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A Novel One-Step Synthesis of 2-Substituted 6-Azaindoles from 3-Amino-4-picoline and Carboxylic Esters

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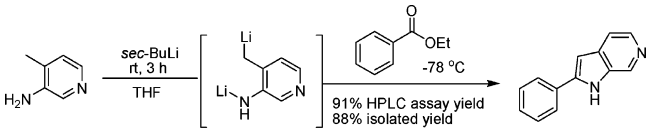

Dilithiation of 3-amino-4-picoline (**1**) was achieved with *sec*-BuLi at room temperature. Condensation of the resulting dianion (**2**) with carboxylic esters afforded a wide range of 2-substituted 6-azaindoles in good yields.

Azaindoles constitute essential subunits in many pharmaceutically important drug substances.[1] In contrast to a vast array of methods for indole synthesis,[2] there are a limited number of methodologies available for azaindole formation.[3] The often employed method involves a Sonogashira coupling of a terminal alkyne with 4-*tert*-butoxycarbonylamino-3-iodopyridine followed by deprotection/cyclization in situ or in a separate step.[4] Palladium-catalyzed heteroannulation of internal alkynes with 2-amino-3-iodo-, 3-amino-4-iodo-, or 4-amino-3-iodopyridine derivatives also proved useful for the synthesis of substituted azaindoles.[5] Hands et al. have developed a convenient azaindole synthesis by reacting Weinreb amides with the dianion of 3-*tert*-butoxycarbonylamino-4-picoline or 4-*tert*-butoxycarbonylamino-3-picoline, followed by Boc deprotection/cyclization.[6] For example, 2-phenyl-6-azaindole was synthesized in two steps in 50% overall yield from 3-*tert*-butoxycarbonylamino-4-picoline, whose synthesis required two additional steps from 3-aminopyridine[6] or one additional step from 3-amino-4-picoline. Certain substituted azaindoles were obtained via photostimulated $S_{RN}1$ reaction between ketone enolates and *N*-protected 2-amino-3-iodo-, 3-amino-4-iodo-, or 4-amino-3-iodopyridines followed by acidic deprotection and cyclization.[7] In a more recent report, 2-arylazaindoles were prepared in multiple steps from substituted pyridines such as 3-nitro-4-[(*E*)-2-phenylethenyl]pyridine via a series of reduction−oxidation reactions.[8] The above and other reported processes[9] often require multiple-step synthesis and suffer from limited generality and/or unsatisfactory overall yields. Therefore, it is highly desirable to investigate new strategies for azaindole synthesis.

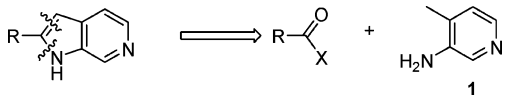

FIGURE 1. Retrosynthetic analysis.

During the course of our search for a general and practical method to prepare 2-substituted 6-azaindoles, we considered the possibility of utilizing the commercially available and inexpensive 3-amino-4-picoline (**1**)[10] as a direct building block, as indicated in the retrosynthetic analysis in Figure 1. Our proposed reaction sequence would involve the initial creation of the C−C bond followed by cyclization and dehydration to give the azaindole derivatives. We believe that this disconnection represents one of the most efficient strategies for 6-azaindole formation since it does not necessitate the use of protecting groups or any oxidation state adjustment. In this paper, we wish to report a novel one-step synthesis of 2-substituted 6-azaindoles via condensation of carboxylic esters with the dianion of 3-amino-4-picoline (Figure 2).

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(10) 3-Amino-4-picoline is commercially available in bulk from multiple sources.

