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A convenient one-pot synthesis of 4-, 6-, and 7-azaindoles from aminopyridines

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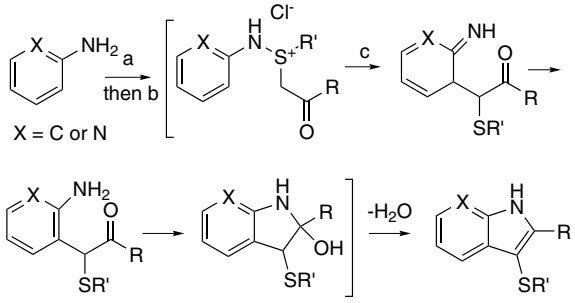
Abstract—A one-pot synthesis of a variety of substituted 4-, 6-, and 7-azaindoles from commercially available aminopyridines in moderate to good yields is described.

Azaindoles are an important component of many natural products and pharmaceuticals.[1] Methods used to construct azaindoles have included palladium(0)-catalyzed coupling of acetylenes and iodinated aminopyridines,[2a–c] palladium-catalyzed annulation of chloroaminopyridines with ketones,[2d] Madelung-type cyclizations,[3] Pictet–Spengler reaction followed by dehydrogenation,[4] modified Reissert reactions,[1f,5b] Lorenz-type cyclization,[5a,6] and Bartoli cyclization.[7] These methods commonly suffer from either poor yields, limited scope or availability of appropriate starting materials. Since construction of the azaindole core is often among the first steps in the synthesis of a more complex molecule, it is desirable to synthesize azaindoles from readily available starting materials in good yields.

Gassman and van Bergen reported a convenient but underutilized process to construct indoles from anilines and ketosulfides.[8] Treatment of an aniline with a halogenating agent (i.e., *t*-BuOCl), followed by addition of a ketosulfide produces an azasulfonium salt. Subsequent treatment with base results in a Sommelet–Hauser type rearrangement, followed by rearomatization. Cyclization of the resultant aniline provides the indoline, which upon dehydration gives the indole (Scheme 1). Yields for this one-pot process are reported to be between 58% and 72%.[8]



Scheme 1. Mechanism of one-pot synthesis of substituted indoles. Reagents: (a) *t*-BuOCl; (b) $RCOCH_2SR'$; (c) NEt_3.

Gassman reported the use of a modified version of this methodology for the construction of the azaindoles 2-methyl-3-thiomethyl-7-azaindole and 2,4-dimethyl-3-thiomethyl-7-azaindole (**2f**), but reported yields were fairly low (45% and 25%, respectively).[9] Because numerous 2- and 3-aminopyridines are commercially available, or readily accessible by amination of the appropriate halopyridine, we elected to expand this methodology for the construction of a variety of 7-azaindoles as well as 4- and 6-azaindoles.

When a solution of 2-amino-6-picoline in CH_2Cl_2 at −78 °C was treated with 2 equiv of *t*-BuOCl followed by the addition of 1 equiv of methylthioacetone then 1 equiv of triethylamine, the 6-methyl-3-thiomethyl-7-azaindole (**2a**) was isolated in 87% yield as an off-white solid after simple flash chromatography.

With the success of 2-amino-6-picoline, reactions with other 2-aminopyridines were investigated. While the

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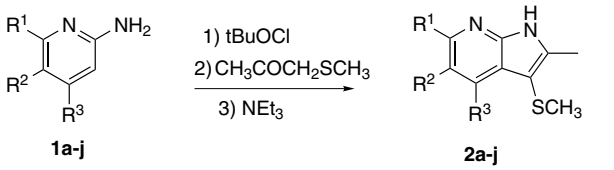
Table 1. Substituted 3-thiomethyl-7-azaindoles



Compound	R^1	R^2	R^3	Temperature (°C)	Yield[d] (%)
2a[a]	CH_3	H	H	−78	87
2b	Br	H	H	−78	59
2c[a]	CH_3	H	CH_3	−40	46
2d[a]	H	NO_2	H	−40	13
2e[a]	H	CH_3	H	−40	63
2f[a]	H	H	CH_3	−40	46
2g[a]	H	CF_3	H	−40	50
2h[c]	OCH_3	H	H	−78	56
2i[b]	H	F	H	−40	22
2j	CF_3	H	H	−40	44

