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Synthesis of 4- and 6-Azaindoles via the Fischer Reaction

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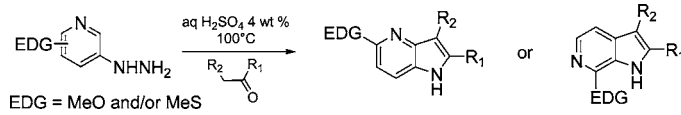
ABSTRACT



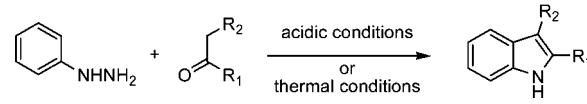
Contrary to the common idea that Fischer indole cyclization often cannot be effectively applied to the synthesis of the corresponding azaindoles, we show that this approach can be actually very efficient for the formation of 4- and 6-azaindoles bearing an electron-donating group on the starting pyridylhydrazines. Two 4-azaindole natural product analogues were synthesized in a few steps and very good overall yields.

Azaindoles are prevalent substructures in naturally occurring and synthetic molecules displaying biological as well as physicochemical activities. In the context of drug discovery, these scaffolds have already shown their potential for example as bioisosteres of the most biologically privileged indole ring system. Consequently, the development of efficient ways to prepare these compounds constitutes an active and essential area of research.[1]

Most of the methods used to form azaindoles have been inspired, over the years, by various synthetic strategies developed for indole ring formation. These methods include the Madelung-type cyclization,[2] the Reissert-type procedure,[3] the Leimgruber−Batcho reaction,[4] the Lorenz-type cyclization,[5] palladium-catalyzed heteroannulations,[6] and the Bartoli sequence.[7]

Among these classical approaches to the formation of indole systems, the most well-known and versatile Fischer indole cyclization[8] (scheme 1) has rarely been applied to azaindole chemistry. This fact can be attributed to the unfavorable electron-deficient character of the pyridine ring in the [3,3]-sigmatropic rearrangement step of heterocyclization.[9]

Scheme 1. Fischer Synthesis of Indoles



Thus, very few examples of Fischer indole syntheses have been reported for the formation of azaindoles. Although the

(1) For general reviews about synthesis and reactivity of azaindoles, see: (a) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031. (b) Popowycz, F.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689. (c) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120.

(2) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Conttrell, I. F.; Wright, S. H. B. A. *Synthesis* **1996**, 877.

(3) (a) Yakhontov, L. N.; Azimov, V. A.; Lapan, E. I. *Tetrahedron Lett.* **1969**, 1909. (b) Fischer, M. H.; Matzuk, A. R. *J. Heterocycl. Chem.* **1969**, *6*, 775. (c) Dodd, R. H.; Doisy, X.; Potier, P. *Heterocycles* **1989**, *28*, 1101. (d) Curtis, N. R.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emms, F.; Freedman, S. B.; Patel, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585. (e) Dodd, R. H.; Ouannès, C.; Robert-Gréco, M.; Potier, P. *J. Med. Chem.* **1989**, *32*, 1272.

(4) (a) Battersby, A. R.; McDonald, E.; Wurziger, H. K. W.; James, K. J. *J. Chem. Soc., Chem. Commun.* **1975**, 493. (b) Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29*, 359.

(5) (a) Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29*, 359. (b) Lorenz, R. R.; Tullar, B. F.; Koelsch, C. F.; Archer, S. *J. Org. Chem.* **2000**, *65*, 1045.

(6) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (b) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307. (c) Curtis, N. R.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emms, F.; Freedman, S. B.; Patel, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585. (d) Park, S. S.; Choi, J.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627. (e) Xu, L.; Lewis, I. R.; Davidsen, S. K.; Summers, J. B. *Tetrahedron Lett.* **1998**, *39*, 5159. (f) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355. (g) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152.

