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One-pot Sonogashira coupling, hydroamination of alkyne and intramolecular C—H arylation reactions toward the synthesis of indole-fused benzosultams

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ABSTRACT

A one-pot Sonogashira coupling, hydroamination of alkyne and C—H arylation reactions for the synthesis of indole-fused benzosultams are described. This method allows access to a variety of indole-fused seven membered benzosultams in good to excellent yields. The free indolyl nitrogen containing indole-fused benzosultams are also prepared by this method. The structures of the synthesized compounds are confirmed by single crystal XRD studies.

Introduction

Indole derivatives are very attractive scaffolds in medicinal chemistry research due to their natural occurrence and pharmacological activities.[1] At present, there are approximately 1500 indole alkaloids described in the literarure[2] which includes varieties of functionalized indole derivatives. Many of the biologically active indole derivatives are fused with six-, seven- and eight-membered ring systems. On the other hand, compounds containing benzosultam core moiety show a wide spectrum of bioactivities, such as antiviral, antimicrobial, antileukemic, anticancer, enzyme inhibition, etc.[3,4] Therefore it is expected that the indole-fused benzosultam derivatives are infused with the potentiality of becoming pharmacologically active compounds commodious for drug developments. Although in the literature, different biologically active heterocycles-fused sultams are reported such as pyridine-,[5] quinoline-,[6] Uracil- and Coumarin-fused[7] sultams but there are few reports available on the synthesis of indole-fused sultums. For instance, Laha and co-workers synthesized indole-fused sultams by palladium catalyzed intramolecular oxidative coupling (Scheme 1, equ. 1).[8] Zhu et al. reported the construction of indole-fused sultams by palladium catalyzed diamination of alkynes (Scheme 1, equ. 2).[9] Therefore, in our continuous effort in the synthesis of biologically active heterocycles,[10] it is now our challenge to synthesize and optimize highly efficient and economical synthetic route towards the formation of novel indole-fused seven-membered benzosultams. Herein we report our results.

Results and discussion

The *o*-iodoaniline derivatives are one of the most prominent starting materials that are widely used for the synthesis of indole nucleus.[11] On the other hand, the 3-position of indole are very susceptible for substitution and based on this feature several indole derivatives including β-carboline had been prepared in past few years.[12] Based on these chemistry here we prepare a new class of indole-fused seven membered benzosultams. To access the indole-fused benzosultams we followed the synthetic route according to the retrosynthetic analysis depicted in Scheme 2. For the purpose, the required precursors *o*-iodoaniline derivatives **5**[10a] and propargylsulfonamides (**6** and **10**)[10b] were prepared following our previously reported procedure.

We started our research for the synthesis of indole-fused benzosultams by the Pd-catalyzed cyclization of compound **8c**. Compound **8c** was prepared according to our previously reported procedure.[10a] Various combinations of Pd-catalysts, bases, additives and solvents were tested in different temperatures for the successful cyclization of compound **8c** to afford the sultam

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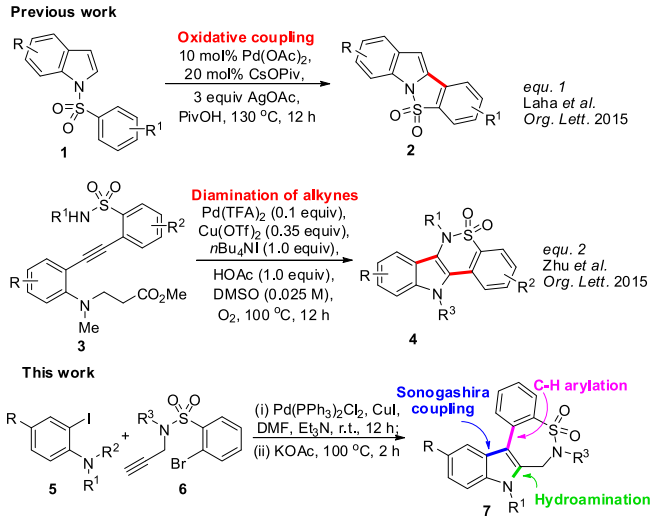
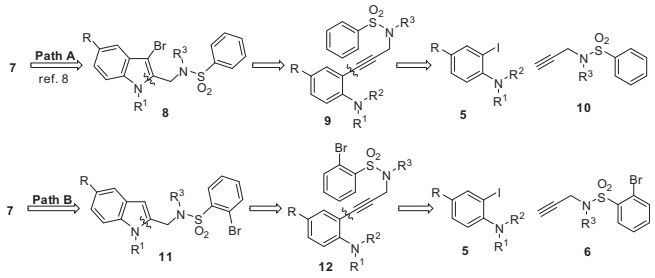


Scheme 1. Some synthetic approaches to indole-fused benzosultams.



