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One-step construction of 2-substituted-4,6-diazaindoles from carboxylic acid derivatives

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ABSTRACT

Treatment of unprotected 5-amino-4-methylpyrimidine (**2**) with *n*-BuLi gave dianion **3**. Direct condensation of the dianion with various carboxylic acid derivatives furnished a range of 2-substituted-4,6-diazaindoles in good yields in one step without the need for protecting groups or oxidation-state adjustment.

1. Introduction

The indole nucleus is one of the most important heterocycles and constitutes an essential structural element for a large number of biologically interesting molecules. The wide application of indoles in medical sciences has stimulated the development of numerous methodologies for its synthesis.[1] Substituting the carbon atoms at positions 4–7 in the indole ring with one or two nitrogen atoms gives the so-called azaindoles or diazaindoles. Azaindoles and diazaindoles are often employed as indole bioisosteres to modulate biological activities of drug molecules. However, in contrast to indole synthesis, there is a very limited collection of methods for the construction of azaindoles and diazaindoles. Furthermore, most of the known methods require multiple steps and/or harsh reaction conditions.[2]

Previously, we have reported a one-step method for the synthesis of 2-substituted-6-azaindoles from carboxylic esters (Fig. 1).[3] Dilithiation of 3-amino-4-picoline (**1**) with *s*-BuLi gave the corresponding dianion which was allowed to condense with a range of esters to furnish 2-substituted-6-azaindoles in one operation without the need for a protecting group.[4] The commercial availability of 3-amino-4-picoline and the ready availability of esters render this method very practical. As part of our research program, we also needed a method for making 4,6-diazaindole analogues. Only a small number of scattering reports could be found in the literature for the synthesis of this structural motif.[5,6] For example, a few 4,6-diazaindoles were synthesized via a sequence consisting of a Sonogashira coupling followed by base-mediated cyclizations. However, the overall transformation to diazaindoles from commercially available materials required at least 4 synthetic steps. To address this synthetic challenge, we wondered if the dianion chemistry that we employed for 6-azaindole formation could be extended to the construction of diazaindoles. In this Letter, we wish to report that this strategy was indeed successful and 2-substituted-4,6-diazaindoles could be constructed in one step via condensation of carboxylic acid derivatives and the commercially available 5-amino-4-methylpyrimidine.[7]

2. Results and discussion

On the basis of our experience with dilithiation of 3-amino-4-picoline, we have started our study by treating 5-amino-4-methylpyrimidine with a few strong bases. The extent of dilithiation was measured by deuterium incorporation at the methyl group as determined using ^{1}H NMRs. It was found that the use of *n*-BuLi was effective to give dianion **3** in 48% yield in THF (Table 1, entry 1).[8] No significant side reaction was occurring with the pyrimidine ring. The use of *s*-BuLi gave the dianion in a much lower yield (entry 2). Treatment of compound **2** with MeLi also afforded the dianion in 47% yield in THF and 16% yield in DME (entries 3 and 4). LDA gave only 12% yield of dianion intermediate (entry 5). LHMDS was not basic enough to effect dilithiation (entry 6).

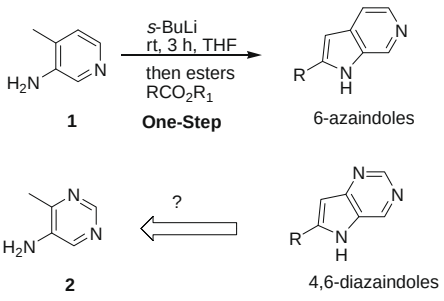

Figure 1.

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
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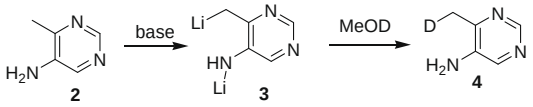
Table 1
Dilithiation of 5-amino-4-methylpyrimidine



Entry	Base	Solvent	Temp (°C)	Time (h)	D-incorporation in **4**[a] (%)
1	*n*-BuLi	THF	−70 to 23	3	48
2	*s*-BuLi	THF	−70 to 23	3	20
3	MeLi	THF	−50 to 10	18	47
4	MeLi	DME	−20	2.5	16
5	LDA	THF	−70 to 23	3	12
6	LHMDS	THF	−70 to 23	3	0

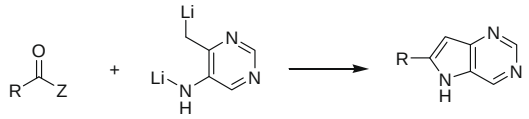
[a] Determined by ^{1}H NMR.

