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# A two-step procedure for the preparation of mono-protected bis-*N*-heterocyclic alkyl ether systems

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**Abstract**—A two-step convenient sequence for the synthesis of previously inaccessible mono-Boc-protected bis-*N*-heterocyclic alkyl substituted ether derivatives **4** is described. Mitsunobu protocol was applied to the preparation of pyridinyl ether precursor **5**. The reduction of the electron rich pyridinyl system **5** has been achieved catalytically using the combination of $PtO_2$–$H_2SO_4$ or $PtO_2$–*p*TsOH under a hydrogen atmosphere maintained by a gas balloon at ambient temperature.


As part of our recent medicinal chemistry efforts, we needed to make bis-*N*-heterocyclic alkyl substituted ether systems, illustrated as general formula **1** in Figure 1. A survey of the literature found no precedent for the construction of such ether systems, in spite of numerous methods for the preparation of substituted piperidines.[1,2] The underlining difficulty lies in connecting two *N*-heterocycles via an ether linkage without using harsh conditions. Only two patent applications to date have reported simple examples containing solely [6,6] bicyclic ring systems (**2** and **3**, Fig. 1), prepared through multi-step synthesis, which are intended for anti-inflammatory use (**2**)[3] or for treatment of neurological and psychiatric disorders (**3**).[4] To serve our purpose, we have developed a two-step sequence, carried out under mild conditions, that has been effective in the preparation of such ether systems (**1**) in various ring sizes. Herein, we report our results and findings.

The preparation of compound **1** could be readily achieved via the mono-protected building block **4**. We envisioned a two-step sequence to access this key intermediate (Scheme 1), by reduction of the pyridinyl–piperidyl ether precursor **5**, which could be generated from hydroxy pyridine **6** and hydroxy-*N*-heterocycle **7** utilizing the Mitsunobu protocol. With the two N-terminals properly differentiated, mono-protected bis-*N*-heterocyclic ethers **4** would allow asymmetric functionalization, thus providing uninhibited access to **1**.

Pyridinyl ethers **5** were smoothly prepared by taking advantage of the Mitsunobu reaction,[5] which offers an

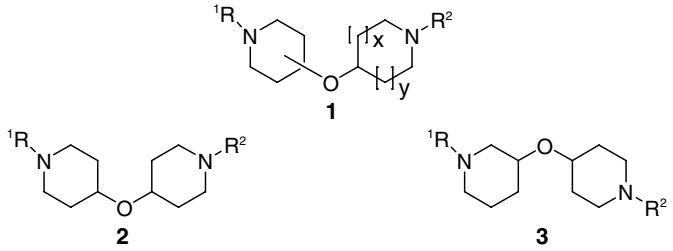


**Figure 1.** Bis-*N*-heterocyclic alkyl substituted ethers.

*Keywords*: Bis-*N*-heterocyclic alkyl ethers; $PtO_2$–$H_2SO_4$ mediated reduction; Mitsunobu reaction.
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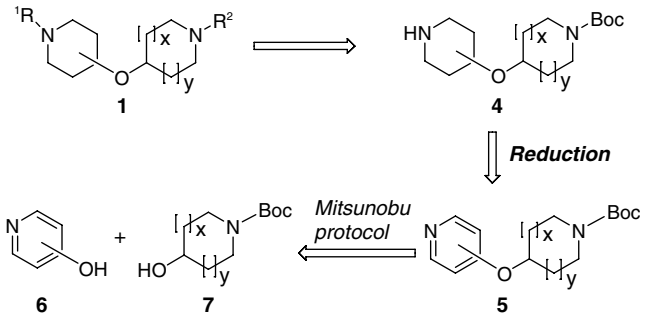
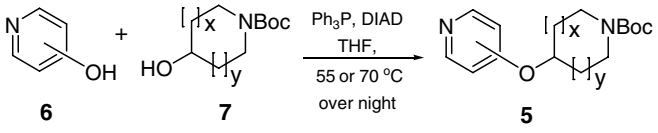



