Synthetic Methods

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Full Functionalization of the 7-Azaindole Scaffold by Selective Metalation and Sulfoxide/Magnesium Exchange**

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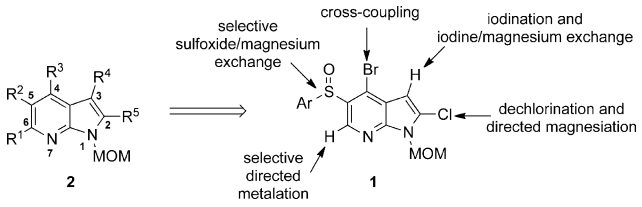
Azaindoles are valuable targets in the pharmaceutical and agrochemical industries due to their interesting cytotoxic activity.[1] 7-Azaindole derivatives in particular have found applications as luminescent molecules[2] and ligands.[3] Thus, synthetic methods for the simple construction and specific functionalization of such N-heterocycles are indispensable. So far, the Fischer[4,5] and Larock[6] indole syntheses have been applied for preparing 7-azaindoles. Functionalization of this heteroaromatic skeleton has also been successfully achieved by Buchwald et al.[7] Furthermore, the application of iterative lithiation for the functionalization of 7-azaindoles has already been elegantly demonstrated by Snieckus et al.[8] However, a general and mild functionalization procedure allowing the substitution of all the ring positions would be highly desirable. Herein, we report the preparation of an appropriately substituted 7-azaindole (**1**), which can undergo successive functionalization of all five carbon positions of the azaindole scaffold in a predictable manner. For achieving this synthetic goal, we used a combination of directed magnesiations and lithiations[9] as well as halogen/magnesium[10] and sulfoxide/magnesium exchanges.[11] To the best of our knowledge, this procedure constitutes a novel methodology for the stepwise full functionalization of these N-heterocycles, which allowed us to prepare various polysubstituted 7-azaindoles of type **2** (Scheme 1).



Scheme 1. The 7-azaindole scaffold **1** crucial for the preparation of fully substituted 7-azaindoles of type **2**. Ar = 4-methoxy-3,5-dimethylphenyl.

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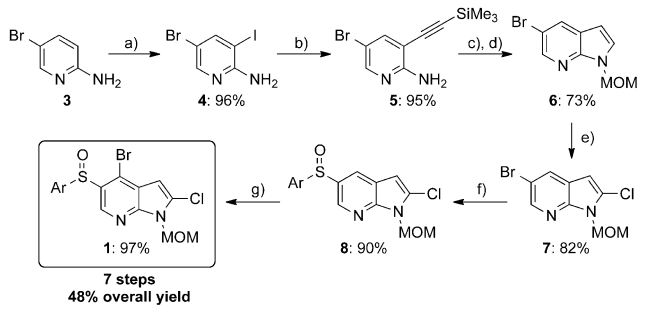
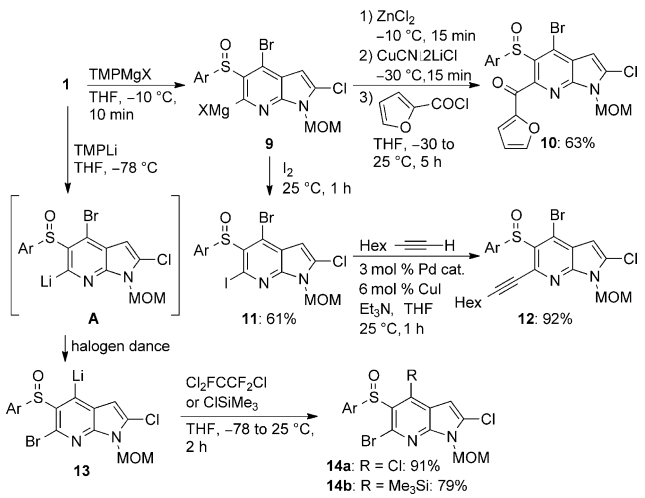
To this end, the sulfoxide group on C5 was found to be essential for the full functionalization procedure, since it allows both the direct metalation in *ortho* position and its replacement by iodine using sulfoxide/magnesium exchange.[11,12] Hence, the key 7-azaindole **1** was prepared in seven steps starting from the commercially available 2-amino-5-bromopyridine (**3**). Thus, the regioselective iodination of **3** (HIO_4, I_2) in a mixture of acetonitrile and acetic acid[13] (80 °C, 5 h) produced the 3-iodopyridine **4** in 96 % yield. Sonogashira cross-coupling[14–16] of **4** with trimethylsilylacetylene in the presence of 1 mol % $[PdCl_2(PPh_3)_2]$ and 2 mol % CuI[17] (25 °C, 1 h) led to aminopyridine **5** in 95 % yield. Ring closure of an intermediate sodium amide generated by addition of NaH in *N*-methylpyrrolidone (NMP)[18] led, after one hour at 80 °C, to the desired 7-azaindole in 80 % yield. Subsequently, protection by a methoxymethyl (MOM) group (NaH, MOM-Cl, DMF, 25 °C, 1 h) furnished the protected bromoazaindole **6** in 91 % yield (73 % yield over two steps). Selective lithiation of **6** with TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) in THF (−60 °C, 1 h) and chlorination with $PhSO_2Cl$[19] provided the dihalogenated 7-azaindole **7** in 82 % yield. Thus, the newly introduced chlorine substituent avoids a competitive metalation in position 3 and serves as protecting group of the 2-position. Br/Li exchange of **7** with *n*BuLi (−78 °C, 5 min) and transmetalation with $MgCl_2$ (0.5 M in THF) followed by sulfinylation using 4-methoxy-3,5-dimethylbenzenesulfinyl chloride[11,12,20] gave azaindole **8** in 90 % yield. Finally, position 4 was regioselectively magnesiated using TMPMgCl·LiCl[21] (−30 °C, 10 min) and quantitatively brominated with $(BrCl_2C)_2$ affording the key azaindole **1**[22] in 48 % overall yield starting from **3** (Scheme 2).

