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A New β-Carbolinone Synthesis Using a Rh(II)-Promoted [3 + 2]-Cycloaddition and Pd(0) Cross-Coupling/Heck Cyclization Chemistry

Joel M. Harris[†] and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

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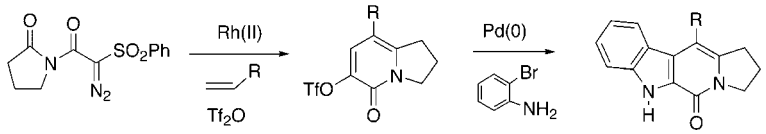
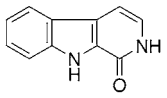
ABSTRACT

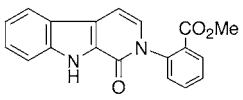


A short and efficient synthesis of the β-carbolinone ring system was achieved using a rhodium(II)-catalyzed [3 + 2]-cycloaddition, a Pd(0)-catalyzed C–N amination reaction, and a subsequent intramolecular Heck reaction as the key synthetic steps.

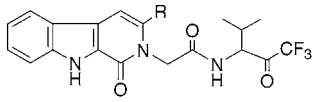
The 1,2-dihydropyrido[3,4-*b*]indol-1-one (i.e., β-carbolinone) nucleus occurs in many natural products,[1] and several of these compounds show significant biological activity.[2] One of the metabolites isolated from the sponge genus *F. reticulata* was identified as secofascaplysin (**1**) and represents the first naturally occurring β-carbolinone.[3] Many β-carbolinone derivatives have been found to exhibit affinity for the benzodiazepine receptor,[4] show antileukemic properties,[5] and function as useful central nervous system depressants.[6] A novel series of human leukocyte elastase (HLE) inhibitors containing the β-carbolinone ring system has also been reported, and these compounds have been used as potential therapy agents in disease states.[7] The β-carbolinone ring can serve as a highly efficient peptidiomimetic and shows significant in vitro potency and selectivity for HLE.[7]



β-carbolinone ring skeleton
1,2-dihydro-pyrido[3,4-*b*]indol-1-one



secofascaplysin (**1**)



non-peptide inhibitor of HLE

Since the biological properties of these heterocycles have spurred considerable preparative efforts,[8] the development of new synthetic methods for the construction of novel β-carbolinone ring systems remains an attractive research

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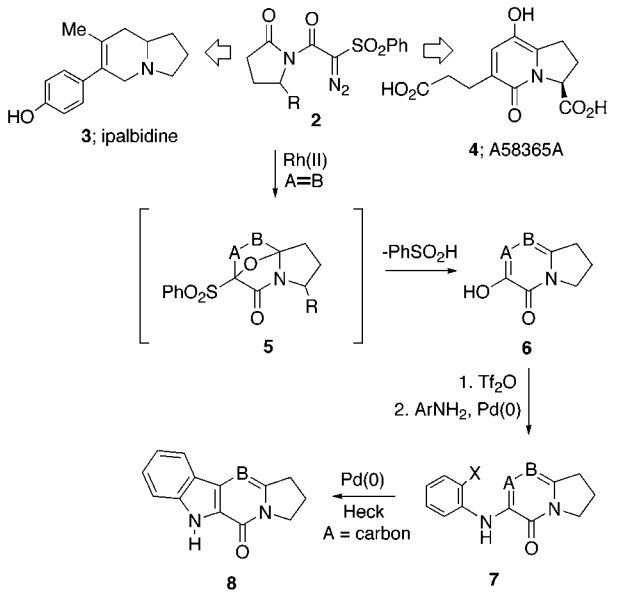
Scheme 1

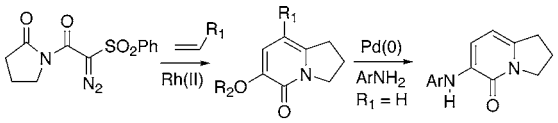


area. Most of the described syntheses of β-carbolinones use a 2-carboxyindole-3-acetic acid as the starting material[9] or are based on the Fischer indole reaction of 3-formyl-2-pyrrolidinone derivatives with aryl hydrazines.[10] We envisaged a conceptually new approach to these heterocycles based upon our recently reported synthesis of 2(1*H*)-pyridones via the [3 + 2]-cycloaddition reactions of isomünchnones derived from the Rh(II)-catalyzed reaction of α-diazoimido sulfones.[11] Herein, we report the scope and generality of this methodology and document its usefulness in the preparation of variously substituted β-carbolinones.

Our laboratory has been involved in the utilization of the Rh(II)-catalyzed cyclization/cycloaddition cascade of diazo-substituted carbonyl compounds for the synthesis of complex azapolycyclic ring systems.[12] Among other examples, this procedure was employed in an efficient synthesis of (±)-ipalbidine (**3**) and the angiotensin inhibitor (−)-A58365A (**4**) (Scheme 1).[13] The versatility of this strategy lies in the fact that by appropriate selection of the diazo precursor and dipolarophile, various groups can be introduced into the N-1 and C-4, C-5, C-6 positions. The cornerstone of the cascade sequence involves the ready ring-opening reaction of the initially formed isomünchnone cycloadduct **5** to give a substituted 3-hydroxy-2(1*H*)-pyridone **6**. It was envisaged that the C_3-hydroxyl group present in **6** could be transformed to an amino group (i.e., **7**) by a palladium-catalyzed amination reaction of its corresponding triflate. Finally, a subsequent Pd(0)-promoted Heck reaction would furnish the desired β-carbolinone ring system **8** as outlined in Scheme 1.

