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# Surprising selectivity in the transformation of dimethoxy azaindoles

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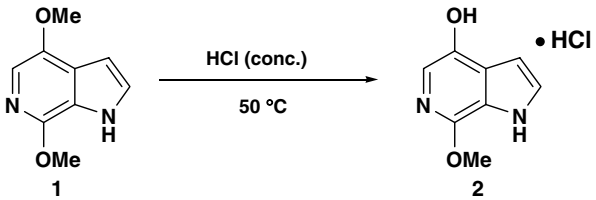
**Abstract**—Transformation of 4,7-dimethoxy-6-azaindole into 4-hydroxy-7-methoxy-6-azaindole or 7-hydroxy-4-methoxy-6-azaindole can be readily controlled by careful selection of a reagent. Treatment with concentrated HCl results in hydrolysis at the 4-position exclusively, while TMS-I provides demethylation at the 7-position only. Products were unambiguously identified by single crystal X-ray crystallography.


Azaindoles are an important heterocyclic core for a variety of medicinal chemistry applications.[1] As part of our investigations of azaindoles, we desired a quantity of 7-hydroxy-4-methoxy-6-azaindole. As we had a ready inventory of 4,7-dimethoxy-6-azaindole,[2] we envisioned a simple selective hydrolysis at the nitrogen-activated 7-methoxy moiety. A seemingly endless choice of reagents are available to enact the hydrolysis of methoxy groups.[3] Another possibility that presented itself was the use of demethylating agents such as Jung's procedure using TMS-I to demethylate alkyl methyl ethers.[3a]

We chose simple hydrolysis as our initial approach to achieve the desired compound. Upon treatment with concentrated HCl at 50 °C the starting 4,7-dimethoxy azaindole gave one compound in high yield, which we assumed was our desired product. In the process of routine analytical characterization of the isolated product, we discovered that we had produced compound **2** instead of the desired compound **3** (Scheme 1).[4]




**Scheme 1.** Unexpected demethylation at the 4-position.

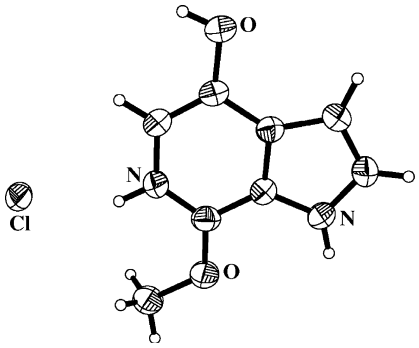



**Figure 1.** ORTEP representation of single crystal of 4-hydroxy-7-methoxy-6-azaindole.

Further evidence in the form of 2D $^1$H NMR as well as X-ray crystallography[5] (Fig. 1) confirmed the unexpected 4-hydroxy-7-methoxy-6-azaindole monohydrochloride as the exclusive product.

As a possible explanation for this counter-intuitive result, we envisioned a transient dicationic intermediate with protonation at the 3- and 5-positions (Scheme 2). Dications of other molecular cores are known in the literature.[6]

This mechanism becomes even more plausible if the hydrogen at the 5-position could be shown to exchange under the reaction conditions. In the laboratory, deuterium exchange was observed exclusively at the 3-position upon treatment of the dimethoxy starting material **1** with concentrated DCl in $D_2O$ at room temperature.

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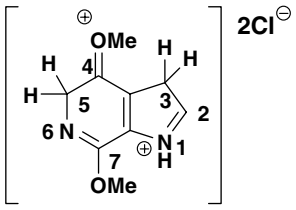



**Scheme 2.** Postulated transient dicationic intermediate.

When the reaction mixture was heated to 50 °C both the 3- and 5-protons were exchanged. In addition, confirmation that we were observing hydrolysis of the 4-methoxy group rather than demethylation was obtained by treating compound **1** with HCl in $H_2{}^{18}O$ at 50 °C. This resulted in a product containing one $^{18}O$ as evidenced by GC/MS. The fragmentation patterns strongly suggest the $^{18}O$ is part of the 4-hydroxy moiety which supports the case for hydrolysis, rather than demethylation. As a control, non-radiolabeled product was subjected to identical reaction conditions and only 30% incorporation of $^{18}O$ was observed, compared to 100% incorporation for the forward reaction.

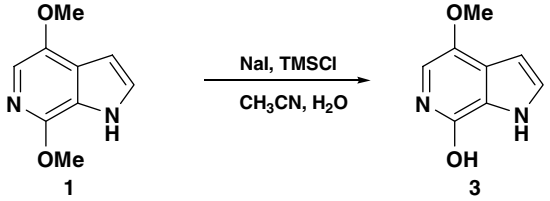
As it was clear that treatment with HCl did not give the desired product, we next chose to treat our starting material with TMS-I following the procedure of Curran et al.[7] (Scheme 3).

This time X-ray crystallography identified the product as the desired 7-hydroxy-4-methoxy-6-azaindole (Fig. 2).

With these two high-yielding procedures, we now had an effective means of derivatizing a 6-azaindole core in a selective manner. With this in mind, we decided to investigate the effects of other reagents on selectivity. Use of sulfuric acid at 50 °C gave results indistinguishable from the HCl results, that is, predominantly the 4-hydroxy-7-methoxy-6-azaindole with ~1% dihydroxy compound present.

Increasing counter-ion nucleophilicity, however, begins to alter selectivity. Hydrobromic acid gave a mixture of isomers, with the 4-hydroxy predominating, while hydroiodic acid produces a 2:1 mixture favoring the 7- over the 4-monohydroxy azaindoles (Fig. 3).