**Scheme 1.** General approach.

efficient approach to the formation of C–O bonds under nearly neutral conditions. Recent advances in this reaction have been reviewed by Dembinski.[6] The coupling of 4-hydroxy pyridine (**6a**), or 3-hydroxy pyridine (**6b**), with various hydroxy substituted *N*-heterocycles **7a**–**d** under the conditions of triphenyl phosphine ($Ph_3P$) and diisopropylazodicarboxylate (DIAD) afforded the desired pyridinyl ether products **5a**–**e** in good yields.[7] Although 4-hydroxy pyridine **6a** is predominantly in the pyridinone tautomer, we have observed that the Mitsunobu reaction proceeded only at the oxygen atom via the minor pyridine tautomer, similar to the tetrahydropyranylation results reported by Azzouz et al.[8] It is also worthy of mention that most of the phosphine oxide and hydrazine byproducts generated during this reaction were efficiently removed by taking advantage of the weakly basic pyridinyl nitrogen in **5** during an acidic work-up.[9] This procedure simplified the isolation process, and helped to avoid the usually time consuming removal of spent reagents from the Mitsunobu reaction. Table 1 summarizes the results of this transformation.

The conversion of the pyridinyl ethers **5** to the saturated ethers **4** was undoubtedly the key step of the sequence. Although reduction of a substituted pyridine to the corresponding piperidine is a common transformation,[10] often the pyridine ring requires activation with the presence of electron withdrawing groups or by the formation of the N-oxide. Without such activation, metal mediated hydrogenation requires high pressure and or high temperature. Initially, we have applied several common reductive methods, known to be effective for substituted pyridines, to the pyridinyl system **5**. Treatment of pyridinyl–piperidyl ether **5a** with samarium diiodide in THF–$H_2O$,[11] or lithium triethylborohydride in THF,[12] produced no reduction product. In order to activate the pyridinyl system, **5a** was oxidized to the corresponding N-oxide using *m*-chloroperoxybenzoic acid (*m*-CPBA).

**Table 1.** Preparation of pyridinyl ether **5**[a,9]




| Entry | Hydroxy pyridine **6** | Alcohol **7** | Pyridyl ether **5** | Yield[c] (%) |
|---|---|---|---|---|
| 1 | **6a** | **7a** | **5a** | 67 |
| 2[b] | **6b** | **7a** | **5b** | 69 |
| 3 | **6a** | **7b** | **5c** | 80 |
| 4 | **6a** | **7c** | **5d** | 78 |
| 5 | **6a** | **7d** | **5e** | 69 |

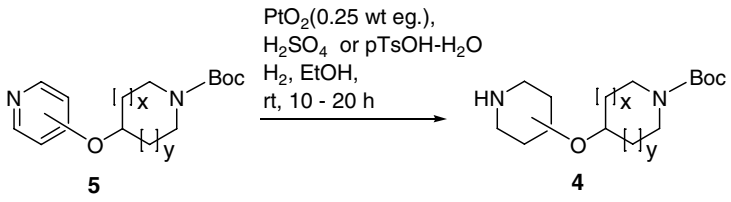
[a] Reaction conditions: 1 mol equiv of hydroxy pyridine **6**, 1.25 mol equiv of alcohol **7**, 1.25 mol equiv of $Ph_3P$, 1.25 mol equiv of DIAD, and 0.3 M of THF, 55 °C, 14–16 h (over night).
[b] Reaction was carried out at 70 °C.
[c] Yields refer to purified products by column chromatography; purity was determined >95% based on LC-MS analysis.

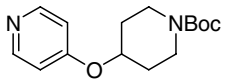
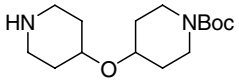
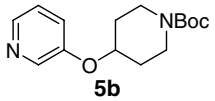
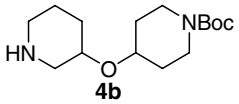
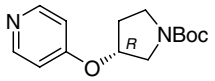
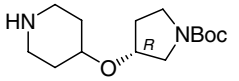
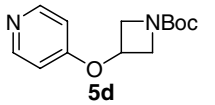
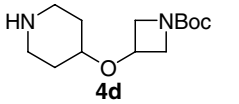
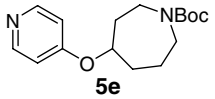
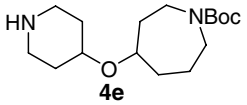
The subsequent reduction of the N-oxide under the conditions of $HCOONH_4$/10% Pd–C in methanol[13] only generated the parent compound **5a**. The use of $PtO_2$ in MeOH–AcOH under a $H_2$ atmosphere was also proved to be ineffective even after employing a stoichiometric amount of $PtO_2$.

