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Graphical Abstract

One-pot Sonogashira Coupling, Hydroamination of Alkyne and Intramolecular C-H Arylation Reactions toward the Synthesis of Indole-fused Benzosultams

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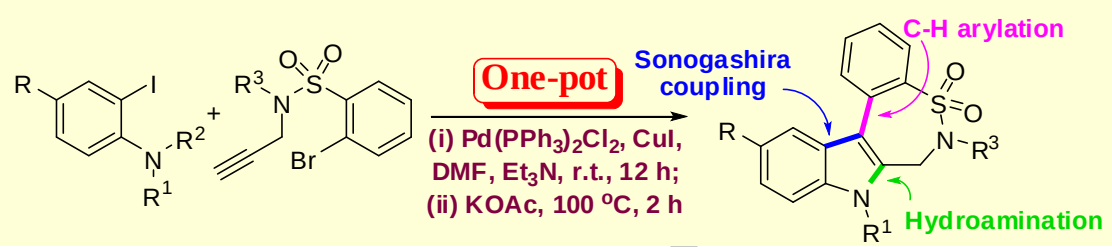

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One-pot Sonogashira Coupling, Hydroamination of Alkyne and Intramolecular C-H Arylation Reactions toward the Synthesis of Indole-fused Benzosultams

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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.

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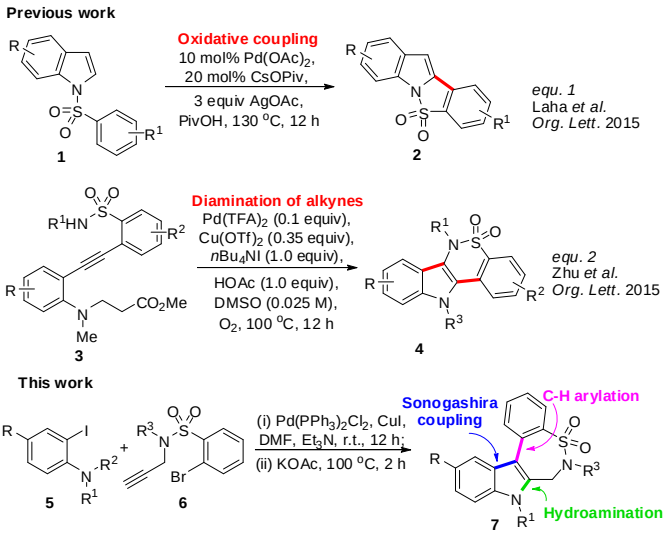
1. Introduction

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.



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

2. 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

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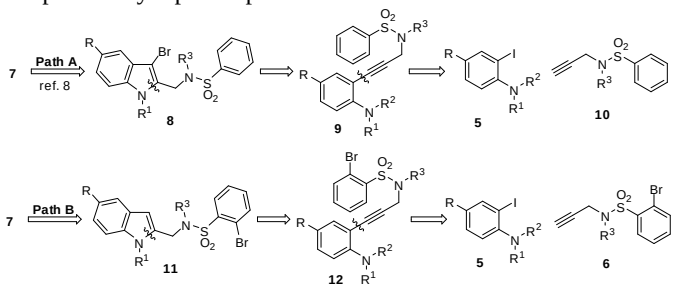
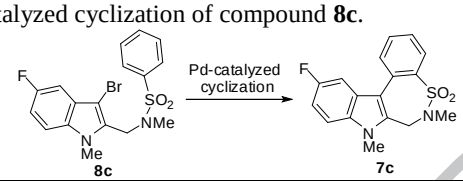
the indole-fused benzosultams we followed the synthetic route according to the retrosynthetic analysis depicted in scheme 2. For the purpose, the required precursors *o*-iodoaniline derivatives **5**[10a] and propargylsulfonamides (**6** and **10**)[10b] were prepared following our previously reported procedure.



Scheme 2. Retrosynthetic approach towards indole-fused benzosultam.