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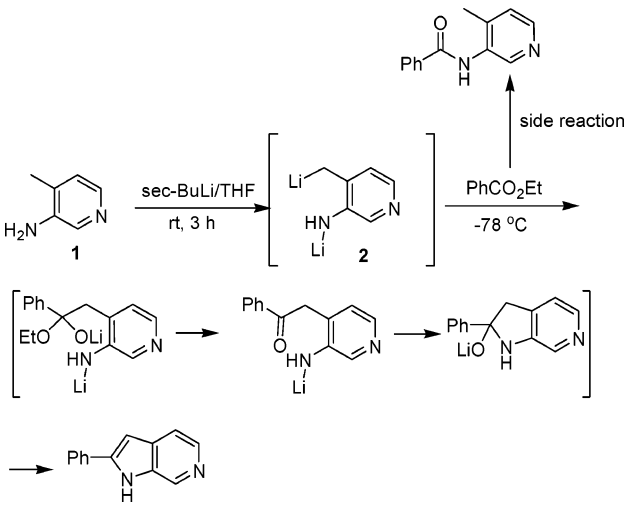

FIGURE 2. Proposed reaction pathway.

Our studies started with the dilithiation[11] of 3-amino-4-picoline. Hands et al. have reported that the dilithiation of 3-*tert*-butoxycarbonylamino-4-picoline could be readily achieved by treatment with *n*-BuLi at −20 °C for 30 min.[6] However, without an anion-stabilizing protecting group such as acyl or Boc on the 3-amino group,[6] dilithiation of the naked 3-amino-4-picoline was challenging. Treatment of 3-amino-4-picoline with 3 equiv of *n*-BuLi at room temperature led to only 25% dilithiation as determined by a deuterium-labeling experiment. The use of *t*-BuLi at 0 °C increased the dilithiation to 45%. However, significant side reaction between *t*-BuLi and the pyridine ring occurred at this temperature. When 3-amino-4-picoline was treated with 3 equiv of *s*-BuLi in THF at room temperature for 3 h, an orange-colored slurry was formed. Upon quenching with MeOH-d_4, 70% deuterium incorporation was detected at the methyl position. Other solvents such as hexane, DME, and ether were found to be less effective.

Ethyl benzoate was first selected for investigation of the reaction with the dianion of 3-amino-4-picoline (Figure 2). Under the initial reaction conditions (6 equiv of ethyl benzoate, −78 °C to room temperature, 15 h), the desired 2-phenyl-6-azaindole was formed along with a large amount of amide (ca. 25%). Apparently, the amide byproduct was derived from nitrogen attack on the ester. To increase the C/N selectivity of the condensation reaction, we carefully studied reaction temperature, reaction time, and stoichiometry. It was found that the reaction was very rapid at −78 °C. If used as the limiting reagent, ethyl benzoate was completely consumed within 30 min at this temperature. We have further determined that excellent C/N selectivity could be achieved as long as the reaction mixture is maintained at <−30 °C. With use of the optimized conditions, 2-phenyl-6-azaindole was formed in 91% HPLC assay yield (88% isolated yield) with minimal formation of the amide byproduct (<1%). This result compares favorably with those reported in the literature where the 2-phenyl-6-azaindole was synthesized in only 50−70% yield over multiple synthetic steps.[6,8]

Presumably a cascade of transformations took place in this one-step construction of 2-phenyl-6-azaindole (Figure 2). Addition of the C-anion to the carbonyl group of the ester furnished the tetrahedral intermediate that fragmented into the ketone, which in turn was trapped immediately by the neighboring N−Li. Dehydration completed the azaindole formation. It is noteworthy that no secondary addition of the dianion to the intermediate ketone was observed. Normally this is an unavoidable side reaction when organolithium reagents are added to esters.[12] It is reasonable to speculate that the facile cyclization of the N−Li into the putative ketone prevented the secondary addition side reaction. Therefore, the use of Weinreb amides is not required for the present methodology.[6]

The scope of this new method was explored by using a wide range of carboxylic esters (Table 1). It can be seen that simple aromatic esters (entries 1 to 4) gave azaindole products in very good yields. An aryl bromide is compatible with the reaction conditions and no Br−Li exchange was observed. Esters derived from furan and thiophene carboxylic acids also condensed smoothly with the dianion to afford the corresponding azaindoles. In reactions with enolizable esters (methyl acetate and methyl β-phenylpropionate), the dianion acted as a typical nucleophile, not a base, to furnish the desired 2-alkyl-6-azaindoles. The strong nucleophilicity of the dianion was also evident in its successful reactions with sterically demanding substrates such as methyl pivalate and ethyl admantane-1-carboxylate, although warming up to −30 °C was required for a complete conversion in these cases. Thioester (entry 11) was found to be suitable for this transformation. Finally, we have shown that the condensation of the dianion with a lactone substrate was also successful (entry 12).