Scheme 2. Retrosynthetic approach towards indole-fused benzosultam.

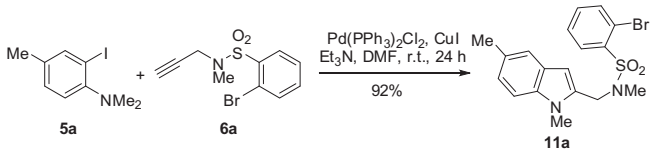
7c. But none of these combinations gave the fruitful results (Table 1).

After getting the unsatisfactory results following path-A, we then attempted the synthesis of benzosultams according to path-B of Scheme 2 with compound **11a**. Compound **11a** was prepared in excellent yield by the Sonogashira coupling and hydroamination of alkyne with the compounds *o*-iodoaniline derivative **5a** (1 equiv.) and propargylsulfonamide **6a** (2 equiv.) in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), in DMF-Et_3N at room temperature for 24 h (Scheme 3). The use of propargylsulfonamide derivative **6a** less than 2 equivalent leads to the decrease of formation of compound **11a**. The Pd-catalyzed cyclization (intramolecular C—H arylation) of compound **11a** to afford indole-fused benzosultam **7a** was then studied according to the Table 1 and the summarized results were depicted in Table 2. Just a small change, i.e., the alternation of the position of bromine from indole nucleus to sulfonamide aryl ring leads to the brilliant result for the cyclization step to afford the indole-fused benzosultam. It is worth mentioning that alteration of catalyst $Pd(PPh_3)_2Cl_2$ by $Pd(OAc)_2$ for the cyclization of compound **11a** gave almost same yield of compound **7a** (Table 2: entry 4 and 7).

We then performed one-pot reaction i.e., the Sonogashira coupling, hydroamination reaction and intramolecular C—H arylation in one-pot for the synthesis of indole-fused benzosultams. The coupling of precursors **5a** and **6a** was carried out in the presence of $Pd(PPh_3)_2Cl_2$-CuI catalyst in DMF using triethylamine as a base at room temperature for 24 h and after this KOAc was added and the temperature was increased from room temperature to 100 °C for 2 h. This condition gave the indole-fused benzosultam **7a**[13] in 93% yield (Scheme 4).

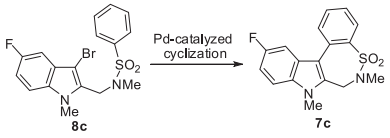
After getting the satisfactory result, the coupling of other precursors i.e. **5b–f** with **6a**,**b** gave the various indole fused benzosultams **7b–h** (Fig. 1). The structure of compound **7a** was confirmed by single crystal XRD analysis (Fig. 2).[14]

The plausible mechanistic pathway for the formation of compound **7** is shown in Scheme 5. First intermediate **12** was formed by the Sonogashira coupling between **5** and **6**. Then Cu(I) may be coordinated to the acetylene and sulfone group to form the complex **13**.[10a] Coordination of Cu(I) with sulfone and triple bond of acetylene may increase the electrophilicity of acetylenic carbon to promote the nucleophilic attack of lone pair of NMe_2 group



Scheme 3. Formation of indole-2-methylsulfonamide **11a** by domino Sonogashira coupling and hydroamination reaction.

Table 1
Synthetic approach towards indole-fused benzosultam via Pd-catalyzed cyclization of compound **8c**.



Entry	Catalyst[a]	Base	Solvent	Time (h)	Yield (%)
1[b]	$Pd(PPh_3)_4$	Et_3N	DMF	2	NP
2[c]	$Pd(PPh_3)_2Cl_2$	KOAc	DMA	1	Trace
3[c]	$Pd(PPh_3)_2Cl_2$	Et_3N	DMF	1	NP
4[b]	$Pd(PPh_3)_2Cl_2$	KOAc	DMF	1	<5
5[b,f]	$Pd(PPh_3)_2Cl_2$	KOAc	DMA	1	<5
6[b,f]	$Pd(OAc)_2$	KOAc	Toluene	1	NP
7[b]	$Pd(OAc)_2$	KOAc	DMF	1	<5
8[d,f]	$Pd(OAc)_2$	KOAc	DMF	12	NP
9[b,f]	$PdCl_2$	K_2CO_3	DMF	5	NP
10[e]	$Pd(PPh_3)_4$	KOAc	DMA	1	NP
11[c]	$Pd(OAc)_2$	Cs_2CO_3	DMF	1	NP

Reactions were carried out at [b]100 °C, [c]120 °C, [d]r.t., [e]reflux, [f]TBAB was used as an additive.
[a] 5 mol% catalyst was used in every case; NP – No Product.