The above unsuccessful reduction attempts of **5a** strongly suggested that this electron rich pyridinyl system needed a much stronger activation in order to facilitate the desired reduction process. Weak acids similar to acetic acid would not be useful, and addition of electron withdrawing groups was not an option either. We decided to approach this in an unconventional way, by employing concentrated sulfuric acid ($H_2SO_4$) as the activator of the pyridinyl system. Under this strongly acidic condition, a pyridinium acid salt would most likely form in situ, thus allowing the ensuing reduction process to succeed. We were certainly concerned about the potential risk of association between such a strong acid with compounds like **5a** where acid labile Boc protecting group and ether linkage were present. However, we believed that under anhydrous conditions, one equivalent of concentrated sulfuric acid would preferably complex with the basic pyridinyl nitrogen. We were gratified to see that treatment of pyridinyl–piperidyl ether **5a** with the combination of $PtO_2$ (1 wt equiv) and $H_2SO_4$ (1 mol equiv) in ethanol under a $H_2$ atmosphere (maintained by a gas balloon) at room temperature afforded the reduced bicyclic ether product **4a**. The reaction was completed within a 10 h period. Following a facile work-up and column chromatography, ether product **4a** was obtained consistently above 50% on reaction scales ranging from 0.1 g to 1 g. The utility of this reduction process was extended to pyridinyl ethers **5b–e**, and the respective saturated ether products **4b–e** were obtained in good yields.

In order to investigate the possibility of a catalytic reduction process, we re-evaluated the amount of $PtO_2$ required for the reduction, even though initially a stoichiometric amount of $PtO_2$ seemed necessary to accomplish such a difficult reduction. Reductions of **5a–e** under the condition of 1, 0.5, and 0.25 wt equiv of $PtO_2$ proceeded similarly well and produced comparable yields of the desired products **4a–e**. However, the amount of $PtO_2$ used influences the duration of the reaction. Longer period of time was needed to ensure the complete consumption of the starting material when lesser amount of $PtO_2$ was employed. Results of the catalytic reduction of the pyridinyl ethers **5** are summarized in Table 2.[14]

**Table 2.** Catalytic reduction of pyridinyl ether **5** with $PtO_2$ in combination with $H_2SO_4$ or *p*TsOH–$H_2O$[a]




| Entry | Pyridyl ether **5** | Bis-*N*-heterocyclic alkyl ether **2** | $PtO_2$[b] (0.25 equiv) | |
|---|---|---|---|---|
| | | | $H_2SO_4$ | *p*TsOH |
| 1 |  **5a** |  **4a** | 55% 14 h | 60% 14 h |
| 2 |  **5b** |  **4b** | 29% 14 h | 28% 14 h |
| 3 |  **5c** |  **4c** | 77% 18 h | NA[c] |
| 4 |  **5d** |  **4d** | 61% 10 h | 80% 20 h |
| 5[d] |  **5e** |  **4e** | 51% 20 h | NA[c] |

[a] Reaction conditions: all reactions were performed on a 1.0 g scale of pyridinyl ether **5**, 0.25 wt equiv of $PtO_2$, 1.0 mol equiv of $H_2SO_4$ or 1.0 mol equiv of *p*TsOH–$H_2O$, 200 proof ethanol (20 mL), $H_2$ supplied by a gas balloon.

[b] Yields refer to purified ether products **2** by column chromatography, purity >95% based on LC-MS analysis.

[c] NA means reaction was not performed.

[d] A 0.5 wt equiv of $PtO_2$ was used.

The bis-*N*-heterocyclic ethers **4** were obtained in moderate to good yields, as illustrated in Table 2, based on the current un-optimized conditions. During the reduction process, we did observe the formation of byproducts consistent with the cleavage of the ether link and the removal of the Boc protection, based on TLC and MS analysis. Byproducts resulting from ether link cleavage were isolated and confirmed to be hydroxy *N*-heterocycles **7** based on H NMR. Additionally, the amount of byproducts formed seems to be substrate dependent. In an effort to minimize the acid induced side reactions, *p*-toluenesulfonic acid was evaluated as a possible alternative. It was found that *p*-toluenesulfonic acid was equivalent to concentrated sulfuric acid in the catalytic reduction of **5a**, **5b**, **5d** (Table 2), but unfortunately byproducts were generated at a similar level as those of the reactions mediated by concentrated sulfuric acid.