In summary, we have developed conditions for direct dilithiation of *unprotected* 3-amino-4-picoline. Condensation of the resulting dianion with various carboxylic esters afforded 2-substituted 6-azaindoles in good yields in a single step. *It is noteworthy that no protecting group or oxidation state adjustment is necessary in this one-step synthesis.* Considering its simplicity, demonstrated generality, and the ready availability of the starting materials, we believe that this methodology will find wide applications in the synthesis of 6-azaindole-containing compounds.

Experimental Section

General procedures: All reactions were performed in oven-dried glassware under nitrogen with magnetic stirring. All commercial reagents were used as received. Flash chromatography was performed with 230−400 mesh silica gel.

Representative procedure: 3-Amino-4-picoline (1.32 g, 12.0 mmol) was dissolved in anhydrous THF (44 mL) in a dry flask under nitrogen. The solution was cooled to −78 °C and a solution of *s*-BuLi (1.4 M in cyclohexane, 26 mL, 36.0 mmol) was added in 10 min. The solution was warmed to room temperature, stirred at that temperature for 3 h, and cooled to −78 °C. Ester

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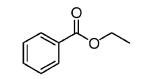
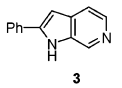
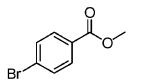
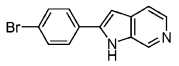
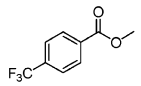
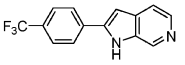
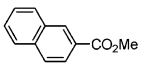
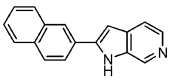
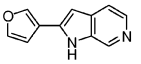
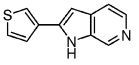
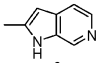
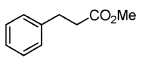
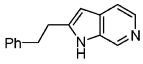
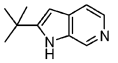
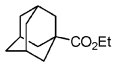
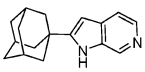
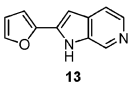
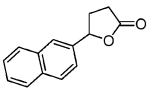
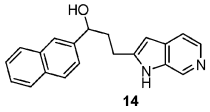
TABLE 1. 6-Azaindole Synthesis via Dianion of 3-Amino-4-picoline

entry	substrate	product	yield (%)[a]	lit. ref.
1		 **3**	88 (91)	8
2		 **4**	78 (80)	8
3		 **5**	80 (83)	8
4		 **6**	79 (82)	1k
5		 **7**	44 (49)	8
6		 **8**	54 (61)	
7		 **9**	33 (53)	7
8		 **10**	57 (67)	
9		 **11**	77 (80)	7
10		 **12**	64 (66)	
11		 **13**	48(57)	
12		 **14**	56 (61)	

[a] Isolated yield (HPLC assay yields in parentheses).

(4.8 mmol) was added and the resulting mixture was stirred at −78 °C for 1 h. Methanol (20 mL) was added in 5 min and the solution was warmed to room temperature and stirred for 1 h. A half-saturated NH_4Cl aqueous solution (30 mL) was added and the organic residue was extracted with MTBE (3 × 50 mL). The combined organic extract was dried over $MgSO_4$ and filtered. Solvents were evaporated under vacuum. The crude product mixture was purified by silica gel chromatography to give product in yields specified in Table 1.

For detailed experimental procedures and copies of ^{1}H NMR spectra for all isolated compounds **3** to **14**, see the Supporting Information.

