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Cyclodehydration of 4-[(Carboxymethyl)amino]pyridin-2-ones. A New, Efficient Synthesis of Pyrrolo[3,2-*c*]pyridin-4-ones and Pyrido[3,4-*b*]pyrrolizidin-1-ones.

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Abstract: This paper describes an efficient new route for the synthesis of pyrrolo[3,2-c]pyridin-2-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones starting from 4-chloro-*N*-benzyl-2(1*H*)-pyridinone and amino acid salts. Intermediate 4-[(carboxymethyl)amino]pyridin-2-ones undergo an acylative cylclodehydration reaction to afford 3-acetoxy pyrroles. These intermediates are then converted into 3-oxytriflate derivatives in high yield using a new one-step method. These compounds undergo palladium catalyzed methoxycarbonylation.

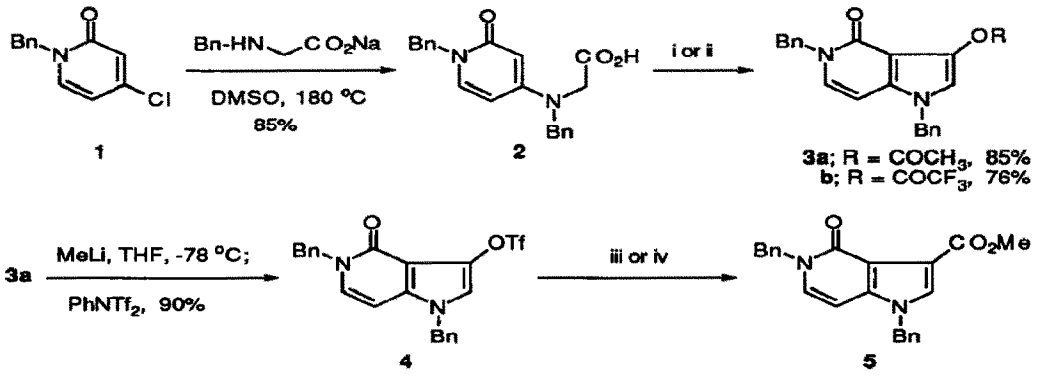
Pyrrolo[3,2-*c*]pyridines (5-azaindoles)[1] have been of interest over the years for applications as elements in new drug design, nucleotide analogues,[2] and biochemical tools. The available synthetic routes to multi-functionalized members from this class of heterocyclic structures is rather limited.[1-3] We now report a new and highly efficient synthesis of pyrrolo[3,2-*c*]pyridin-2-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones starting from 4-chloro-*N*-benzyl-2(1*H*)-pyridinone and amino acid salts. This represents our continued interest in the development of a common method for the synthesis of heterocycles having the structural feature of a highly substituted pyrrole ring fused adjacent to a six-membered ring. Previously we have reported the efficient synthesis of pyrrolo[2,3-*d*]pyrimidin-2,4-diones (7-deazaxanthines), as demonstrated by total synthesis of the novel marine alkaloid, rigidin.[4]

Our synthetic route is shown in Scheme 1. The requisite cyclization precursor **2** was obtained by heating *N*-benzyl-4-chloro-2(1*H*)-pyridinone (**1**)[5] with sodium *N*-benzylglycinate in DMSO for 45 min followed by an acidic workup. Exposure of the isolated free acid **2** to acetic anhydride with added base catalyst, and then heating for 4 hrs, afforded the 3-acetoxy pyrrole derivative **3a**[6] in high yield.[7] This acylative cyclodehydration reaction could also be effected using trifluoroacetic anhydride (TFAA) and added base with lower reaction temperatures being required. Notably, even in the presence of excess acetic anhydride or TFAA, further acylation at the electron-rich C-2 position of the pyrrole ring was not observed.

Conversion of the 3-acetoxy pyrrole **3a** into its triflate derivative **4** proved more difficult that expected. Reaction conditions that had proven successful in the case of pyrrolo[2,3-*d*]pyrimidi-2,4-diones (Na_2CO_3, MeOH, Δ, 5 min; Tf_2O, collidine, -78 °C)[4] afforded none of the desired

triflate **4**. During the base hydrolysis step, rapid and drastic color changes were noted.[8] ^{1}NMR analysis of the crude reaction mixture indicated that the formation of the intermediate pyrrolo[3,2-*c*]pyridin-2,3-dione was accompanied by extensive formation of uncharacterized by-products.[9] Fortunately, this problem was surmounted by reaction of **3a** with 2 equivalents of methyl lithium at -78 °C which presumably lead to the formation of an enolate intermediate. This species could then efficiently trapped with *N*-phenyl triflimide at low temperature[10] before it had an opportunity to self condense. In this way, high yields of the desired triflate **4** were routinely obtained. At this stage the triflate intermediate **4** can be seen as a general building block for a variety of 3-substituted pyrrolo[3,2-*c*]pyridin-2-ones by use of palladium-catalyzed functionalizations of organotriflates.[11] For example, methoxycarbonylation of **4** leading to the ester **5** was effected in 65% yield utilizing the procedure of Dolle and coworkers.[12a] By using Ph_3P as the ligand and DMF as the solvent, the carbonylation yield increased to 80%.[12b]