Having identified a procedure that allowed for the generation of the key dianion intermediate **3**, we proceeded to test its condensation reactions with carboxylic acid derivatives using ethyl benzoate as the initial substrate. Ethyl benzoate was added into the dianion at −40 °C. After 0.5 h at that temperature, the reaction mixture was warmed to room temperature for 1 h. The reaction was quenched with methanol and treated with aq HCl to complete the cyclization/dehydration. Then the reaction mixture was neutralized to pH 8 and extractive workup was carried out to give the product mixture which was subjected to crystallization in EtOAc to furnish compound **6a** in 68% yield as a tan-colored solid (Table 2, entry 1). Presumably, the reaction proceeded through a number of transformations as indicated in Figure 2.

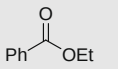
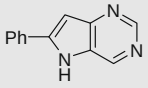
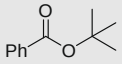
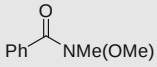
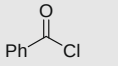
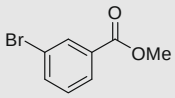
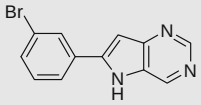
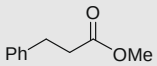
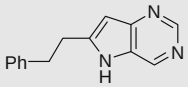
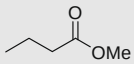
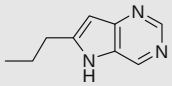
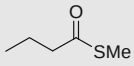
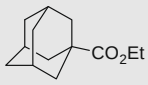
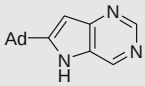
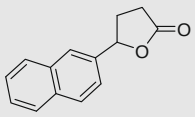
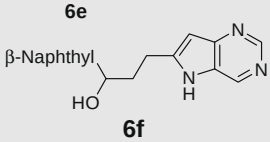
The new method was also applied to a variety of other carboxylic acid derivatives. It is worth noting that *t*-butyl benzoate and Weinreb amide of benzoic acid worked equally well to give compound **6a** in 68% yields (Table 2, entries 2 and 3). Even benzoyl chloride could be condensed with this dianion to provide the desired product **6a** in 24% yield (entry 4). Reaction with methyl 3-bromobenzoate gave 67% yield without the detection of the debrominated byproduct (entry 5). Enolizable esters such as methyl hydrocinnamate and methyl butyrate gave 63% and 54% yields, respectively (entries 6 and 7). Thioester was also successfully utilized for this reaction (entry 8). The sterically demanding adamantyl-substituted ester gave product **6e** in 77% yield (entry 9). Finally a lactone substrate was converted into compound **6f** in 51% yield (entry 10).

In conclusion, we have described a one-step method for an expedient and facile access to a range of 2-substituted-4,6-diazaindoles in good to moderate yields. Treatment of the unprotected 5-amino-4-methylpyrimidine with *n*-BuLi generated dianion **3** which was allowed to react with various esters, an amide, an acid chloride, and a thioester to give the corresponding diazaindole products in a single synthetic step. This method uses inexpensive reagents and readily available starting materials. It does not require the use of protecting groups and is operationally simple. We believe that this new method will prove to be useful for the synthesis of diazaindole-containing compounds.

Table 2
One-step diazaindole formation via dianion of 5-amino-4-methylpyrimidine



Z = OR_1, SR_1, Cl or NR_1R_2

Entry	Substrate	Product	Yield (%)
1		 **6a**	68[a]
2			68[a]
3			68[a]
4			24[a]
5		 **6b**	67[a]
6		 **6c**	63[b]
7		 **6d**	54[b]
8			47[a]
9		 **6e**	77[a]
10		 **6f**	51[b]

[a] Isolated yields by crystallization.
[b] Isolated yields by chromatography.

3. Experimental

3.1. General procedure

5-Amino-4-methylpyrimidine (1.09 g, 10 mmol) was dissolved in anhydrous THF (50 mL) in a dry flask under nitrogen. The solution was cooled to −20 °C and a solution of *n*-BuLi (2.5 M in hexanes, 10 mL, 25 mmol) was added in 10 min. The solution was kept at −20 °C for 30 min and then warmed to rt, stirred at that temperature for 3 h, and cooled to −40 °C. Substrate (3 mmol, dissolved in ca. 2 mL THF; ca. 0.5 mL rinse) was added and the resulting mixture was stirred at −40 °C for 0.5 h and warmed to rt for 1 h. Methanol (15 mL) was added in 5 min followed by HCl (10 mL 6 N aq). The solution was stirred for 15 h at rt. The mixture was neutralized with $NaHCO_3$ (50 mL, pH 8). EtOAc (100 mL) and water (50 mL) were added. Then organic layer was washed with water (50 mL) three times. The crude product mixture was purified by silica gel chromatography (CH_2Cl_2/MeOH) or crystallization (EtOAc/hexanes) to give product in yields reported in Table 2. Copies of ^{1}H and ^{13}C NMR of isolated products are provided as Supplementary data to demonstrate homogeneity of samples. Purities of