In conclusion, we have demonstrated easy access to both 4-hydroxy-7-methoxy-6-azaindole and 7-hydroxy-4-methoxy-6-azaindole from 4,7-dimethoxy-6-azaindole depending on reagent selection. Treatment with concentrated HCl results in hydrolysis at the 4-position, while TMS-I provides 7-demethylation, exclusively.




**Scheme 3.** Demethylation with sodium iodide/trimethylsilyl chloride to give the desired 7-hydroxy-4-methoxy-6-azaindole.

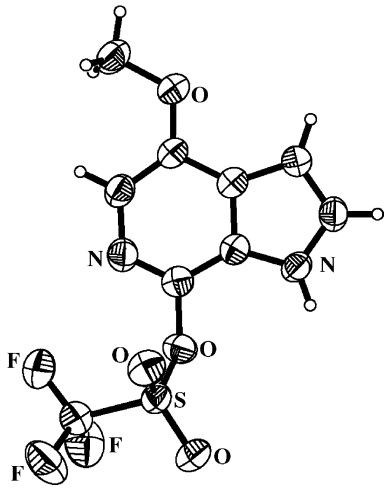



**Figure 2.** ORTEP representation of single crystal of 7-trifluoromethylsulfonyloxy-4-methoxy-6-azaindole.

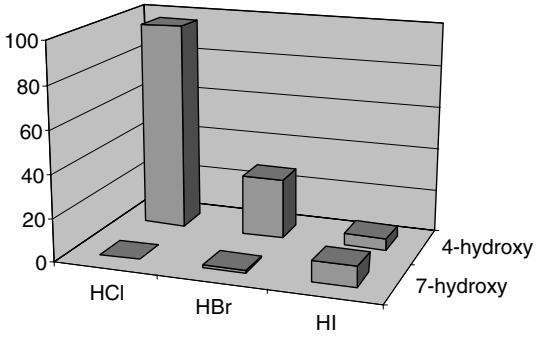



**Figure 3.** Product distribution depending on acid.

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## References and notes

1. (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045; (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 October 14, 1998; (d) Desarbre, E.; Coudred, S.; Meheust, C.; Merour, J.-Y. *Tetrahedron* **1997**, *53*, 3637; (e) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703; (f) Cassidy, F.; Hughes, I.; Rahman, S. S.; Hunter, D. J. WO 96/11929 April 25, 1996; (g) Clark, R. D.; Clarke, D. E.; Fischer, L. E.; Jahangir, A. U.S. Patent 5,212,195 May 18, 1993; (h) Dormoy, J.-R.; Heymes, A. *Tetrahedron* **1993**, *49*, 2885.
2. (a) Zhang, Z.; Yang, Z.; Meanwell, N.; Kadow, J.; Wang, T. *J. Org. Chem.* **2002**, *67*, 2345; (b) Yeung, K.-S.; Farkas,

M.; Kadow, J.; Meanwell, N.; Taylor, M.; Johnston, D.; Coulter, T. S.; Wright, J. J. K. PCT Int. Appl. WO 004801, 2005; *Chem. Abstr.* **2005**, *142*, 155974.

3. (a) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761; (b) Liang, X.; Desai, H. K.; Joshi, B. S.; Pelletier, S. W. *Heterocycles* **1990**, *31*, 1889; (c) Harrison, I. T.; Harrison, S. In *Compendium of Organic Synthetic Methods*; Wiley: New York, 1971; Vol. 1, p 92; (d) Harrison, I. T.; Harrison, S. In *Compendium of Organic Synthetic Methods*; Wiley: New York, 1974; Vol. 2, p 34.
4. *Standard experimental procedure*: 4,7-Dimethoxy-6-azaindole was dissolved in concentrated HCl (0.2 M). The light-brown solution was heated to 50 °C for 18 h. The reaction mixture was cooled to 0 °C and vacuum filtered. The solids were washed with acetonitrile and dried under vacuum to yield 73% of the 4-hydroxy-7-methoxy-6-azaindole. Spectral data below.
   Compound **2**: $^{1}$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.78 (s, 1H), 7.19 (s, 1H), 6.78 (s, 1H), 5.29 (s, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$): $\delta$ 56.1, 100.7, 104.2, 124.2, 126.0, 127.4, 139.8, 154.5; Anal. Calcd for $C_8H_9N_2O_2Cl$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.99; H, 4.48; N, 13.84.
5. Crystallographic data for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 618500 and CCDC 618501. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK [fax: +44 0 1223 336033; e-mail: depositr@ccdc.cam.ac.uk].
6. de Frutos, O.; Curran, D. P. *J. Comb. Chem.* **2000**, *2*, 639–649.
7. *Standard experimental procedure*: 4,7-Dimethoxy-6-azaindole was dissolved in acetonitrile (1.0 M). Sodium iodide (1.6 equiv) was then added to the solution followed by slow addition of trimethylsilyl chloride (1.6 equiv) and dropwise addition of water (0.5 equiv) (exotherm). The thick slurry was heated to 65 °C for 1–3 h. The reaction mixture was cooled to room temperature and water (0.3 M) was added dropwise. The solution was cooled to 0 °C and held for 1 h followed by vacuum filtration. The solids were washed with cold ethyl acetate and dried under vacuum (35 °C) to yield 87% of the 4-hydroxy-7-methoxy-6-azaindole. Spectral data below.
   Compound **3**: $^{1}$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.30 (s, 1H), 6.44 (s, 1H), 6.37 (s, 1H), 3.73 (s, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$): $\delta$ 101.1, 104.5, 124.6, 126.0, 126.9, 129.7, 154.2; Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.06; H, 4.77; N, 16.83.