with 35 wt % hydrazine did not lead to any reaction at room temperature. In the cases of **24e–h**, heating to 80 °C for 1 h was required to affect full conversion to pyrazoles **25e–h** (entries 2–5). The short reaction times and good yields observed for the pyrazole closures with this group of ketones, especially in the case of **24h**, are quite surprising considering that the treatment of **7h** with hydrazine led to none of the corresponding pyrazole! In all examples shown in Table 2, no phenol formation was observed by HPLC. The variable reactivity of the ketones in Table 2 with hydrazine is also intriguing since it is unclear how the alkoxy group would affect the rate of pyrazole closure. A likely explanation for these differences could be the poor solubility of the phenoxy substituted ketones in IPA at room temperature.

A comparison of the reactions of the 4-chlorophenol containing ketones **7g** and **24g** illustrates the dramatic reactivity differences between ketones in the 2-fluoropyridine series and those in the 2-chloro-6-fluoropyridine series (Scheme 7). In the case of **7g**, reaction proceeded slowly over 15 h at 80 °C giving a ~1:1 mixture of the desired pyrazole **10g** and 4-chlorophenol (eq 1, Scheme 7). In the case of **24g**, the reaction proceeded quickly to give a good yield of pyrazole **25g** in 1 h with no 4-chlorophenol being detected by HPLC (eq 2, Scheme 7). The observed reactivity differences between **7g** and **24g** could be ascribed to a change in the relative rates of pyrazole formation vs elimination or a change in reaction mechanism (Scheme 8). Such an alternative mechanism which does not involve hydrazone formation proceeds through initial S$_N$Ar displacement of the fluoride, leading to formation of a hydrazide intermediate (Route C). Since no hydrazones would be formed, the proposed pathway for elimination of the phenol is no longer available. A mechanism involving an initial S$_N$Ar step, rather than direct hydrazone formation, has been proposed in the formation of indazoles from *o*-fluorobenzaldehydes.[27]

To differentiate these two possiblities, careful examination of the cyclization of ketones in the 2-chloro-6-fluoropyridine series was undertaken. Analysis by LC–MS revealed the
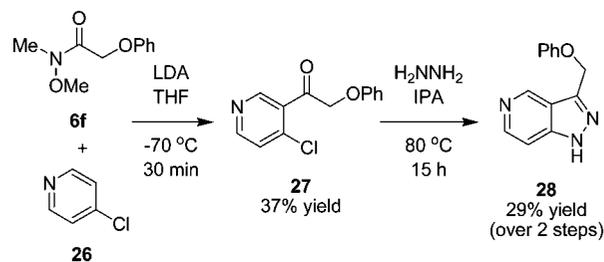
formation of the corresponding hydrazones, lending support to pyrazole formation via a hydrazone as in Route A. Although not conclusive, this suggests that pyrazole formation might proceed via identical mechanisms for 2-fluoropyridine and 2-chloro-6-fluoropyridine derived ketones.[27] However in contrast to 2-fluoropyridine derived ketones, both hydrazone formation and pyrazole closure appears to be rapid for ketones in the 2-chloro-6-fluoropyridine series, even at room temperature. The lack of phenol elimination is likely due to a change in the relative rates of intramolecular S$_N$Ar displacement of the fluoride in the hydrazone intermediate (Scheme 8, Route A) and phenol elimination (Scheme 8, Route B). The presence of an electron withdrawing chloride on the pyridine ring simultaneously activates the fluoride bearing 2-position of the pyridine ring toward attack of the hydrazone while removing electron density from the hydrazone and disfavoring elimination.

2.3. Synthesis of Pyrazolo[4,3-*c*]pyridines Derived from 2-Chloro-6-fluoropyridine. A further demonstration of the diversity of pyrazolopyridine structures that can be prepared by this methodology is found through the use of 4-chloropyridine which provides access to the isomeric pyrazolo[4,3-*c*]pyridines. (Scheme 9). Compounds in this class have demonstrated some biological activity.[33] Fewer examples of this ring system appear in the literature, although some methods have been developed to access them.[11,34] Following the strategy reported herein, lithiation of 4-chloropyridine[35] **26** and addition to Weinreb amide **6f** gave **27** with good regioselectivity but only moderate yield (37% yield). Cyclization under the standard

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conditions then provided the desired pyrazolo[4,3-*c*]pyridine **28**. Due to the instability of **27**, its isolation was avoided, and crude **27** was used in the cyclization step without purification (29% yield over 2 steps).

3. Conclusion

In summary, we have developed an efficient method for the preparation of a structurally diverse group of 3-alkoxymethyl- and 3-aminomethyl-pyrazolo[3,4-*b*]pyridines. The use of α-substituted Weinreb amides as a starting point for the synthesis of 3-substituted pyrazolo[3,4-*b*]pyridines provides a facile way to introduce functionality in a rapid manner. In cases where the desired substituent might be incompatible with these conditions, the mesylation/displacement of alcohols **13** and **16** allows for the rapid diversification of pyrazolo[3,4-*b*]pyridines. The investigation of 2-chloro-6-fluoro pyridine revealed that subtle changes in the electronic nature of the pyridine ring can lead to significant reactivity differences in the pyrazole formation. Taken together, these results demonstrate that this is a versatile strategy for pyrazolo[3,4-*b*]pyridine synthesis, allowing for straightforward preparation of a wide range of compounds. These results should enable further exploration of the medicinal properties of this interesting class of heterocycles.