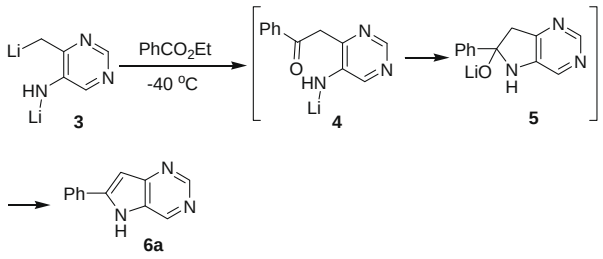


Figure 2. Proposed reaction pathway.

isolated products were also measured by HPLC. HPLC method: Tosohass super-ODS column 4.6 mm × 5 cm, particle size 2 μm; wavelength 220 nm; gradient 10% acetonitrile/water (with 0.05% trifluoroacetic acid) to 90% in 3.5 min, hold 1.5 min; flow rate 2 mL/min at 25 °C.

3.1.1. 6-Phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6a)

^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.31 (br s, 1H), 8.87 (s, 1H), 8.81 (s, 1H), 8.00 (d, J = 7.36 Hz, 2H), 7.54 (t, J = 7.32 Hz, 2H), 7.45 (m, 1H), 7.14 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.5, 150.2, 144.9, 139.3, 130.6, 129.4, 129.1, 128.4, 126.2, 98.3. HPLC: 100 area%. HRMS calcd for the $[M+1]^+$: 196.0869, found: 196.0873.

3.1.2. 6-(3-Bromophenyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (6b)

^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.38 (br s, 1H), 8.90 (s, 1H), 8.82 (s, 1H), 8.24 (s, 1H), 8.01 (d, J = 7.80 Hz, 1H), 7.63 (d, J = 7.96 Hz, 1H), 7.49 (t, J = 7.88 Hz, 1H), 7.24 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.6, 149.9, 143.0, 139.7, 132.9, 131.9, 131.2, 128.5, 128.4, 126.2, 125.2, 122.5, 99.4. HPLC: 100 area%. HRMS calcd for the $[M+1]^+$: 273.9974, found: 273.9989.

3.1.3. 6-Phenethyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6c)

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.78 (br s, 1H), 8.74 (s, 1H), 8.70 (s, 1H), 7.27 (m, 4H), 7.18 (m, 1H), 6.36 (s, 1H), 3.12 (m, 2H), 3.05 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.2, 149.9, 148.4, 140.7, 138.1, 128.3, 128.2, 127.1, 126.0, 98.8, 34.0, 29.7. HPLC: 98.9 area%. HRMS calcd for the $[M+1]^+$: 224.1182, found: 224.1190.

3.1.4. 6-Propyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6d) (known compound[5a])

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.70 (br s, 1H), 8.72 (s, 1H), 8.71 (s, 1H), 6.35 (d, J = 1.00 Hz, 1H), 2.79 (t, J = 7.52 Hz, 2H), 1.74 (m, 2H), 0.94 (t, J = 7.32 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.3, 149.8, 149.1, 146.6, 137.9, 127.2, 98.5, 29.9, 21.6, 13.6. HPLC: 100 area%. HRMS calcd for the $[M+1]^+$: 162.1025, found: 162.1030.

3.1.5. 6-Adamantan-1-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6e)

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.63 (s, 1H), 8.71 (s, 2H), 6.30 (s, 1H), 2.05 (s, 3H), 1.97 (s, 6H), 1.74 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.6, 149.8, 138.1, 127.1, 95.5, 41.2, 36.0, 34.0, 27.7. HPLC: 100 area%. HRMS calcd for the $[M+1]^+$: 254.1651, found: 254.1657.

3.1.6. 1-Naphthalen-2-yl-3-(5*H*-pyrrolo[3,2-*d*]pyrimidin-6-yl)-propan-1-ol (6f)

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.71 (br s, 1H), 8.71 (s, 1H), 8.70 (s, 1H), 8.00–7.85 (m, 4H), 7.57–7.42 (m, 3H), 6.38 (s, 1H), 5.50 (d, J = 4.40 Hz, 1H), 4.78 (ddd, J = 7.20, 5.30, 5.30 Hz, 1H), 2.97–2.82 (m, 2H), 2.22–2.05 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.3, 149.8, 149.1, 143.3, 137.9, 132.8, 132.2, 127.7, 127.6, 127.5, 127.2, 126.0, 125.5, 124.5, 124.0, 98.4, 71.5, 37.7, 24.6. HPLC: 100 area%. HRMS calcd for the $[M+1]^+$: 304.1444, found: 304.1454.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.080.

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