Notes

A General Method for the Preparation of 4- and 6-Azaindoles

Zhongxing Zhang, Zhong Yang, Nicholas A. Meanwell, John F. Kadow, and Tao Wang*,†

Department of Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492

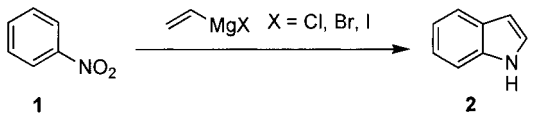
wangta@bms.com

Received December 20, 2001

Abstract: Nitropyridines reacted with an excess of vinyl Grignard reagent to produce 4- or 6-azaindoles. Improved yields were obtained when a halogen atom was present at the position α to the nitrogen atom in the pyridine ring.

The azaindole ring system is a structural motif present in a variety of natural products, pharmaceuticals, and diverse synthetic intermediates.[1] Investigations into the preparation of this heterocycle can be traced back to 1943.[2a] To date, the most common methods used for the preparation of azaindoles include the Madelung-type cyclization,[2b] a Reissert-type procedure,[2c−e,3a] the Leimgruber−Batcho reaction[2f,g] and a Lorenz-type cyclization.[2g,h] Recently, several groups have described an elegant, palladium(0)-catalyzed methodology for the construction of azaindoles starting from acetylenes and iodinated amino-pyridines.[3] However, due to the limited availability of appropriately substituted substrates for many of these procedures, significant effort is required to secure starting materials for their implementation. Prompted by a need to synthesize azaindoles from readily available starting materials, we developed a general and efficient method for preparing azaindoles from nitropyridines using the protocol originally developed by Bartoli for the synthesis of indoles.

Scheme 1



1 **2**

The Bartoli cyclization (Scheme 1) has been extensively utilized in the synthesis of indole derivatives from nitrobenzene derivatives.[4] Due to the close structural similarity between the indole and azaindole ring systems, it was anticipated that the Bartoli reaction would provide a concise, preparative approach to azaindoles. Surprisingly, the reaction of nitropyridines with vinylmagnesium halides to afford azaindole derivatives appears to be undocumented.

To test the feasibility of applying the Bartoli cyclization strategy to the synthesis of azaindoles, commercially available 2-methoxy-3-nitropyridine **3a** was treated with 3 to 4 equiv of vinylmagnesium bromide in THF at −78 °C. After warming to −20 °C, the reaction mixture was quenched with 20% aqueous NH_4Cl to afford a crude product that appeared surprisingly clean by LC analysis. Purification via flash chromatography provided a 20% yield of the desired 7-methoxy-6-azaindole **4a**. Although modest, this yield is comparable to that obtained in the preparation of indoles.

Encouraged by this result, the procedure was examined in the context of a variety of commercially available nitropyridines, and as summarized in Table 1, reliably produced either 4- or 6-azaindole derivatives. Generally, yields were only low to moderate, as is often observed in the preparation of indoles, but two phenomena are noteworthy. First, consistent with an observation reported by Dobson and co-workers,[4c] larger substituents directly adjacent to the nitro group produced higher yields of the azaindole products, as demonstrated by entries 1, 2, 8, and 9 in Table 1. A second observation, which appears to be unique to azaindole series, is that a halogen atom at the α- or 4-position of the pyridine ring is associated with a significantly increased yield of product. For example, while 4-methyl-3-nitro-pyridine **3f** afforded the corresponding azaindole **4f** in 18% yield (Table 1, entry 6), 2-chloro-4-methyl-3-nitropyridine **3g** provided the cognate azaindole **4g** in 50% yield (Table 1, entry 7). Further evidence of this phenomenon can be found by comparing the matched pairs represented by entries 4 and 5 and entries 9 and 10.

Although the precise origin of this effect remains to be elucidated, it may be a consequence of an overall enhanced electrophilicity of the substrate. Nevertheless, this observation has practical consequences since the

† This report is dedicated to Professor Gilbert Stork on the occasion of his 80th birthday.

