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A one-pot conversion of ortho-alkynyl benzaldehydes into indolo[2,1-*a*]isoquinolines

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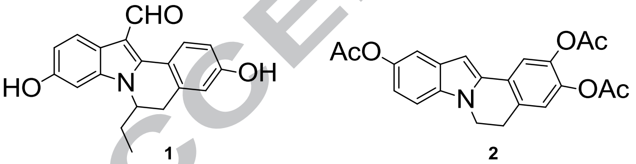
ABSTRACT

The conversion of readily available 2-halobenzaldehydes into indolo[2,1-*a*]isoquinolines in two operations represents a very direct entry to this class of molecules.

1. Introduction

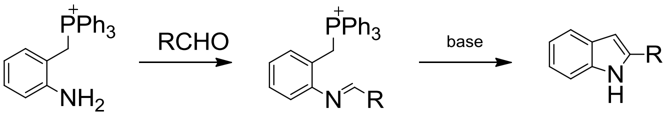
Indolo[2,1-*a*]isoquinolines and their dihydro analogs exhibit a diverse array of activities. These compounds are components in tubulin-binding drugs,[1] estrogen receptor modulators,[2] and organic semiconductors[3]. Some members of this class are natural products.[4] Representative compounds are shown below in Figure 1.



1 2

Figure 1. Representative indolo[2,1-*a*]isoquinolines

Because of their biological activity, a number of approaches to this class of molecules have been reported. The most commonly used approach involves organopalladium couplings of 2-aryl indoles through both intermolecular[5] and intramolecular[6] pathways. However, some innovative routes involving rhodium-based cyclizations,[7] copper-mediated cyclizations,[8] and platinum-based cyclizations[9] have recently been reported. Approaches utilizing metalation[10] have also been reported. We recently reported an indole synthesis shown in Scheme 1 utilizing a two-step approach in one pot involving imine formation and six-electron ring closure, followed by a 1,5-hydrogen shift.[11] In the process of extending our indole synthesis, we have discovered a novel tandem cyclization to indolo[2,1-*a*]isoquinolines.



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Scheme 1. Indole synthesis of Kraus and Guo

2. Results and discussion

The reaction of 2-bromobenzaldehyde with the methyl ether of propargyl alcohol under Sonogashira reaction conditions developed by Shu[12] afforded the 2-alkynylbenzaldehyde **4**. Formation of the imine using aniline **3** and treatment with potassium tert-butoxide according to the conditions of Kraus and Guo did not generate the expected indole **5**.[13] The major organic product lacked the N-H as evidenced by NMR and the acetylenic resonances were absent from the carbon NMR. The mass spectrum and proton and carbon NMR supported the assignment of structure **6**. Presumably, compound **6** arose from the cyclization of the anion of **5** under the basic conditions, as shown in Scheme 2.

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