To investigate the potential of this strategy, diazoimide **2** (R = H) was chosen as the starting substrate. Formation of the isomünchnone dipole was achieved by reaction of **2** with $Rh_2(OAc)_4$ to first give the rhodium carbenoid species that undergoes a subsequent intramolecular cyclization onto the neighboring carbonyl oxygen. Bimolecular trapping of the dipole with either methyl acrylate or phenyl vinyl sulfone gave pyridones **9** and **11** in 86% and 85% yield, respectively. Pyridone **9** was easily decarboxylated by heating with 48% HBr at 135 °C for 12 h to furnish the unsubstituted pyridone **10** in 90% yield. All three 2(1*H*)-pyridones (**9**−**11**) were readily converted to the corresponding triflates (**12**−**14**) using *N*-phenyl trifluoromethanesulfonamide and triethylamine in high yield (Scheme 2).[13,14]

Scheme 2



HBr, Δ

9; R_1 = CO_2Me; R_2 = H
10; R_1 = R_2 = H
11; R_1 = SO_2Ph; R_2 = H
12; R_1 = CO_2Me; R_2 = Tf
13; R_1 = H; R_2 = Tf
14; R_1 = SO_2Ph; R_2 = Tf

15; Ar = C_6H_5; 65%
16; Ar = *p*-$OMeC_6H_4$; 70%
17; Ar = *p*-$NO_2C_6H_4$; 76%
18; Ar = 3,5-$(OMe)_2C_6H_3$; 70%
19; Ar = *o*-$CF_3C_6H_4$; 73%
20; Ar = *o*-$NH_2C_5H_4N$; 88%
21; Ar = *o*-BrC_6H_4; 80%
22; Ar = $C_6H_5CH_2$; 65%
23; Ar = C_6H_5CO; 74%
24; Ar = $C_6H_5CH_2OCO$; 71%

C−N cross-coupling of aryl halides and triflates with amines has been the subject of intense studies in recent years, primarily by the groups of Buchwald[15] and Hartwig.[16] Application of this methodology to various heteroaromatic compounds is still a relatively unexplored process. We initially investigated the cross-coupling of pyridone **13** and aniline. The amination reaction proceeded quite well using 5 mol % $Pd(OAc)_2$, 10 mol % Xantphos, and 1.5 equiv of Cs_2CO_3 in refluxing toluene for 6 h (method A) to give 6-phenylamino-2,3-dihydro-1*H*-indolizin-5-one (**15**) in 62% isolated yield. The use of $Pd_2(dba)_3$ (method B) gave a

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slightly higher yield of the coupled product and with a significant decrease in reaction time (65%, 1.5 h). Other ligands investigated included (±)-BINAP, tri-*tert*-butylphosphine, DPPF, and 2-(dicyclohexylphosphino)biphenyl. However, with these ligands a much lower yield of the coupled product was obtained or else no reaction occurred. The cross-coupling reaction was also carried out using a microwave reactor available from CEM at 25 W for 20 min which afforded a 60% yield of the coupled product (method C). Both electron-rich and electron-deficient anilines underwent efficient coupling. 2-Aminopyridine was the most efficient coupling partner giving rise to pyridone **20** in 88% yield. The use of $Pd_2(dba)_3$ facilitated the coupling of benzylamine, benzamide and benzyl carbamate in good yield. Similar cross-couplings were also carried out with both the 5-carbomethoxy- (**12**) and 5-phenylsulfonyl-substituted (**14**) pyridones in good yield with a variety of amines.

With an efficient method available for the synthesis of 3-anilino-substituted 2(1*H*)-pyridones in hand, we set out to prepare an *o*-bromo-substituted anilino derivative to use as a precursor for the Heck cyclization[17] as proposed in Scheme 1. The cross-coupling reaction of 2-bromoaniline with triflate **13** proceeded smoothly affording an excellent yield of the required product **21** in 80% yield. Similar results were obtained with the carbomethoxy-substituted pyridone-triflate **12**. Construction of the β-carbolinone system was next investigated using these readily available pyridones. Indeed, it was found that treatment of both compounds **21** and **25** with 10 mol % $Pd(PPh_3)_4$ and 1.2 equiv of Cs_2CO_3 in dioxane

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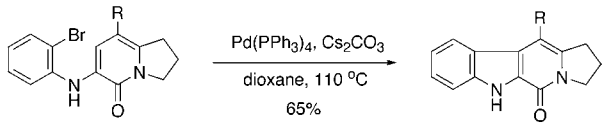
Scheme 3



21; R = H
25; R = CO_2Me

26; R = H
27; R = CO_2Me

at 110 °C gave the desired β-carbolinones **26** and **27** in 65% unoptimized yield (Scheme 3).

In summary, we have shown that the β-carbolinone ring system can be rapidly assembled by (i) a Rh(II)-promoted [3 + 2]-cycloaddition of a phenylsulfonyl-stabilized isomünchnone intermediate, (ii) conversion of the resulting 3-hydroxy-2(1*H*)-pyridone into the corresponding triflate, (iii) a Pd(0)-catalyzed C−N amination reaction, and (iv) a Pd(0)-catalyzed intramolecular Heck reaction. Further utilization of this methodology for the construction of β-carbolinone natural products and bicyclic peptide mimics is under current investigation and will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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