(1) (a) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 3217. (b) Shin-Ya, K.; Kim, J.-S.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Asian Nat. Prod. Res.* **2000**, *2*, 121. (c) Nagel, A. A. EP 0870768 Oct 14, 1998. (d) Clark, R. D.; Clarke, D. E.; Fischer, L. E.; Jahangir, A. US 5,212, 195 May 18, 1993. (e) Cassidy, F.; Hughes, I.; Rahman, S. S.; Hunter, D. J. WO 96/11929 April 25, 1996. (f) Desarbre, E.; Coudred, S.; Meheust, C.; Merour, J.-Y. *Tetrahedron* **1997**, *53*, 3637. (g) Dormoy, J.-R.; Heymes, A. *Tetrahedron* **1993**, *49*, 2885. (h) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

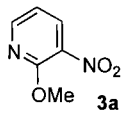
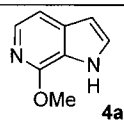
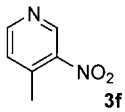
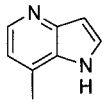
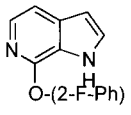
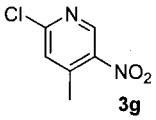
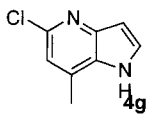
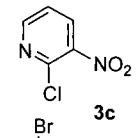
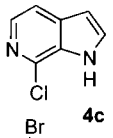
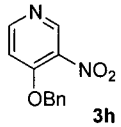
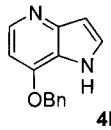
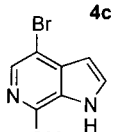
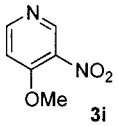
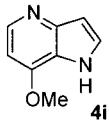
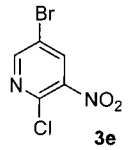
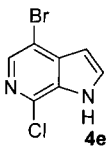
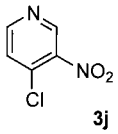
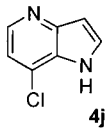
(2) (a) Kruber, O. *Chem. Ber.* **1943**, *76*, 128. (b) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Conttrell, I. F.; Wright, S. H. B. A. *Synthesis* **1996**, 877. (c) Yakhontov, L. N.; Azimov, V. A.; Lapan, E. I. *Tetrahedron Lett.* **1969**, 1909. (d) Fisher, M. H.; Matzuk, A. R. *J. Heterocycl. Chem.* **1969**, *6*, 775. (e) Dodd, R. H.; Doisy, X.; Potier, P. *Heterocycles* **1989**, *28*, 1101. (f) Battersby, A. R.; McDonald, E.; Wurziger, H. K. W.; James, K. J. *J. Chem. Soc., Chem. Commun.* **1975**, 493. (g) Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29*, 359. (h) Lorenz, R. R.; Tullar, B. F.; Koelsch, C. F.; Archer, S. *J. Org. Chem.* **1965**, *30*, 2531.

(3) (a) Curtis, N. R.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emms, F.; Freedman, S. B.; Patel, S.; Patel, S. *Biorg. Med. Chem. Lett.* **1999**, *9*, 585. (b) Park, S. S.; Choi, J.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627. (c) Xu, L.; Lewis, I. R.; Davidsen, S. K.; Summers, J. B. *Tetrahedron Lett.* **1998**, *39*, 5159. (d) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355.

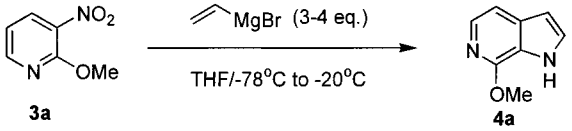
(4) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozz, R. *Tetrahedron Lett.* **1989**, *30*, 2129. (b) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991** 657. (c) Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611. (d) Dobbs, A. B.; Voyle, M.; Whittall, N. *Synlett.* **1999**, 1594.

10.1021/jo0111614 CCC: $22.00
Published on Web 03/09/2002

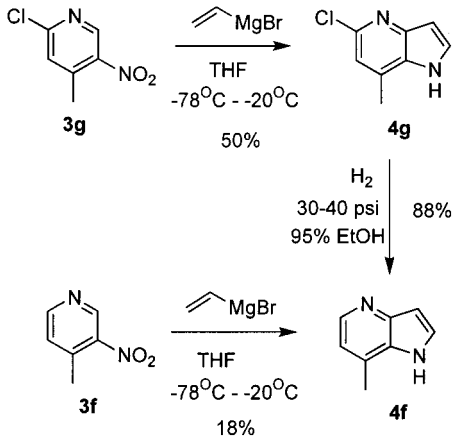
Table 1. Preparation of 4- and 6-Azaindole from Nitropyridine