The polyfunctional 7-azaindole scaffold **1** offers hidden organometallic pathways for the functionalization of all five carbon positions of the 7-azaindole scaffold. First the functionalization of position 6 was achieved by using the highly chemoselective base TMPMgCl·LiCl[21] (1.50 equiv, −10 °C, 10 min) leading to the magnesiated 7-azaindole **9**. Transmetalation of **9** with $ZnCl_2$ (1 M in THF, 1.50 equiv) followed by a copper-mediated acylation[23] (CuCN·2 LiCl, 1 M in THF, 1.50 equiv) with furan-2-carbonyl chloride (1.50 equiv) led to the 6-substituted azaindole **10**[22] in 63 % yield. Furthermore, iodolysis of **9** provided the iodide **11**[22] in 61 % yield, which proved to be an excellent intermediate for further functionalization reactions. Thus, Sonogashira cross-coupling[14–16] of **11** using 3 mol % $[PdCl_2(PPh_3)_2]$, 6 mol % CuI, Et_3N (10.0 equiv, 25 °C, 1 h) and 1.20 equiv of 1-octyne furnished the expected alkyne **12** in 92 % yield. Interestingly, the lithiation of **1** with TMPLi (1.30 equiv, −78 °C) gave a transient lithium reagent **A** which underwent a "halogen dance"[24] leading to the 4-lithiated 7-azaindole **13**. The best



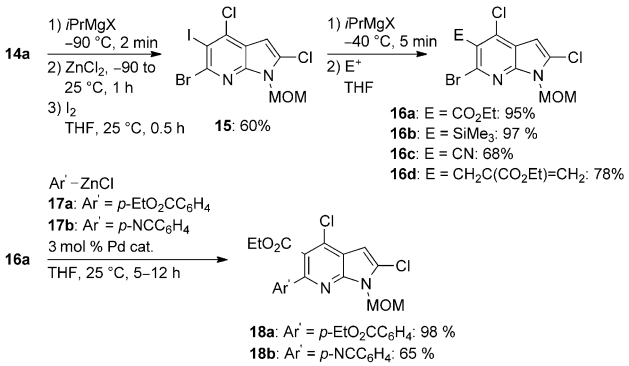
Scheme 2. Key steps in the synthesis of 7-azaindole **1** starting from commercially available 2-amino-5-bromopyridine **3**: a) HIO_4 (0.3 equiv), I_2 (0.5 equiv), MeCN/AcOH, 80 °C, 5 h; b) trimethylsilylacetylene (1.2 equiv), $[PdCl_2(PPh_3)_2]$ (1 mol%), CuI (2 mol%), Et_3N, 25 °C, 1 h; c) NaH (1.2 equiv), NMP, 80 °C, 1 h, 80%; d) NaH (1.2 equiv), MOMCl (1.2 equiv), DMF, 25 °C, 1 h, 91%; e) TMPLi (1.1 equiv), −60 to −45 °C, 1 h, $PhSO_2Cl$ (1.2 equiv), THF, 2 h; f) *n*BuLi (1.0 equiv), −78 °C, 5 min, $MgCl_2$ (0.5 M in THF, 1.1 equiv), 4-methoxy-3,5-dimethylbenzenesulfinyl chloride (1.2 equiv), −78 to −30 °C; THF, 1 h; g) TMPMgCl·LiCl (1.5 equiv), −30 °C, 10 min 1,2-dibromo-1,1,2,2-tetrachloroethane (1.2 equiv), −30 to 25 °C, THF, 2 h. Ar = 4-methoxy-3,5-dimethylphenyl.

yields were obtained by generating the lithiated intermediate **13** in the presence of the electrophile (Barbier in situ conditions[25,26]). Thus, in the presence of 1,1,2-trichloro-1,2,2-trifluoroethane (Cl_2FCCF_2Cl, 1.50 equiv), the corresponding 4-chloro-7-azaindole **14a**[22] was obtained in 91% yield. Similarly, performing this lithiation in the presence of an excess of Me_3SiCl provided the silylated azaindole **14b**[22] in 79% yield (Scheme 3).