4. Experimental Section

Preparation of 1-(2-Fluoro-pyridin-3-yl)-2-benzyloxy-ethanone (7a). To a solution of 4.4 mL diisopropylamine (31.1 mmol, 1.3 equiv) in 25 mL THF at −40 °C was added 12.4 mL 2.5 M *n*-BuLi in hexanes (31.1 mmol, 1.3 equiv), dropwise. The resulting yellow solution was stirred at −40 °C for 30 min then cooled to −70 °C for dropwise addition of 2.6 mL 2-fluoropyridine (31.1 mmol, 1.3 equiv). The resulting yellow suspension was stirred for 30 min at −70 °C prior to slow addition of a solution of 5 g of *N*-methoxy-2-benzyloxy-*N*-methyl-acetamide **6a**[36] (23.9 mmol) in 5 mL THF from a dropping funnel. The internal temperature was kept below −60 °C. After completion of the addition, the solution was stirred for 30 min at −70 °C prior to pouring into 100 mL saturated aqueous ammonium chloride, extraction with 25 mL MTBE and drying the combined organic layers over MgSO$_4$, filtration and concentration. The resulting orange oil could be purified by silica gel chromatography (7:3 hexane:ethyl acetate, R_f = 0.37), to afford 3.6 g (61% yield) of **7a** as a colorless solid. mp 45−47 °C; ^{1}H (400 MHz, CDCl$_3$) δ 8.42 (m, 2H), 7.41−7.31 (m, 6H), 4.73 (d, 2H, *J* = 3.1 Hz), 4.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.7 (d, *J* = 8.8 Hz), 161.4 (d, *J* = 243.3 Hz), 152.1 (d, *J* = 16.1

Hz), 142.0 (d, *J* = 3.6 Hz), 137.17, 128.6, 128.1, 122.3 (d, *J* = 6.8 Hz), 122.2, 118.0 (d, *J* = 31.8 Hz), 75.5 (d, *J* = 11.2 Hz), 73.7; HRMS calcd for C$_{14}$H$_{12}$FNO$_2$ (M+H): 246.0930, found: 246.0957.

Preparation of 3-(Benzyloxymethyl)-1H-pyrazolo[3,4-*b*]pyridine (10a). To a solution of 5.90 g of 1-(2-fluoro-pyridin-3-yl)-2-benzyloxy-ethanone **7a** (22.37 mmol) in 10 mL of isopropanol was added 10.1 mL of a 35 wt % aqueous solution of hydrazine (112 mmol, 5.0 equiv). The resulting yellow solution was then heated at 80 °C for 15 h or until complete conversion was observed by HPLC. The solution was then cooled to room temperature, diluted with 10 mL EtOAc, washed with 20 mL water, dried over MgSO$_4$, filtered and concentrated. Purification by silica gel chromatography (7:3 hexane:ethyl acetate, R_f = 0.14) afforded 4.29 g (80% yield) of **10a** as a colorless solid. mp 96−97 °C; ^{1}H (400 MHz, CDCl$_3$) δ 8.62 (dd, 1H, *J* = 4.6, 1.5 Hz), 8.26 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.36 (m, 5H), 7.20 (dd, 1H, *J* = 8.0, 4.6 Hz), 4.97 (s, 2H), 4.62 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.8, 148.9, 143.3, 137.9, 130.8, 128.5, 128.0, 127.9, 117.0, 114.5, 72.5, 65.9; HMRS calcd for C$_{14}$H$_{13}$N$_3$O (M+H): 240.1137, found: 240.1184.

Preparation of 3-(4-tert-Butoxycarbonyl-piperazin-1-ylmethyl)-pyrazolo[3,4-b]pyridine-1-carboxylic acid tert-butyl ester (21). To a solution of 1.10 g of 3-hydroxymethyl-pyrazolo[3,4-*b*]pyridine-1-carboxylic acid *tert*-butyl ester **13** (4.41 mmol, 1.0 equiv) in 15 mL of 2-Me-THF at 0 °C was added 0.7 mL of triethylamine (4.85 mmol, 1.1 equiv). To the mixture was added dropwise 0.36 mL of methanesulfonyl chloride (4.63 mmol, 1.05 equiv) at such a rate that the internal temperature was maintained <8 °C and the resulting slurry was stirred at this temperature for 45 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude mesylate was dissolved in 7 mL of DMAc and added dropwise to a slurry of 822 mg of 1-*N*-Boc-piperazine (4.41 mmol, 1.0 equiv), 1.25 g of KI (7.50 mmol, 1.7 equiv), and 3.35 g of CsF (22.06 mmol, 5.0 equiv) in 12 mL of DMAc. The reaction mixture was stirred at rt for 18 h and diluted with 25 mL of MTBE and 25 mL of water. The layers were separated and the aqueous layer back extracted with 15 mL of MTBE. The combined organic extracts were washed with water (3 × 20 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (6:4 hexane:ethyl acetate, R_f = 0.10) to afford 1.84 g (97% yield) of **21** as a clear oil. ^{1}H (CDCl$_3$, 400 MHz) δ 8.66 (dd, 1H, *J* = 4.7, 1.7 Hz), 8.32 (dd, 1H, *J* = 7.9, 1.7 Hz), 7.27 (m, 1H), 3.88 (s, 2H), 3.39 (m, 4H), 2.43 (m, 4H), 1.67 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 154.7, 152.8, 150.7, 148.0, 147.0, 131.1, 119.0, 117.5, 85.1, 79.7, 56.2, 55.1, 43.3, 28.2, 28.1; HRMS calcd for C$_{21}$H$_{31}$N$_5$O$_4$ (M+H): 418.2454, found: 418.2478.

Supporting Information Available: Experimental procedures and data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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