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

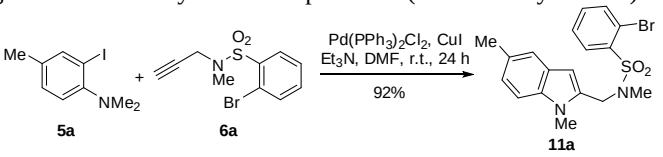
Table 1. Synthetic approach towards indole-fused benzosultam via Pd-catalyzed cyclization of compound **8c**.



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

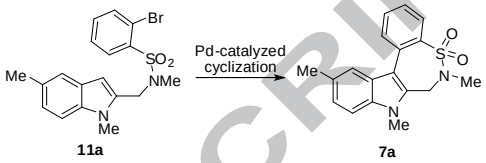
[a]5 mol% catalyst was used in every case; NP – No Product. Reactions were carried out at [b]100 °C, [c]120 °C, [d]r.t., [e]reflux. [f]TBAB was used as an additive.

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).



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

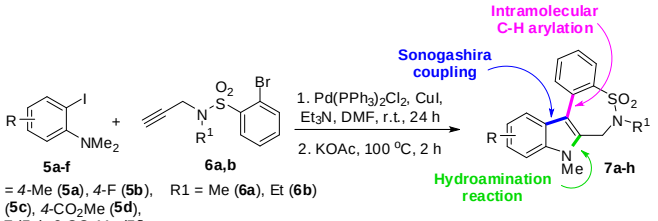
Table 2. Synthetic approach towards indole-fused benzosultam via Pd-catalyzed cyclization of compound **11a**.



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	92
3[c]	$Pd(PPh_3)_2Cl_2$	Et_3N	DMF	1	trace
4[b]	**$Pd(PPh_3)_2Cl_2$**	**KOAc**	**DMF**	**1**	**96**
5[b,f]	$Pd(PPh_3)_2Cl_2$	KOAc	DMA	1	95
6[b,f]	$Pd(OAc)_2$	KOAc	Toluene	1	82
7[b]	**$Pd(OAc)_2$**	**KOAc**	**DMF**	**1**	**96**
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[e]	$Pd(OAc)_2$	Cs_2CO_3	DMF	1	NP

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

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).



Scheme 4. One-pot synthesis of indole fused benzosultam.

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** (figure 1). The structure of compound **7a** was confirmed by single crystal XRD analysis (figure 2).[14]

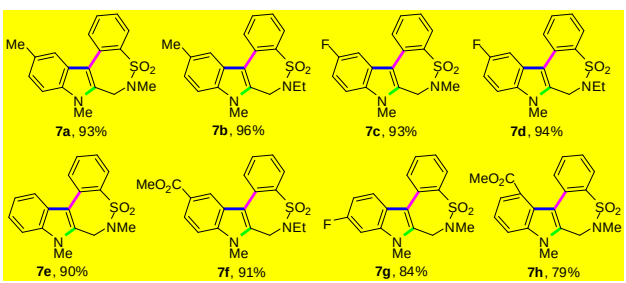


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Figure 1. Summarized results of indole-fused benzosultams**.**

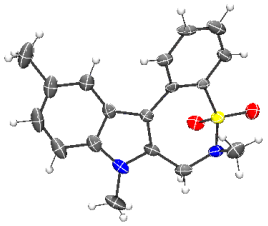
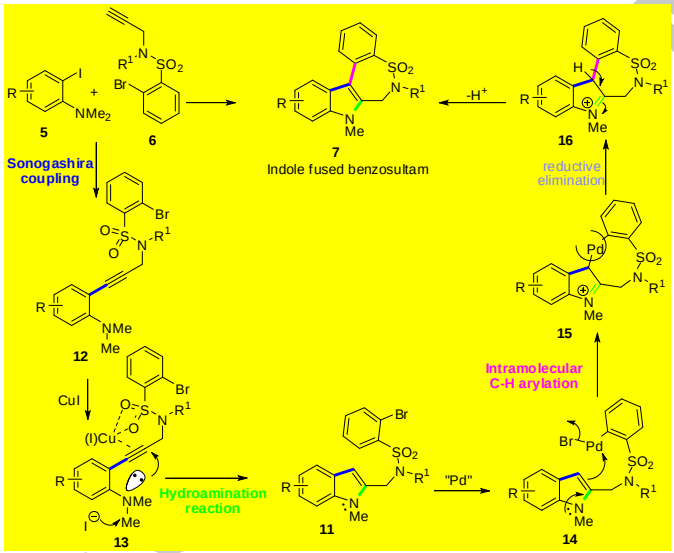