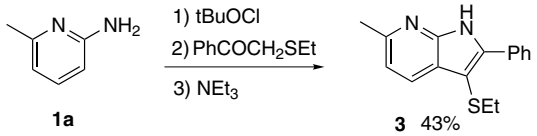
[a] Reactions run with 2 equiv of *t*-BuOCl.
[b] Product isolated as the 2-hydroxy-2-methyl indoline.
[c] *t*-BuOCl was added to a solution of aminopyridine and ketone. See text for details.
[d] Refers to isolated product yields.

unoptimized yields were somewhat variable with 87% yield for the preparation of **2a** to 13% for 5-nitro-3-thiomethyl-7-azaindole (**2d**), most yields were approximately 45–60% (Table 1). In the case of 2-amino-6-methoxypyridine, the inverse addition of *t*-BuOCl to a solution of **2j** and methylthioacetone was used to prevent halogenation of the aromatic ring. It was found that for many substrates, yields could be improved by running the reaction at −40 °C. In all cases, the majority of the remainder of the mass balance was unreacted starting material.

When desired, treatment with Raney Nickel in EtOH for 15 min provides the dethiolated material in excellent yield. It should be noted that in the case of halogenated substrates such as **2b**, addition of 1–5% acetic acid to the Raney Nickel dethiolation reaction suppresses dehalogenation to allow for isolation of the 6-bromo-2-methyl-7-azaindole in 40% yield from the remaining 2-methyl-7-azaindole.

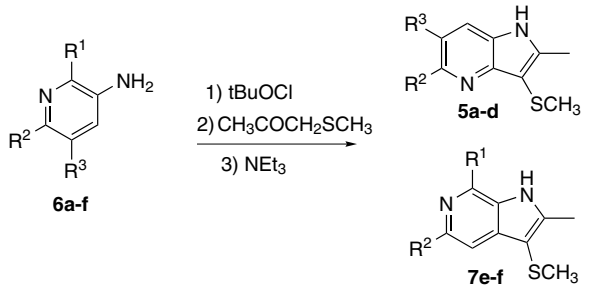
Ketosulfides other than methylthioacetone were briefly examined (Scheme 2). For example, reaction of **1a** with ethylthioacetophenone gave **3** in modest yield (48%).

Synthesis of 4- or 6-azaindoles would require the use of 3-aminopyridines (**6a**–**f**). 6-Azaindoles were prepared using 2-substituted 3-aminopyridines (Table 2). For example, 3-amino-2-chloropyridine was used to prepare



Scheme 2. Synthesis of 3-(ethylthio)-6-methyl-2-phenyl-1*H*-pyrrolo-[2,3-*b*]pyridine from 2-amino-6-picoline.

Table 2. Synthesis of substituted 4- and 6-azaindoles



Product	R^1	R^2	R^3	Temperature (°C)	Yield[b] (%)
5a[a]	H	$-CH(CH)_2CH-$		0	91
5b	H	Cl	H	−78	70
5c	H	CF_3	H	−10	41
5d	H	H	H	−40	25
7e	Cl	H	H	−78	94
7f	OCH_3	H	H	−78	35

[a] Reaction run with 2 equiv of *t*-BuOCl.
[b] Refers to isolated product yields.

7e in 94% yield. However, when 3-aminopyridine or 6-substituted-3-aminopyridines were used, the corresponding 4-azaindoles (**5a**–**d**) were isolated from the reaction mixture exclusively.

A limited number of 4-aminopyridines are available commercially from which 5-azaindoles could be prepared via this route. To date, 4-aminopyridines have been unreactive to these reaction conditions even at room temperature.

In conclusion, this methodology provides a one-pot synthesis of 4-, 6-, and 7-azaindoles from readily available aminopyridines.[10] Yields for the transformation vary with respect to substrate but are generally moderate to good.

General procedure for the preparation of azaindoles as exemplified by the preparation of 2,6-dimethyl-3-thiomethyl-7-azaindole. To a solution of 2-amino-6-picoline (840 mg, 7.78 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added a solution of *t*-BuOCl (2 equiv, 1.76 mL) in CH_2Cl_2 (6 mL). The reaction stirred for 10–15 min prior to the addition of methylthioacetone (1 equiv, 0.8 mL) in CH_2Cl_2 (6 mL). After 90 min, a solution of NEt_3 (1 equiv, 1.2 mL) in CH_2Cl_2 (6 mL) was added and the reaction warmed to ambient temperature. The reaction was quenched by the addition of water and the layers allowed to separate. The organic layer was dried over Na_2SO_4 and concentrated. Purification, when necessary, was by flash chromatography, which provided the product (87%).

