New Directions of the Fischer Indole Synthesis

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We have previously demonstrated that aryl hydrazides are effective surrogates of aryl hydrazines, undergoing various reactions including the Fischer indolization reaction to afford the corresponding indoles, when treated with enolizable aldehydes and ketones in the presence of an acid. Unlike aryl hydrazines, the aryl hydrazides are readily accessed from aryl halides via the Pd(0) or Cu(I)-catalyzed coupling reaction with *N*-Boc hydrazine.[2] Also reported was that *N*-Cbz-aryl hydrazide can proceed in a Fischer indolization reaction to give *N*-Cbz-indole without the elimination of *N*-Cbz group.

Prompted by our recent interest on the synthesis of 3,4-fused tricyclic indole alkaloids (Figure 1), we set out to study the intramolecular Fischer indolization reaction of the aryl hydrazide that are linked to carbonyl functions by various tether groups as a new synthetic means to the construction of tricyclic indole system. We found that aryl hydrazide with carbonyl function tethered at the C(4) position of the aromatic ring undergoes intramolecular Fischer indolization to afford novel indolophanes. In addition, strategic insertion of a double or triple bond in the tether allowed for an aromatic Claisen rearrangement to proceed in a tandem fashion, providing 3,4-fused tri- or tetracyclic system.

More recently, we have found that aryl hydrazide can be directly coupled to vinyl triflate to generate ene-hydrazide, the key intermediate in the Fischer indole synthesis. Heating in the presence of catalytic amount of an acid effected the [3,3]-sigmatropic rearrangement reaction *en route* to the indole product without scrambling of the regiochemistry. Our recent discovery on the veneer Fischer indolization chemistry will be discussed