Characterization data for 2-thiophen-3-yl-1*H*-pyrrolo-[2,3-*c*]pyridine (8): mp 247−249 °C. IR (cm^{-1}) 3230, 3212, 1266, 730. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.95 (s, 1H), 8.72 (s, 1H), 8.08 (d, J = 5.32 Hz, 1H), 8.04 (m, 1H), 7.70 (m, 2H), 7.48 (d, J = 5.32 Hz, 1H), 6.85 (d, J = 1.00 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 136.2, 135.5, 131.8, 131.2, 130.8, 125.5, 124.2, 120.0, 112.3, 95.8. HRMS calcd for the [M + 1]$^+$ 201.0480, found 201.0491.

Characterization data for 2-phenethyl-1*H*-pyrrolo[2,3-*c*]pyridine (10): mp 172−173 °C. IR (cm^{-1}) 3451, 3227, 1459, 1266, 822, 741, 699. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.50 (s, 1H), 8.62 (s, 1H), 8.01 (d, J = 5.28 Hz, 1H), 7.38 (d, J = 5.32 Hz, 1H), 7.27 (m, 4H), 7.19 (m, 1H), 6.24 (s, 1H), 3.05 (m, 4H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 144.2, 141.4, 138.1, 133.6, 133.5, 128.7, 128.6, 126.3, 114.2, 98.5, 98.4, 34.8, 29.8. HRMS calcd for the [M + 1]$^+$ 223.1229, found 223.1238.

Characterization data for 2-adamantan-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine (12): mp 216−219 °C. IR (cm^{-1}) 3462, 3234, 3053, 2987, 2910, 2852, 1571, 1466, 1266, 822, 733. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.31 (s, 1H), 8.57 (s, 1H), 7.96 (d, J = 5.28 Hz, 1H), 7.34 (d, J = 5.32 Hz, 1H), 6.13 (d, J = 1.52 Hz, 1H), 2.03 (s, 3H), 1.94 (s, 6H), 1.72 (m, 6H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 153.9, 153.8, 138.0, 133.8, 133.7, 133.6, 132.5, 114.4, 95.1, 95.0, 42.0, 36.7, 36.6, 34.1, 28.2. HRMS calcd for the [M + 1]$^+$ 253.1699, found 253.1711.

Characterization data for 2-furan-2-yl-1*H*-pyrrolo[2,3-*c*]pyridine (13): mp 214−216 °C. IR (cm^{-1}) 3235, 3204, 1610, 1567, 1532, 1266, 1015. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.04 (s, 1H), 8.70 (s, 1H), 8.06 (d, J = 5.48 Hz, 1H), 7.83 (d, J = 1.76 Hz, 1H), 7.47 (dd, J = 0.96, 4.96 Hz, 1H), 7.02 (d, J = 3.32 Hz, 1H), 6.74 (s, 1H), 6.66 (dd, J = 1.76, 3.32 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 146.5, 144.0, 137.3, 133.4, 133.2, 133.1, 133.0, 114.6, 112.2, 108.5, 96.9. HRMS calcd for the [M + 1]$^+$ 185.0709, found 185.0718.

Characterization data for 1-naphthalen-2-yl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)propan-1-ol (14): mp 73−76 °C. IR (cm^{-1}) 3235, 1266. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.65 (s, 1H), 8.64 (s, 1H), 8.03 (d, J = 5.56 Hz, 1H), 7.90 (m, 4H), 7.55 (d, J = 8.56 Hz, 1H), 7.51 (m, 3H), 6.33 (s, 1H), 5.53 (d, J = 4.28 Hz, 1H), 4.78 (m, 1H), 2.89 (m, 2H), 2.14 (m, 2H) .^{13}C NMR (DMSO-d_6, 125 MHz) δ 143.7, 136.5, 133.2, 132.6, 132.3, 128.1, 128.0, 127.8, 126.4, 125.9, 124.9, 124.4, 114.4, 98.7, 72.0, 71.9, 38.4, 24.6, 24.3. HRMS calcd for the [M + 1]$^+$ 303.1491, found 303.1499.

Supporting Information Available: Detailed experimental procedures and copies of ^{1}H NMR spectra for compounds **3** to **14** as well as ^{1}H NMR data for known compounds **3**−**7**, **9**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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