In summary, we have reported here a two-step sequence for the synthesis of previously inaccessible mono-Boc-protected bis-*N*-heterocyclic alkyl substituted ethers **4a**–**e**. The reduction of electron rich pyridinyl system was realized with the combination of $PtO_2$–$H_2SO_4$ (or *p*TsOH). Furthermore, the reduction can be carried out catalytically. The ethers **4a**–**e** thus prepared have become versatile building blocks in our SAR development being further elaborated into biologically important chemical entities.

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## Supplementary data

Experimental procedures, characterization data, and NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.161.

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7. For O-alkylation of 3-hydroxy pyridine under $Ph_3P$/DEAD condition, see: (a) Dolle, F.; Dolci, L.; Valette, H.; Hinnen, F.; Vaufrey, F.; Guenther, I.; Fuseau, C.; Coulon, C.; Bottlaender, M.; Crouzel, C. *J. Med. Chem.* **1999**, *42*, 2251–2259, and references cited therein; (b) We did not pursue the coupling reaction of 2-hydroxy pyridine and **7a** under the discussed Mitsunobu protocol since the fully saturated bis-*N*-heterocyclic alkyl ether was considered unsuitable for our SAR purpose. However, O-alkylation of 2-hydroxy pyridine under Mitsunobu condition might be possible, see Ref. 8 for details.
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9. General procedure for the preparation of pyridyl ethers **5**: To a stirred solution of 4-hydroxy pyridine **6a** (2.0 g, 21.03 mmol) in 70 mL of anhydrous THF at room temperature was added *N*-Boc-4-hydroxy piperidine **7a** (5.3 g, 26.28 mmol). Triphenyl phosphine (6.9 g, 26.31 mmol) was added followed by dropwise addition of diisopropylazodicarboxylate (DIAD, 5.2 mL, 26.41 mmol). The mixture was heated at 55 °C over night (14 h). Solvent was evaporated in vacuo. The resulting oil was treated with a 1.0 M HCl aqueous solution (30 mL). The acidic mixture was washed with $CH_2Cl_2$ (30 mL × 2). The combined $CH_2Cl_2$ washings were re-extracted with a 1.0 M HCl aqueous solution (10 mL) and $H_2O$ (20 mL), then discarded. The aqueous fractions were combined, basified to pH ~ 12 using a 1.0 M NaOH aqueous solution, and extracted with $CH_2Cl_2$ (50 mL × 4). The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo to a residue, which was purified by flash column chromatography, eluting with EtOAc–hexanes–MeOH (5:1:0.1, v/v/v). Removal of solvents afforded 3.92 g (67%) of pyridyl ethers **5a** as a colorless solid.
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13. Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* **2001**, *66*, 5264–5265.
14. General procedure for bis-*N*-heterocyclic alkyl ethers **4**: A stirred solution of pyridyl ether **5a** (1.0 g, 3.6 mmol) in 20 mL of 200 proof ethanol was degassed via house vacuum, and refilled with nitrogen. $PtO_2$ (0.25 wt equiv) was added. The mixture was degassed again and refilled with nitrogen. Concentrated sulfuric acid (0.19 mL, 3.6 mmol, 1 equiv) was added. The resulting mixture was degassed a third time, and refilled with $H_2$ via a stainless needle connected to a gas balloon. Reaction was continued at room temperature under a $H_2$ atmosphere for 14 h. The mixture was poured into 50 mL of an ice cold 1.0 M NaOH aqueous solution, rinsing with a small volume of $CH_2Cl_2$, and filtered through a Celite® pad. The filtrate was concentrated in vacuo to remove ethanol, and the remaining aqueous solution was extracted with $CH_2Cl_2$ (50 mL × 3). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo to an oily residue, which was purified by flash column chromatography, eluting with $CH_2Cl_2$–MeOH (10:1, 5:1, and 1:1, v/v). Removal of solvents afforded 0.61 g (60%) of ether **4a** as a colorless solid.