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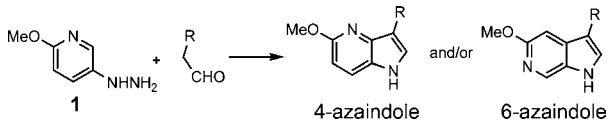
earliest attempts can be traced back to 1913,[10] the first positive result for 4-azaindoles appeared in the 1940s with the synthesis of 5-chloro-2-methyl-4-azaindole in 12% yield.[11]

In 1957, Fischer reactions were reported to run in the absence of acid[12] or in the presence of $ZnCl_2$[13] by heating to 180−250 °C. These harsh thermal conditions have proved unpopular for the preparation of azaindoles,[14] and the published results remained moderate in terms of yields, chemical functions tolerance, and/or isomers formation selectivity. Over the past 20 years, despite sporadic examples of azaindole ring formation via the Fischer reaction,[15] this method is still perceived as inappropriate for the synthesis of azaindoles.[16] In this Letter, we wish to counteract this idée reçue and show the extraordinary efficiency of Fischer cyclization for the formation of 4- and 6-azaindoles.

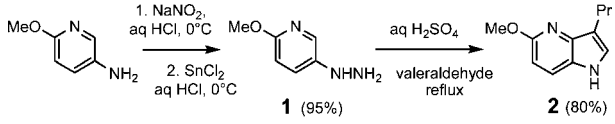
Considering that Fischer indole syntheses are often more efficient when involving arylhydrazines bearing electron-donating groups,[17] we started our investigation on the aza-Fischer cyclization with 6-methoxypyrid-3-ylhydrazine **1**. At this stage, it is worth noting that the absence of symmetry in **1** could allow the formation of two azaindole isomers (Scheme 2).

Scheme 2. Expected Isomers in the Azaindole Fischer Synthesis from Pyrid-3-ylhydrazines



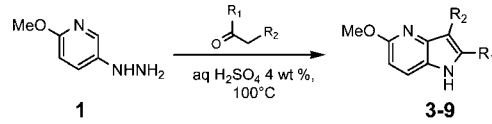
We first treated pyridylhydrazine **1**, prepared by formation and reduction of the corresponding diazonium salt,[18] with valeraldehyde in refluxing aqueous H_2SO_4 (4 wt %). After 2 h, we successfully isolated the 4-azaindole isomer **2** in 80% yield with no detectable amounts of the 6-azaindole isomer as determined by NMR (Scheme 3).

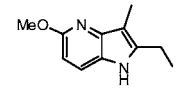
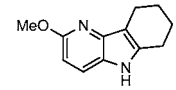
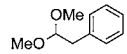
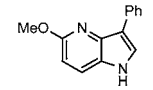
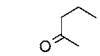
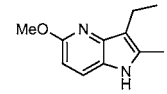
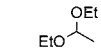
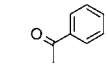
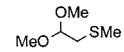
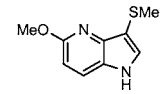
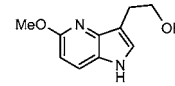
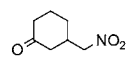
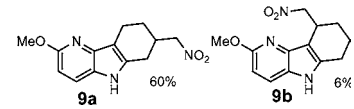
Scheme 3. Synthesis of 5-Methoxy-3-propyl-4-azaindole **2** via the Fischer Reaction



Evaluation of various carbonyl derivatives showed that this strategy is effective for a range of ketones or ketals (aldehyde deprotection proceeding in situ) (Table 1). Linear and cyclic alkyl ketones as well as alkylketals were efficient substrates

Table 1. Aza-Fischer Cyclization from **1** and Ketones or Ketals



entry	ketones or ketals	reaction time (h)	products[a]
1		2	 **3** 45%
2		2	 **4** 80%
3		15	 **5** 70%
4		2	 **6** 45%
5		15	0%[b]
6		2	0%[b]
7		24	 **7** 46%
8		24	 **8** 40%
9		2	 **9a** 60% **9b** 6%

[a] Isolated yield after column chromatography. [b] Degradation products were observed.