	Pyridine	Azaindole	Isolated Yield		Pyridine	Azaindole	Isolated Yield
1	 **3a**	 **4a**	20%	6	 **3f**	 **4f**	18%
2	 **3b**	 **4b**	35%	7	 **3g**	 **4g**	50%
3	 **3c**	 **4c**	33%	8	 **3h**	 **4h**	25%
4	 **3d**	 **4d**	22%	9	 **3i**	 **4i**	11%
5	 **3e**	 **4e**	35%	10	 **3j**	 **4j**	30%

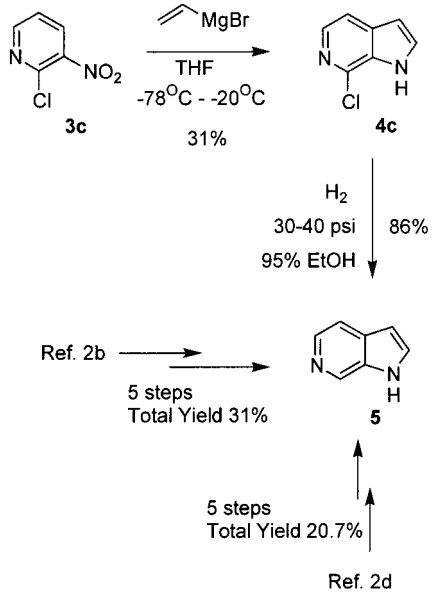
Scheme 2



Scheme 3



Scheme 4



halogen atom may be exploited as a protecting element in the preparation of azaindole derivatives, as summarized in Scheme 3. While the direct reaction of 7-methyl-4-azaindole **3f** with vinylmagnesium bromide afforded the azaindole **4f** in 18% yield (Table 1, entry 6), a two-step procedure comprised of a Bartoli reaction using 2-chloro-5-nitro-4-methylpyridine **3g** followed by a raised-pressure hydrogenolysis afforded 7-methyl-4-azaindole **4f** in an overall yield of 44%.

To further illustrate the advantage of this process, comparison can be drawn with known procedures. For example, Fisher and Matzuk developed a five-step procedure to synthesize 6-azaindole in an overall yield of 20%[2d] and Hands et al reported a four-step process that produced the product in an overall yield of 31%.[2b] The process depicted in Scheme 4 provided 6-azaindole **5** in 27% overall yield in only two steps.

The method reported herein provides the first examples of the preparation of azaindoles via the Bartoli reaction, and it is useful for the synthesis of 4- and 6-azaindoles, offering simplicity and efficiency. In principle, 5- and 7-azaindoles should be available through a similar approach using the appropriate nitropyridine starting materials.

Experimental Section

General. Vinylmagnesium bromide, tetrahydrofuran, and nitropyridines in entries 1−3, 6, 7, 9, and 10 (Table 1) are

commercially available and were used as received. Nitropyridines in entries 4, 5, and 8 (Table 1) were prepared according to published procedures.[5−7] ^{1}H and ^{13}C NMR spectra were obtained at 500 MHz with samples dissolved in CD_3OD, $CDCl_3$, or DMSO-d_6.

General Procedure for the Preparation of Azaindoles as Exemplified by the Preparation of 7-Chloro-6-azaindole 4c. 2-Chloro-3-nitropyridine **3c** (5.0 g, 31.5 mmol) was dissolved in dry THF (200 mL) under N_2, and the solution was cooled to −78 °C. Excess vinylmagnesium bromide (1.0 M in THF, 100 mL, 100 mmol) was added and the reaction mixture stirred at −20 °C for 8 h before the reaction was quenched with 20% NH_4Cl (150 mL). The aqueous phase was extracted with EtOAc (3 × 150 mL) and the combined organic layer dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography to afford 7-chloro-6-azaindole **4c** (1.5 g, 31%).

(5) Lindstroem, S.; Eriksson, M.; Grivas, S. *Acta Chem. Scand.* **1993**, *47*, 805.
(6) Sharnin, G. P.; Falyakhov, I. F.; Khairutdinov, F. G. *Khim. Geterotsikl. Soedin.* **1980**, *12*, 1632.
(7) Daisley, R. W.; Hanbali, J. R. *Synth. Commun.* **1981**, *11*, 743.

Acknowledgment. The authors are very grateful to Ms. Marie D'Andrea for assistance in obtaining exact MS spectra.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra and HRMS data of compounds **4a**−**j** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0111614