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10. Selected data for the aforementioned azaindoles. Compound **2a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.28 (br s, 1H); 7.87 (d, J = 7.8 Hz, 1H); 7.00 (d, J = 7.8 Hz, 1H); 2.69 (s, 3H); 2.61 (s, 3H); 2.25 (s, 3H). Compound **2b**: ^{1}H NMR (500MHz, $CDCl_3$): δ 9.45 (br s, 1H); 7.81 (d, J = 5 Hz, 1H); 7.27 (d, J = 5 Hz, 1H); 2.61 (s, 3H); 2.25 (s, 3H). Compound **2c**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.74 (s, 1H); 2.85 (s, 3H); 2.60 (s, 3H); 2.58 (s, 3H); 2.29 (s, 3H). Compound **2d**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.29 (br s, 1H); 9.17 (d, J = 1.2 Hz, 1H); 8.81 (d, J = 1.2 Hz, 1H); 2.68 (s, 3H), 2.31 (s, 3H). Compound **2e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.25 (br s, 1H); 8.08 (d, J = 1.6 Hz, 1H); 7.78 (d, J = 1.6 Hz, 1H); 2.62 (s, 3H); 2.49 (s, 3H); 2.25 (s, 3H). Compound **2f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.32 (br s, 1H); 8.09 (d, J = 5.1 Hz, 1H); 6.86 (d, J = 5.1 Hz, 1H); 2.91 (s, 3H); 2.63 (s, 3H); 2.24 (s, 3H). Compound **2g**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.17 (br s, 1H); 8.52 (s, 1H); 8.23 (s, 1H); 2.68 (s, 3H); 2.29 (s, 3H). Compound **2h**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (br s, 1H); 7.83 (d, J = 8.4 Hz, 1H); 6.60 (d, J = 8.4 Hz, 1H); 3.95 (s, 3H); 2.50 (s, 3H); 2.25 (s, 3H). Compound **2i**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, J = 2.9 Hz, 1H); 7.34 (m, 1H); 6.63 (d, J = 6.9 Hz, 1H); 6.10 (br s, 1H); 5.56 (s, 1H); 2.42 (s, 3H); 1.87 (s, 3H). Compound **2j**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.10 (br s, 1H); 8.09 (d, J = 8 Hz, 1H); 7.52 (s, J = 8 Hz, 1H); 2.63 (s, 3H); 2.27 (s, 3H). Compound **3**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.14 (br s, 1H); 7.98 (d, J = 7.3 Hz, 2H); 7.89 (d, J = 7.9 Hz, 1H); 7.50 (t, J = 8.0 Hz, 2H); 7.40 (t, J = 7.4 Hz, 1H); 7.03 (d, J = 7.9 Hz, 1H); 2.65 (m, 2H); 2.54 (s, 3H); 1.00 (t, J = 5.3 Hz, 3H). Compound **5b**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 (br s, 1H); 7.51 (d, J = 4.2 Hz, 1H); 7.08 (d, J = 4.2 Hz, 1H), 2.59 (s, 3H); 2.36 (s, 3H). Compound **5c**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.90 (br s, 1H); 7.66 (d, J = 3.9 Hz, 1H); 7.46 (d, J = 3.9 Hz, 1H); 2.77 (s, 3H); 2.60 (s, 3H); 2.39 (s, 3H). Compound **7d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (br s, 1H); 8.49 (dd, J = 1,5 Hz, 1H); 7.66 (d, J = 8 Hz, 1H); 7.11 (dd, J = 5,8 Hz, 1H); 2.62 (s, 3H); 2.36 (s, 3H). Compound **7e**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.2 (br s, 1H); 8.08 (d, J = 6.0 Hz, 1H); 7.69 (d, J = 6.0 Hz, 1H); 2.68 (s, 3H); 2.25 (s, 3H). Compound **7f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (br s, 1H); 7.80 (d, J = 5.7 Hz, 1H); 7.21 (d, J = 5.5 Hz, 1H); 4.06 (s, 3H); 2.51 (s, 3H); 2.24 (s, 3H).