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An effective procedure for the preparation of 3-substituted-4- or 6-azaindoles from *ortho*-methyl nitro pyridines

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Abstract—3-Substituted-4- and 6-azaindoles were prepared from *ortho*-methyl-nitropyridines in a practically convenient, one-pot process based on the Leimgruber–Batcho reaction. The procedure comprises a sequence of (a) condensation of an *ortho*-methyl-nitropyridine with *N*,*N*-dimethylformamide dimethyl acetal; (b) alkylation or acylation of the enamine intermediate; (c) reduction of the nitro group to an aniline with in situ cyclization and elimination of dimethylamine to generate the 3-substituted azaindole heterocycle.

Derivatives of 3-substituted-4- and 6-azaindole have been reported to be associated with a range of biological activities and representative molecules offer potential for the treatment of infection, inflammation, asthma, pain and CNS disorders.[1] Functionalization at C-3 of indoles is well documented and many of the synthetic processes that have been developed rely upon the electron-rich nature of the enamine-like heterocycle ring.[2] However, when one carbon atom of the benzene ring is replaced by a nitrogen atom, the direct introduction of substituents at the C-3 position of azaindoles is considerably more difficult.[3] This is largely due to the reduced reactivity of the 3-position of azaindoles when compared to that of indole, a result of the electron deficient nature of the azaindole heterocycle. As a consequence, general procedures for the preparation of 3-substituted azaindoles are relatively sparse in the literature and direct functionalization at C-3 position of azaindoles is restricted to Lewis acid-mediated acylation,[3,4] halogenation[5] and participation in the Mannich reaction.[6]

The two-step Leimgruber–Batcho procedure is a well established process for synthesizing indoles[7] that has been extended to the preparation of both 4- and 6-azaindole from the appropriate *ortho*-methyl nitropyridine.[8] In this process, illustrated in Scheme 1, *ortho*-methyl-nitropyridines **1a** and **1b** are first condensed with DMF-dimethylacetal to produce the enamine intermediates **2a** and **2b**. The subsequent reduction of the nitro group to the aniline is accompanied by in situ cyclization to afford 6-azaindole **3a** or 4-azaindole **3b**.

By analogy with the corresponding phenyl derivatives,[9] we anticipated that the enamine intermediates **2a** and **2b** would react with electrophiles to generate the substituted enamines **4a** and **4b** (Scheme 1), a process that has not been reported previously. Reduction of the nitro group with concomitant cyclization of the aniline and enamine would then furnish the 3-substituted azaindoles **5a** and **5b**. In this letter, we demonstrate the reactivity of the enamine intermediates **2a** and **2b** towards electrophiles and describe a practical process that allows installation of substituents at the C-3 position of 4- and 6-azaindoles.

Enamines **2a** and **2b** were prepared by treating 4- or 2-methyl-3-nitro pyridine with DMF-dimethylacetal or Bredereck's reagent at 115 °C. The reactivity of enamine intermediate **2** towards electrophiles was explored initially using (E)-*N*,*N*-dimethyl-2-(3-nitropyridin-4-yl)ethenamine (**2a**) in order to establish the potential and scope of the reaction. Alkylation of **2a** with an alkyl bromide (e.g., benzyl bromide, 4-phenyl benzyl bromide,