Scheme 3. Functionalization of positions 6 and 4. X = Cl·LiCl; Ar = 4-methoxy-3,5-dimethylphenyl.

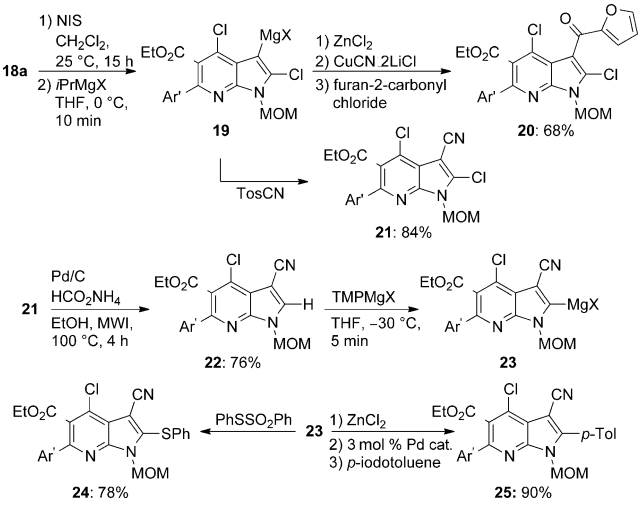
The next functionalization was performed in position 5 by means of a sulfoxide/magnesium exchange.[11,12] Thus, treatment of **14a** with *i*PrMgCl·LiCl[10] (1.00 equiv) at −90 °C for 2 min[27] led to a magnesium intermediate which was immediately transmetalated with $ZnCl_2$ (1.00 equiv) and then treated with I_2. The resulting iodide **15** was obtained in 60% yield and conveniently converted to a magnesium reagent using *i*PrMgCl·LiCl[10] (1.05 equiv, −40 °C). This highly functionalized heterocyclic Grignard reagent was trapped with various electrophiles (NC-CO_2Et, Cl-$SiMe_3$, Tos-CN, and ethyl (2-bromomethyl)acrylate[28]) leading to the expected 5-substituted azaindoles **16a–d** in 68–97% yield.[29] 7-Azaindole **16a** was then further functionalized in position 6 by performing Negishi cross-couplings[30,31] with *para*-substituted arylzinc reagents (1.30 equiv, **17a**: R = CO_2Et; **17b**: R = CN) in the presence of 3 mol% $[Pd(PPh_3)_4]$ (25 °C, 5–12 h) to furnish the 6-arylated azaindoles **18a**,**b** in 98 and 65% yield, respectively (Scheme 4).



Scheme 4. Functionalization of positions 5 and 6. X = Cl·LiCl.

The remaining position 3 of **18a** was functionalized by selective iodination with *N*-iodosuccinimide (2.20 equiv) in CH_2Cl_2 to give a 3-iodoazaindole in 87% yield. Subsequent I/Mg exchange with *i*PrMgCl·LiCl[10] (1.10 equiv) provided the magnesium reagent **19**, which was transmetalated using $ZnCl_2$ (1.20 equiv) followed by a copper-mediated acylation[23] with furan-2-carbonyl chloride (2.00 equiv) to afford **20** in 68% yield. Cyanation of **19** with TosCN (1.50 equiv) led to the desired product **21** in 84% yield (Scheme 5).

Selective dechlorination of **21**[32] according to the Schlosser method[33] with 3.00 equiv of HCO_2NH_4 in the



Scheme 5. Functionalization of positions 3 and 2. X = Cl·LiCl; Ar′ = *p*-$EtO_2CC_6H_4$.

presence of 2% Pd/C using microwave irradiation (MWI, 100 °C, 4 h) provided the monochlorinated azaindole **22**[22] in 76% yield. This azaindole was readily metalated with TMPMgCl·LiCl[21] (1.10 equiv, −30 °C, 5 min) leading to the magnesium reagent **23** which was functionalized by a reaction with $PhSSO_2Ph$ (1.30 equiv) affording the thioether **24** in 78% yield. Alternatively, after transmetalation with $ZnCl_2$ (1.20 equiv), a Negishi cross-coupling[30,31] with *p*-iodotoluene (1.50 equiv) using 3 mol% $[Pd(PPh_3)_4]$ provided the azaindole **25** in 90% yield (Scheme 5).

In summary, we have demonstrated a novel methodology for the mild full functionalization of the 7-azaindole scaffold by a combination of directed metalation and halogen/magnesium and sulfoxide/magnesium exchange, using the appropriately substituted 7-azaindole **1** as a key intermediate. In this context, the introduction of the sulfoxide substituent on C5 was essential for all further functionalization procedures. Thus, with this sequential substitution approach all five carbon positions of the 7-azaindole skeleton could be functionalized in a predictable manner, leading to highly substituted 7-azaindoles of type **2**. Further extensions for the full functionalization of other azaindole isomers are underway in our laboratory.

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