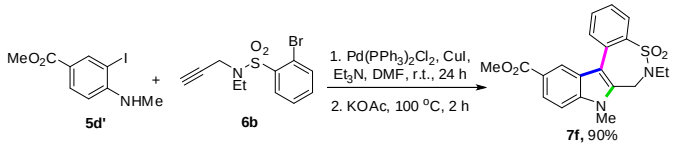
Figure 2. Ortep diagram of compound **7a**

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 which will result the formation of compound **11**. The interaction of Cu(I) with sulfone may play a crucial role for the cyclization of **12**. Here it is worth mentioning that Larock et al. synthesized 3-iodo-indole derivatives where this type of hydroamination step was not occurred which might be due to the absence of sulfone moiety.[11a] After that, the complex **14** may be formed by oxidative addition of "Pd" at C-Br bond in compound **11** and then intramolecular arylation may be taken place at 3-position of indole nucleus to form the intermediate **15**. The reductive elimination of Pd(0) from intermediate **15** may lead to the complex **16** which was then aromatized to compound **7** in presence of KOAc.



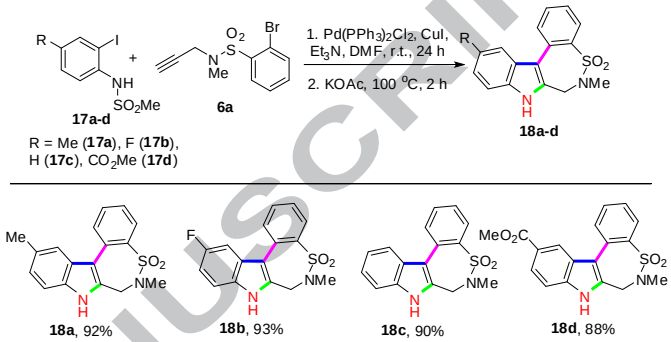
Scheme 5. The probable mechanism for the one-pot synthesis of indole fused benzosultam.

We investigated the role of protecting group of N atom in *o*-iodoaniline derivatives. The *N*-methyl-*o*-iodoaniline derivative **5d'** gave the same result as *N*,*N*-dimethyl-*o*-iodoaniline (scheme 6), but *N*-unsubstituted-*o*-anilines did not give any cyclized product.

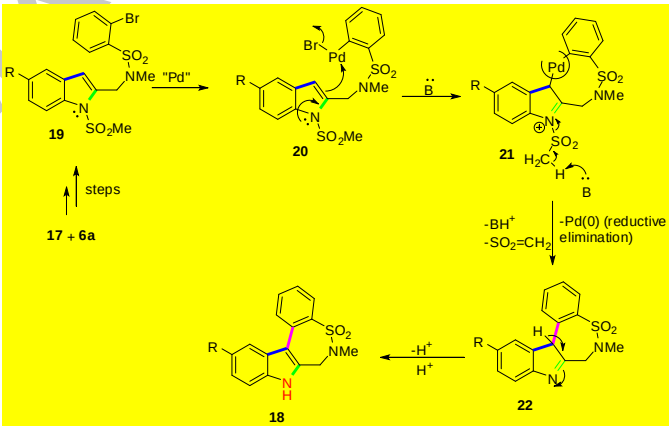


Scheme 6. Formation of indole fused benzosultam using *N*-methyl-o-iodoaniline derivative.