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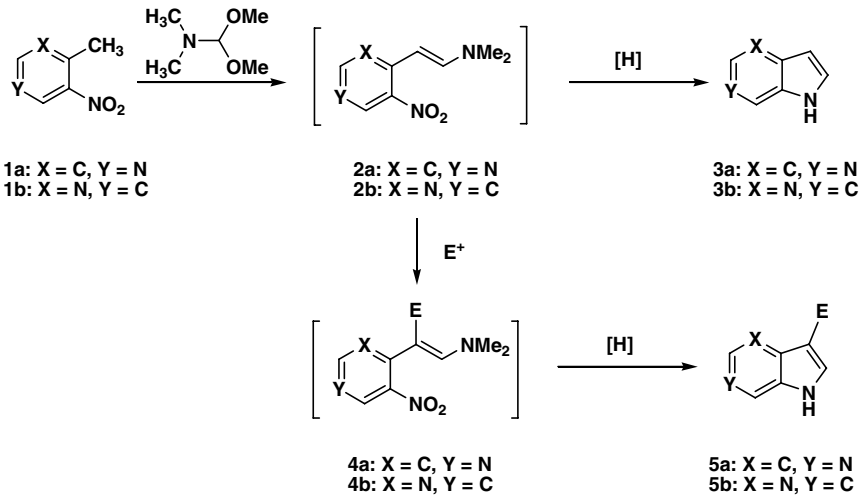
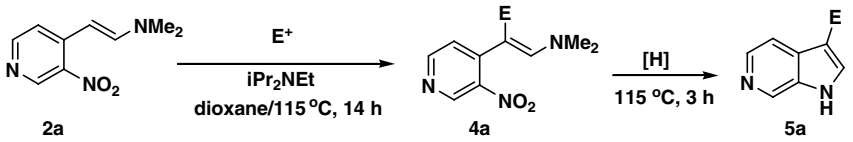
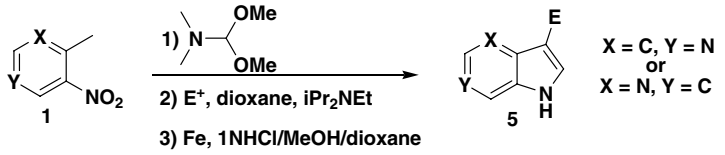


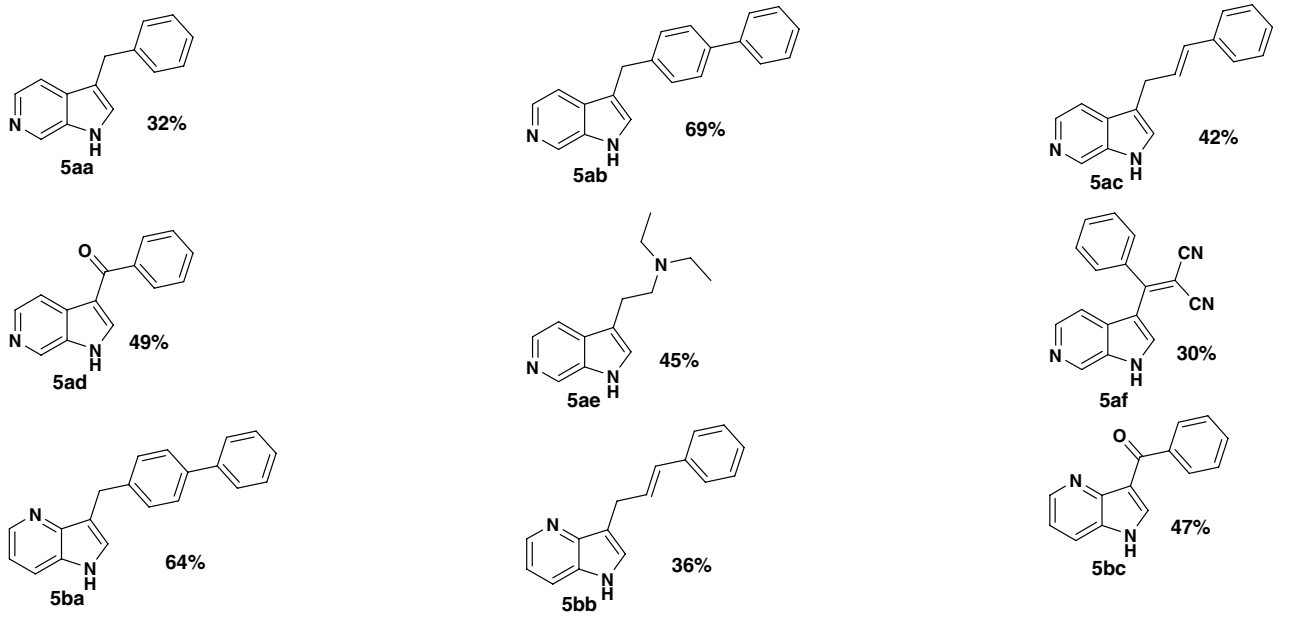
Scheme 1.



