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Practical and efficient synthesis of N-fused tricyclic indoles

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ABSTRACT

A practical and efficient synthesis of methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate derivatives **6** is reported. This synthetic approach featured the nucleophilic aromatic substitution of 2-piperidinemethanol derivatives **2** with aryl fluorides **1**, and the intramolecular Heck coupling as key steps to afford the desired N-fused tricyclic indoles **6**.

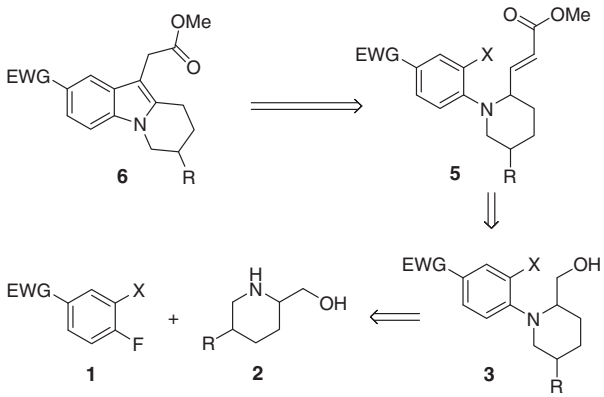
6,7,8,9-Tetrahydropyrido[1,2-*a*]indole core is commonly found in various therapeutic compounds, such as prostaglandin D_2 receptor DP_2 (CRTH2) antagonists,[1] protein kinase C inhibitors,[2] and GSK-3β inhibitors.[3] Despite broad medicinal chemistry interest in 6,7,8,9-tetrahydropyrido[1,2-*a*]indole core, there are relatively few synthetic methods for its preparation. The construction of the N-fused tricyclic indole structural motif generally relies on indole substrates as the starting material for the ring expansion strategies.[4] The transition metal-catalyzed cyclization is also reported as a key step for the preparation of N-fused tricyclic indoles from the optionally substituted aromatics. A drawback associated with these approaches is that the intermediates for the cyclization reaction require multistep syntheses.[5] Moreover, C-3 substituted methyl acetate is notoriously difficult to access from these available synthetic methods. Hence, there is a need for a new methodology that would allow rapid access to methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate analogues **6**.

Herein, we report a practical and efficient method for the synthesis of methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate derivatives **6**. We envisioned that **6** could be prepared via the palladium-catalyzed intramolecular Heck coupling of functionalized α,β-unsaturated ester **5** (Scheme 1). This key intermediate could be derived from the nucleophilic aromatic substitution (S_NAr) of 2-piperidinemethanol derivatives **2** with aryl fluorides **1** followed by oxidation and Wittig reactions.

We began our investigation with 3-bromo-4-fluorobenzonitrile **1a** and 2-piperidinemethanol **2a** as model substrates to explore the nucleophilic aromatic substitution reaction (Scheme 2). We first tried standard S_NAr conditions using DMSO as the solvent and cesium carbonate as the base.[6] These conditions resulted in predominant displacement of fluoride by the alcohol functional group to provide O-arylated product **3f**.[7] Variation of the temperature did not improve the N-arylated product ratio. The key breakthrough in our search for the optimal S_NAr reaction conditions occurred when we treated 3-bromo-4-fluorobenzonitrile **1a** with 2-piperidinemethanol **2a** in DMSO in the absence of cesium carbonate at 100 °C. These reaction conditions gave N-arylated piperidinemethanol **3a** in 22% yield. Although the yield of **3a** was modest, we decided to pursue the reaction sequence toward intramolecular Heck coupling to evaluate the viability of our methodology.

N-Arylated piperidinemethanol **3a** was submitted to the Swern oxidation conditions to afford aldehyde **4a**, which was then treated with methyl (triphenylphosphoranylidene)acetate to generate the corresponding α,β-unsaturated methyl ester **5a** in 80% yield. Next, we investigated the reactivity of **5a** under intramolecular Heck reaction conditions. Palladium(II) acetate, *N*-methyldicyclohexylamine, and tetrabutylammonium bromide were quickly found to be the best combination to prepare methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate **6a** in 67% yield from **5a**.[8]

Encouraged by our initial results, we sought to examine the scope and the generality of the method by exploring the effects of other electron-withdrawing groups on the aryl fluorides **1** in S_NAr reaction conditions. General reaction conditions of S_NAr were



Scheme 1. Retrosynthetic analysis of methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate analogues.

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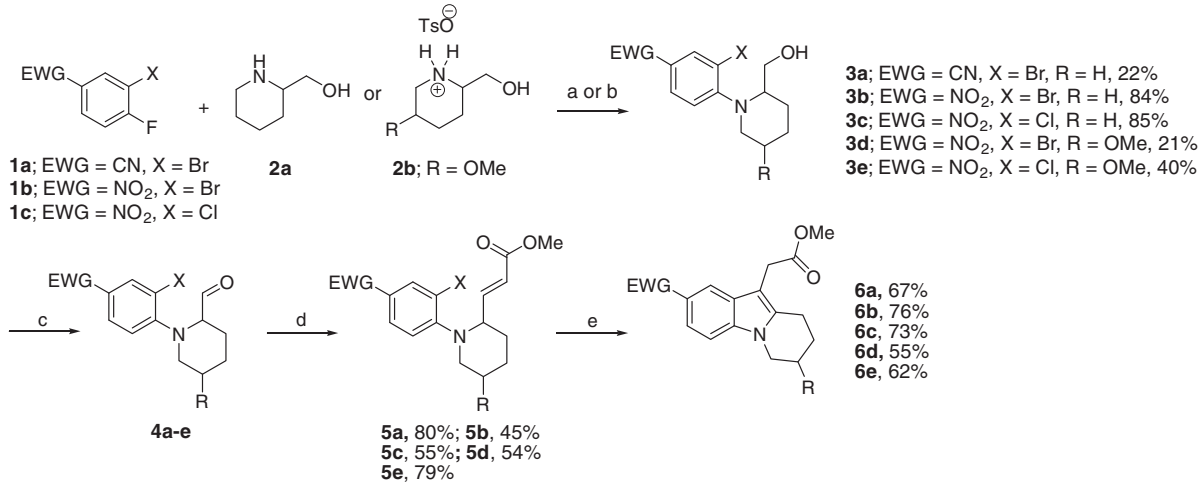