When *N*-mesylated *o*-iodoaniline derivatives **17** are used, the free indolyl nitrogen containing indole-fused benzosultam **18** was obtained with excellent yields (scheme 7). For the synthesis of compound **18**, the reaction was passed through one pot Sonogashira coupling, hydroamination of alkyne, intramolecular C-H arylation and desulfonation reaction (scheme 8). First intermediate **19** was formed from **17** and **6a** by Sonogashira coupling and hydroamination reaction. Then complex **20** may be formed by the oxidative insertion of "Pd" into C-Br bond of intermediate **19** which may be converted to complex **21** by the nucleophilic attack of delocalized π-electron. The reductive elimination of Pd(0) and demesylation in complex **21** may lead to intermediate **22** which may then rearranged to free indolyl nitrogen containing indole-fused benzosultam **18**.



Scheme 7. Synthesis of free indolyl nitrogen containing indole-fused benzosultams



Scheme 8. The probable mechanism for the formation of free indolyl nitrogen containing indole-fused benzosultam

3. Conclusion

In conclusion, we have developed an innovative, facile and efficient one-pot method for the formation of indole fused benzosultam derivatives via Sonogashira coupling, hydroamination reaction and intramolecular C-H arylation. Our method allowed the synthesis of a variety of indole fused benzosultum derivatives with excellent yields. This method also afforded the preparation of free indolyl nitrogen containing indole-fused benzosultams. The structures of the newly synthesized indole fused benzosultums have been confirmed from XRD data. The biological activities of the synthesized indole fused benzosultums are in progress in our laboratory and will be published in due course.

Acknowledgments

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13. To a solution of compound **11a** (0.50 mmol) and KOAc (1.50 mmol) in anhyd DMF (3 mL) N_2 gas was bubbled for 10 min. Then $Pd(OAc)_2$ (5 mol%) was added and the whole reaction mixture was stirred at 100 ^oC for 1 h. Water (10 ml) was then added, and the solution was extracted with ethyl acetate (3 x 10 ml). The organic extracts were washed with water (4 x 20 ml) and brine (10 ml), dried over Na_2SO_4 and the solvent was distilled off to furnish a viscous mass that was purified by column chromatography on silica gel to yield compound **7a** (96%) as white solid. m.p.: 221-223 ^oC. IR (KBr) 2943, 1505, 1352, 1150 cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz) δ** = 8.17-8.15 (m, 1H), 8.08 (dd, J = 8.0, 1.2 Hz, 1H), 7.74 (s, 1H), 7.69-7.65 (m, 1H), 7.35-7.31 (m, 1H), 7.23−7.21 (m, 1H), 7.11-7.09 (m, 1H), 4.78 (s, 2H), 3.65 (s, 3H), 2.70 (s, 3H), 2.47 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ** = 135.7, 135.6, 133.6, 132.7, 132.7, 130.5, 130.2, 129.8, 126.5, 124.9, 124.1, 119.8, 109.5, 108.9, 50.8, 37.5, 30.0, 21.8; **DEPT-135 (100 MHz, CDCl3) δ** = 132.7, 130.6, 129.8, 124.9, 124.1, 119.8, 108.9, 50.8, 37.5, 30.0, 21.8; **HRMS** (ES^+): MH^+, found 327.1163. **$C_{18}H_{19}N_2O_2S^+$** requires 327.1162.
14. The CCDC reference number for the CIF file of compound **7a**: CCDC 1827890

Supplementary Material

Supplementary Copies of NMR spectra of all new compounds are available. Mass spectra of target compounds are available. CIF file of compound **7a** is also available.

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Highlights

- A methodology for the preparation of medicinally important Benzosultams.
- Molecules are completely new and applied Sonogashira Coupling for synthesis.
- There are no any literature procedures, similar to present documented molecules.
- These products are important in natural product synthesis and medicinal chemistry development.

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