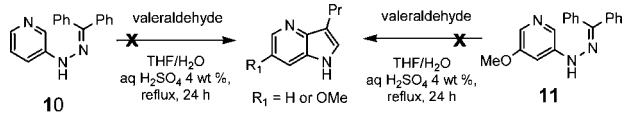
(entries 1−4). Nonsymmetric pentan-2-one was treated through the thermodynamic ene-hydrazine isomer to furnish only azaindole **6** (entry 4). The azaindole isomer resulting from cyclization through the terminal CH_3 of the methylketone was not observed. This lack of reactivity was confirmed with acetophenone (entry 6) and protected acetaldehyde (entry 5), no azaindole being recovered. The reaction was also applicable in the presence of functional groups (entries 7−9). Interestingly, using protected 4-chlorobutanal, we did not recover the expected azatryptamine as observed for indole series,[19] but we isolated the hydroxy derivative **8** resulting

(7) Zhang, Z.; Yang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002**, *67*, 2345.
(8) For reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, *25*, 607. (c) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.
(9) (a) Dollinger, M.; Henning, W.; Kirmse, W. *Chem. Ber.* **1982**, *115*, 2309. (b) Crooks, P. A.; Robinson, B. *Can. J. Chem.* **1969**, *47*, 2061.
(10) (a) Perkin, W. H.; Robinson, R. *J. Chem. Soc.* **1913**, 1973. (b) Fargher, R. G.; Furness, R. *J. Chem. Soc.* **1915**, 688.
(11) Takahashi, T.; Saikachi, H.; Goto, H.; Shimamura, S. *J. Pharm. Soc. Jpn.* **1944**, *64*, 7.
(12) Fitzpatrick, J. T.; Hiser, R. D. *J. Org. Chem.* **1957**, *22*, 1703.
(13) (a) Abramovitch, R. A.; Adams, K. A. *Can. J. Chem.* **1962**, *40*, 864, and references therein. (b) Ficken, G. E.; Kendall, J. D. *J. Chem. Soc.* **1959**, 3202.

probably from chlorine substitution prior to Fischer cyclization. Finally, using a nonsymmetric ketone, the competing formation of two different stable ene-hydrazine intermediates was observed, and the regioselectivity of the cyclization seemed to be oriented by steric effects (entry 9).

These excellent results prompted us to investigate the influence of the methoxy group on the starting pyridylhydrazine **1** in achieving this cyclization. We first replaced the methoxy group with a hydrogen atom. Attempts to synthesize the corresponding hydrazine were plagued by the formation of a complex mixture of products, probably due to the lack of stability of the hydrazine function. At this stage, the corresponding highly stable bisphenylhydrazone **10** was synthesized and led to a total absence of cyclization after 24 h (Scheme 4). A similar assessment was noted when the

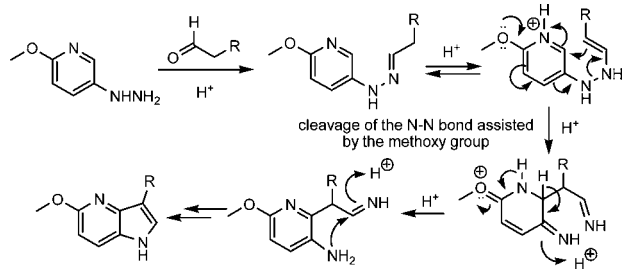
Scheme 4. Substituent Effects on the Aza-Fischer Cyclization



methoxy group is *meta* to the hydrazone function (compound **11**).[20]

From all of these considerations, the following mechanism was postulated to explain the crucial role played by the electron-donating group on the increased reactivity and high regioselectivity of the cyclization process (Scheme 5).

Scheme 5. Proposed Mechanism

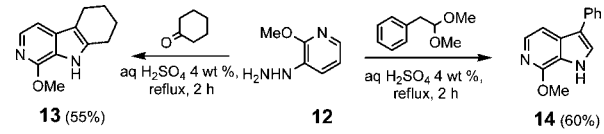


Following the generally accepted pathways for Fischer indole synthesis formulated by Robinson and Robinson in 1924,[21] the mesomeric effect of the methoxy group is thought to promote the N−N bond cleavage (push effect).[9,17,22] Concomitantly, the pyridinium nitrogen may help the new C−C bond formation (pull effect).