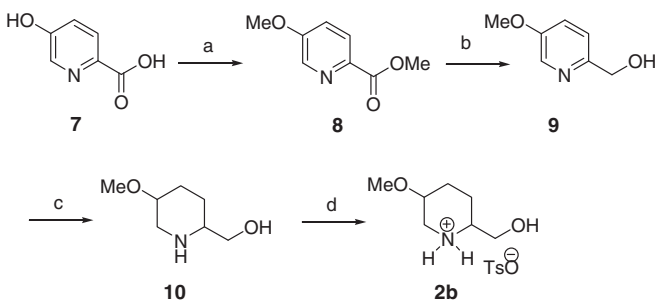
Scheme 2. Reagents and conditions: (a) **1a–c** (1.0 equiv), **2a** (1 equiv) in DMSO at 100 °C; (b) **1b–c** (2.0 equiv), **2b** (1.0 equiv), *N*-methyldicyclohexylamine (2.0 equiv) in NMP at 120 °C; (c) $(CO)_2Cl_2$ (1.2 equiv), DMSO (3.0 equiv), CH_2Cl_2, −78 °C to −40 °C, then Et_3N (5.0 equiv), −78 °C to 0 °C; (d) methyl (triphenylphosphoranylidene)acetate (1.5 equiv), THF, rt, except for **4a** at 40 °C; (e) *N*-methyldicyclohexylamine (2.6 equiv), Bu_4NBr (1 equiv), $Pd(OAc)_2$ (0.2 equiv), DMF, 120 °C.

used. Using nitro as electron-withdrawing group on the benzene ring **1b–c** gave high isolated yields of **3b** and **3c** (84 and 85% yield, respectively). Interestingly, the S_NAr reaction was more efficient with nitro group on the benzene ring. N-arylated piperidinemethanols **3b** and **3c** were subsequently converted into the corresponding N-fused tricyclic indoles **6b** using the same Swern, Wittig, and Heck reaction sequence.

Next, we examined the effect of amines on the S_NAr reaction by using (5-methoxypiperidin-2-yl)methanol **2b**. A methoxy group was introduced to the piperidine to act as a masked ketone in cases of further functionalization.

As **2b** is not commercially available, we needed to design a synthetic method for the preparation of this key intermediate. The reaction sequence is shown in Scheme 3. One-pot esterification and etherification of 5-hydroxypicolinic acid **7** using silver carbonate and methyl iodide in acetonitrile afforded ester **8**. Treatment of **8** with 3.5 equiv of Dibal-H converted the methyl ester into the corresponding alcohol **9** in 78% yield. Hydrogenation using 5% rhodium on alumina in methanol under 50 psi pressure of hydrogen yielded (5-methoxypiperidin-2-yl)methanol **10** as an oil.[9] To ease the handling, the crude (5-methoxypiperidin-2-yl)methanol **10** was converted into the corresponding tosylate salt **2b** in 75% yield.

With tosylate salt **2b** in hand, it was allowed to react with 2-bromo-1-fluoro-4-nitrobenzene **1b** and 2-chloro-1-fluoro-4-nitrobenzene **1c** under S_NAr conditions. It was found that NMP at 120 °C was the best condition for the preparation of **3d** and **3e**.



Scheme 3. Reagents and conditions: (a) Ag_2CO_3 (4.0 equiv), MeI (4.0 equiv), CH_3CN; (b) Dibal-H (3.5 equiv), toluene, −78 °C to 0 °C; (c) 5% Rh/Al_2O_3 (0.12 equiv), H_2 (50 psi), MeOH; (d) TsOH (1.0 equiv), EtOAc.

Following the same Swern, Wittig, and Heck reaction sequence, we successfully prepared **6d**.

So far, only α,β-unsaturated methyl ester partner was explored in the intramolecular Heck coupling which allowed direct access to C-3 methyl acetate. We believe that such strategy will have useful application in the synthesis of CRTH2 antagonists which are commonly constituted of acetic acid functional group at C-3.[1]

In conclusion, we have developed a novel and practical method for the preparation of methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate analogues. The efficient synthesis of piperidinemethanol, the convenient four step sequence, and the various aryl fluorides commercially available make this methodology a very attractive alternative for the synthesis of methyl 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-ylacetate analogues. Application of Buchwald–Hartwig amination or Ullmann N-arylation for the preparation of analogues **3** to expand the scope of N-arylation, and ultimately this methodology, are underway, and will be reported in due course.

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Supplementary data

Supplementary data (experimental details for all reactions and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.155.

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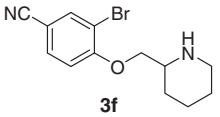

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