Scheme 1

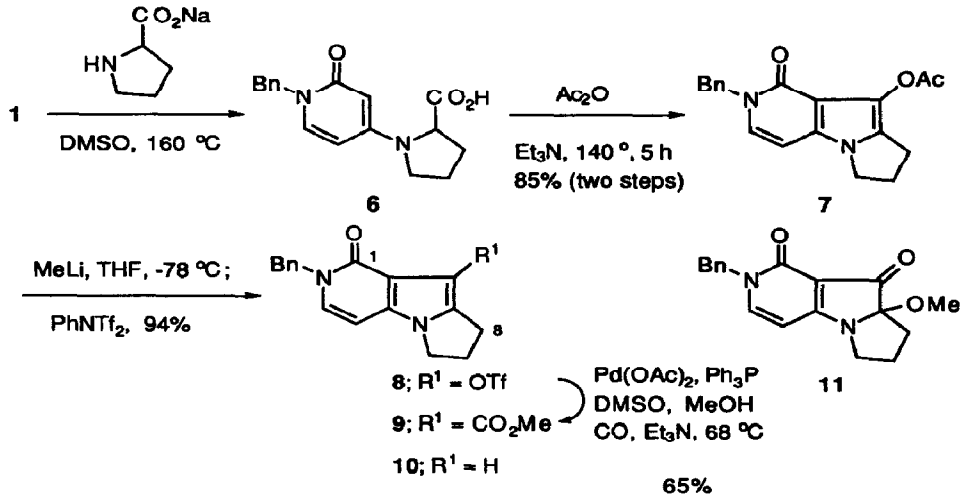


i Ac_2O, Et_3N, 130 °C. ii TFAA, Et_3N, CH_2Cl_2, 35 °C. iii $Pd(OAc)_2$:dppp (1:1), DMSO, CO, MeOH, Et_3N, 65%. iv $Pd(OAc)_2$:Ph_3P (1:4.5), DMF, CO, MeOH, Et_3N, 80%.

In order to expand the utility of our methodology, compound **1** was treated with sodium prolinate in hot DMSO to afford the crude substitution adduct **6** (Scheme 2). Subsequent cyclodehydration using acetic anhydride provided the pyrido[3,4-*b*]pyrrolizidin-1-one **7**[13] in high overall yield for the two steps. Following the protocol described above, this compound was converted into the triflate intermediate **8** in high yield. The methoxycarbonylation of triflate **8**, leading to the ester **9**, proved somewhat difficult and was attributed to the steric hinderance at the C-9 position which arises from peri-interactions at the adjacent C-1 and C-8 positions. For

example, using dppp as the ligand[12a] and $Pd(OAc)_2$ as the catalyst source, the reduction product, **10**, was co-produced along with the desired product and a new compound, **11**, which apparantly results from an oxidative hydrolysis process.[14] Procedures[12b] using Ph_3P as the ligand with 5-10% palladium catalyst gave mixtures of ester **9** and compound **11** and depended upon the time required to consume the starting material.[15] It was found that the desired carbonylation reaction could be best reproduced in 60-65% yield using 30% catalyst and Ph_3P as the ligand (ligand to palladium ratio of 4.5:1). These conditions greatly accelerated the consumption of the triflate and minimized formation of the by-product **11**.

Scheme 2



We have demonstrated an efficient new approach for the synthesis of pyrrolo[3,2-*c*]pyridin-2-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones starting from a simple 4-chloro-2-pyridinone intermediate and amino acid salts. Synthetically versatile triflate intermediates **4** and **8** are provided which can serve as precursors for a variety of novel structures. The development of this methodology for the synthesis of aza-mitosene[16] and 5-azaindole nucleoside analogues is currently being pursued.

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5. This compound was made by the simple alkylation of 4-chloro-2-pyridinone (NaH, BOMCl, DMF) which, in turn, was derived in four steps from 2-pipecolinic acid. Graf, R. *Chem. Ber.* **1931**, *64*, 21.
6. All new compounds have been fully characterized by ^{1}H and ^{13}C NMR, IR, and either elemental analysis or high resolution mass spectroscopy.
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9. We attribute these observations to the rapid self condensation of the intermediate pyrrolo[3,2-*c*]pyridin-2,3-dione in analogy with the known sensitivity of 3-oxindole to basic reaction conditions which leads to the rapid formation of indigo. Russell, G. A.; Kaupp, G. *J.Am. Chem. Soc.* **1969**, *91*, 3851.
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14. The structure confirmation of this unusual oxidative hydrolysis product and the mechanistic details regarding its formation are currently being explored in greater detail. The results of this study will be reported elsewhere.
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16. For examples of ring modified mitosene or mitomycin analogues, see: Köhler, B.; Su, T. L.; Chou, T. C.; Jiang, X. J.; Watanabe, K. A. *J. Org. Chem.* **1993**, *58*, 1680. Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. *Ind. J. Chem.* **1990**, *29B*, 901.

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