Therefore, a tandem push−pull effect could explain the unusual reactivity of this aza-indolization (Scheme 5), the cyclization at the α-position of the pyridine ring being in accordance with literature results.[11,13] On the basis of these mechanistic considerations, the success of Fischer azaindolization may be predicted with simple rules: pyridylhydrazine substrates bearing an electron-donating group on a position *ortho* or *para* to the hydrazine function could preferably help the heterocyclization in position 2 of the pyridine ring (or position 4 if position 2 is already substituted) in refluxing aqueous H_2SO_4 (4 wt %).

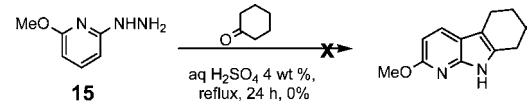
To check the relevance of these rules, we first used 3-hydrazinyl-2-methoxypyridine **12**,[23] expected to be a favorable substrate for Fischer cyclization. Cyclohexanone and protected phenylacetaldehyde were refluxed in aqueous H_2SO_4 (4 wt %) for 2 h with **12**, and the corresponding 6-azaindoles were indeed isolated in 55% and 60% yields, respectively (Scheme 6).

Scheme 6. Favorable 6-Azaindoles Aza-Fischer Synthesis



On the other hand, the expected unfavorable substrate 2-hydrazinyl-6-methoxypyridine **15**, obtained by aromatic nucleophilic substitution of the 2-chloro-6-methoxy-pyridine with hydrazine, was treated with cyclohexanone. As postulated, the 7-azaindole product was not isolated under the previously defined experimental conditions (Scheme 7).

Scheme 7. Unfavorable 7-Azaindole Aza-Fischer Synthesis



To check whether other electron-donating groups would be suitable for this Fischer cyclization, we introduced the

(14) (a) Okuda, S.; Robison, M. *J. Am. Chem. Soc.* **1959**, *81*, 740. (b) Kelly, A. H.; McLeod, D. H.; Parrick, J. *Can. J. Chem.* **1965**, *43*, 296. (c) Kelly, A. H.; Parrick, J. *Can. J. Chem.* **1966**, *44*, 2455. (d) Crooks, P. A.; Robinson, B. *Can. J. Chem.* **1969**, *47*, 2061.

(15) (a) Bernardino, A. M.; Ain Khan, M.; de Oliveira Gomes, A. *Heterocycl. Commun.* **2000**, *6*, 463. (b) Helissey, P.; Parrot-Lopez, H.; Renault, J.; Cros, S.; Paoletti, C. *Eur. J. Med. Chem.* **1987**, *22*, 277. (c) Shindo, H.; Fujishita, T.; Sasatani, T.; Chomei, N.; Takada, S. *Heterocycles* **1989**, *29*, 899. (d) Ain Khan, M.; da Rocha, J. F. *J. Heterocycl. Chem.* **1978**, *15*, 913. (e) Bisagni, E.; Nguyen, C. H.; Pierré, A.; Pépin, O.; de Cointet, P.; Gros, P. *J. Med. Chem.* **1988**, *31*, 398. (f) Chen, Y.; Chung, C.; Chen, I.; Chen, P.; Jeng, H. *Bioorg. Med. Chem.* **2002**, *10*, 2705. (g) Nguyen, C. H.; Bisagni, E. *Tetrahedron* **1987**, *43*, 527. (h) Bisagni, E.; Ducrocq, C.; Civier, A. *Tetrahedron* **1976**, *32*, 1383. (i) Hung, N. C.; Bisagni, E. *Tetrahedron* **1986**, *42*, 2303. (j) Nguyen, C.; Lhoste, J.-M.; Lavelle, F.; Bissery, M.-C.; Bisagni, E. *J. Med. Chem.* **1990**, *33*, 1519.