Scheme 2.

Table 1.





allyl bromide, diethylaminoethyl bromide) occurred readily in the presence of Hunig's base in dioxane at 115 °C based on LC–MS analysis of the reaction mixture, as summarized in Scheme 2. Similarly, acylation with ben-

zoyl chloride and Michael addition to 2-(chloro(phenyl)-methylene)malononitrile occurred under the same conditions. However, mesylation using mesyl chloride and heteroarylation with 2-chloroquinoxaline were unsuccessful.

Several reagents and conditions were evaluated in order to optimize the final reduction–cyclization step to form the 3-substituted-6-azaindole **5a**, as shown in Scheme 2. The reduction of **4aa** ($E = CH_2Ph$) was used as the prototype to examine the potential of zinc or iron as reductants in a variety of co-solvents that included mixtures selected from dioxane, MeOH, EtOH, saturated aqueous $NaHCO_3$ solution, H_2O, 0.1 N and 1 N HCl solutions and saturated aqueous NH_4Cl solution. Based on this survey, iron was determined to be superior to zinc and a relatively strong acidic medium (0.1 N HCl or 1 N HCl aqueous solution) with either MeOH or EtOH as co-solvent proved beneficial for completing the transformation. Under these conditions, **4aa** ($E = CH_2Ph$) was completely converted to **5aa** ($E = CH_2Ph$).

Encouraged by these results, a one-pot procedure was developed to prepare 3-substituted-4- or 6-azaindole derivatives from *ortho*-methyl nitropyridines, and the results are summarized in Table 1.[10] The appropriate *ortho*-methyl nitropyridine was treated with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine at 115 °C to provide *ortho*-(*N*,*N*-dimethylamino)ethenyl nitropyridines **2a** and **2b**. Volatile material was removed under vaccum and the crude enamine **2a** and **2b** reacted with an electrophile in the presence of *N*,*N*-diisopropylethylamine in dioxane at 115 °C. Excess 1 M aqueous HCl solution, MeOH and iron were added to the flask and the mixture heated at 115 °C for 3 h to complete the synthesis by reducing the nitro group and effecting in situ cyclization of aniline and enamine to furnish 3-substituted-4- or 6-azaindole **5**. This process is operationally simple, effective and reasonably efficient, offering easy access to novel 3-substituted-4- and 6-azaindoles with overall yields of 30–69% for the three steps. This process provides a convenient means to introduce 3-alkyl moieties at the C-3 position of azaindoles, noteworthy since the direct alkylation at C-3 of indoles is quite challenging and this reaction has not been documented with azaindoles.

In summary, we have reported an experimentally convenient, one-pot procedure for the preparation of C-3-substituted-4- and 6-azaindoles starting from the corresponding *ortho*-methyl nitro pyridine. C-3 substituents were installed via reaction of the intermediate enamine prior to the final reductive cyclization. This modified Leimgruber–Batcho procedure is attractive due to the simplicity of the operational procedure, the mildness of the conditions and the potential applicability to other azaindoles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.017.

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10. Typical procedure—Preparation of 3-(4-phenyl)benzyl-6-azaindole (**5ab**): 4-Methyl-3-nitropyridine (500 mg, 3.62 mmol) was dissolved in 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (10 ml) and the reaction mixture heated at 115 °C for 14 h. Volatile material was removed under vaccum to provide 4-(*N*,*N*-dimethylamino)ethenyl-3-nitropyridine which was mixed with 4-bromomethylbiphenyl (2.69 g, 10.9 mmol) and *N*,*N*-diisopropylethylamine (2 ml) in dioxane (20 ml). The reaction mixture was stirred at 115 °C for 14 h before cooling and adding aqueous 1 N HCl solution (2 ml), MeOH (5 ml) and iron (2.02 g, 36.2 mmol). The mixture was stirred at 115 °C for 3 h, cooled and filtered. The filtrate was concentrated under vaccum and the residue purified by silica gel column chromatography using $CH_2Cl_2/CH_3OH = 9{:}1$ to 4:1 as eluant to afford 708 mg of product **5ab** (69%).