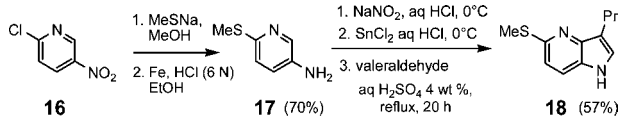
(16) Only very recently, Lachance and colleagues described the 6-azaindole synthesis under thermal conditions. Lachance, N.; Bonhomme-Beaulieu, L.-P.; Joly, P. *Synthesis* **2009**, 721.

(17) (a) Ishii, H. *Acc. Chem. Res.* **1981**, *14*, 275. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, *25*, 607.

(18) Regan, J.; Capolino, A.; Cirillo, P. F.; Gilmore, T.; Graham, A. G.; Hickey, E.; Kroe, R.; Madwed, J.; Moriak, M.; Nelson, R.; Pargellis, C. A.; Swinamer, A.; Torcellini, C.; Tsang, M.; Moss, N. *J. Med. Chem.* **2003**, *46*, 4676.

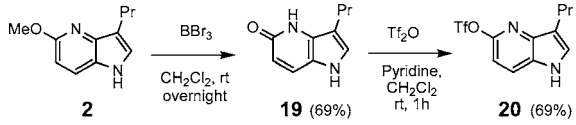
methylsulfanyl electron-donating group on the 2-chloro-5-nitropyridine **16**. Reduction of the nitro group into the amine **17**[24] followed by hydrazine synthesis according to the standard procedure allowed Fischer cyclization with valeraldehyde to afford 5-methylsulfanyl-4-azaindole **18** in 57% yield (Scheme 8).

Scheme 8. Methylsulfanyl Group in the Fischer Azaindole Synthesis



To further extend the scope of this efficient synthesis of 4- and 6-azaindoles, the methoxy group of **2** was treated with BBr_3,[25] and the resulting 5-hydroxy-4-azaindole **19** was isolated in 69% yield and afterward transformed in the corresponding triflate derivative **20** with Tf_2O (Scheme 9).[26]

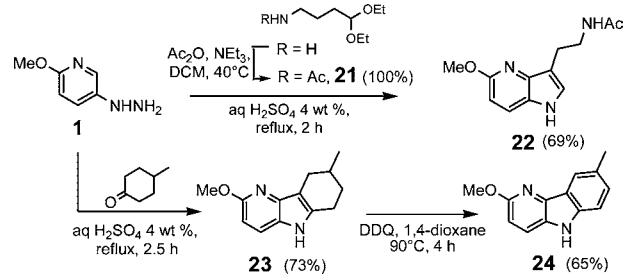
Scheme 9. Toward a Wider Scope of Subsituents in the Azaindole Core



At this stage, the triflate moiety could allow the introduction of numerous substituents.

Finally, to show the great interest of this methodology in term of simplicity, step economy, and efficiency, we performed the synthesis of the 4-azaindole analogue **22** of the well-known melatonin neurohormone[27] in 69% yield over only two steps from **1** (Scheme 10). We then focused on the

Scheme 10. Synthesis of 4-Azamelatonin and 4-Azaglycozoline



anticancer carbazoles series and synthesized in two steps from **1** the 4-aza analogue **24** of the natural glycozoline (extracted from the root bark of *Glycosmis pentaphylla*)[28] (Scheme 10).

In summary, we have shown that Fischer indole synthesis can indeed be used efficiently for the synthesis of 4- and 6-azaindoles and thus presents most of the advantages known and recognized for this cascade cyclization. The ubiquity of the indoles in natural products combined with the pharmaceutical relevance of this heterocyclic substructure should render this approach broadly useful to develop azaindole analogues. Work is in progress to extend the scope of this efficient synthesis.

Acknowledgment. The authors acknowledge Les Laboratoires Servier for financial support (M.J.).

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

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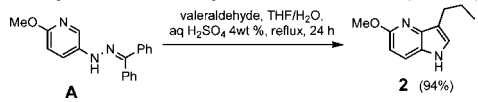
(20) We first confirmed that hydrazone **A** reacts as well as hydrazine **1** with valeraldehyde to successfully furnish azaindole **2** (scheme).



This result is in accordance with a report by Buchwald and colleagues: Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621.

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