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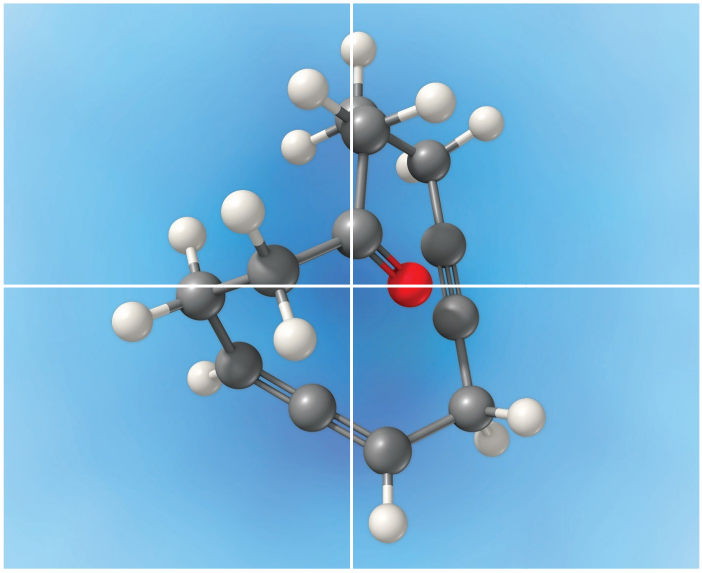

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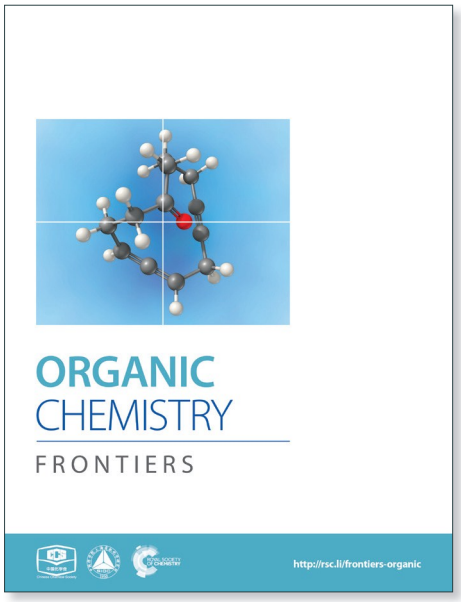

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Journal Name

COMMUNICATION

Cu–Catalyzed Sequential C–N Bond Formations: Expeditious Synthesis of Tetracyclic Indoloindol-3-ones

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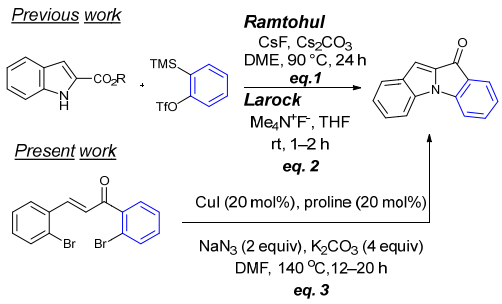
The tetracyclic indoloindol-3-one core has been forged from easily accessible 2,2'-*bis*-bromochalcones employing a reaction cascade comprising Cu-catalyzed SNAr with azide; nitrene C–H insertion and intramolecular Ullmann reaction with all three C–N bond formations in one-go.

The synthesis of substituted indoles and of azaaurones[2-(benzylidene)indol-3-ones, also referred as indoxyls] is an important aspect in organic synthesis mainly due to the occurrence of these substructural units in various biologically active natural products and/or clinically relevant entities.[1,2] The tetracyclic indoloindol-3-one (Figure 1) resulting from the fusion of these two scaffolds has been recently revealed by Biosynth AG as dyes and as fluorogenic indicators for external stimuli such as temperature or vibrations, with a potential for fluorophores for bioconjugation.[3] There are only very few reports on the synthesis of this type of scaffold in the literature.[4-7] A general method available for the synthesis of this skeleton founded upon the coupling of the arynes with α-aminoesters has been independently reported by Larock[5] and Ramtohul[6] groups (eqs. 1/2, Fig. 1). Recently, we have documented a simple approach for the synthesis of 3-indolones and 2-aroylindoles comprising a one-pot construction of both C–N bonds present in these scaffolds employing the Cu-catalyzed S_NAr of aryl halides using azide and subsequent formation of the next C–N bond either *via* the intramolecular addition of a carbon centered nucleophile on to azide or the generation of nitrene followed by its insertion across the C–H bond.[8] To further extend the scope of this approach, we presumed that if a suitable leaving group is available at the ortho position, the subsequent Ullmann coupling will complete the formation of the third C–N bond, thus leading to these indoloindol-3-one scaffolds in one pot – with the synchronized construction of all the three C–N bonds in one-go (eq. 3, Fig. 1).[9] We focus on the feasibility of this one-pot [Cu]-catalysed synthesis of fused tetra cyclic indoloindol-3-one scaffold from 2,2'-*bis*-bromochalcones.

Figure 1. Methods for indoloindol-3-one synthesis



Initial experiments with simple bisbromochalcone **1a**[10] under the previously established conditions [20 mol% of each of CuI and L-proline, of K_2CO_3 (4 equiv) and NaN_3 (1.2 equiv) in NMP at 110 °C for 12 h] led to the formation of 2-aroylindole as one of the products. We speculated that the second cyclisation leading to the indolone ring is more demanding and increased the reaction temperature from 110 °C to 140 °C.[11] This change gave the first optimistic result of fabrication of the parent indoloindol-3-one scaffold **2a**. Subsequently, we moved towards the development of ambient reaction conditions. The optimisation of reaction conditions started from solvent screening. Various solvents were screened and DMF was found to be a better solvent with improvement in yield from 30% to 52% (Table 1, entries 1-4). Afterwards, the focus was shifted to check the copper (Cu) source other than CuI. However, it was found that CuI is the best copper source for the present cascade reaction (Table 1, entries 4-7).The presence of the base K_2CO_3 (4.0 equiv) is required. However, other bases such

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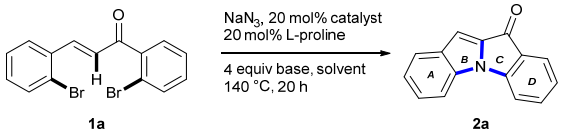
as Cs_2CO_3, Na_2CO_3, NaOH and *t*-BuOK did not show any improvement in the yield (Table 1, entries 8–10). Increasing the concentration of the ligand L-proline from to 20 to 50 mol% did not show any fruitful effect on the reaction. The change in azide concentration from 1.5 equiv. to 2.5 equiv. was also carried out but these changes did not improve the results (Table 1, entries 12–14). Hence the concentration of azide was kept as it is. The final reaction condition was ascertained as, 20 mol% of each of CuI and L-proline, 4 equiv K_2CO_3 and 1.5 equiv NaN_3 in DMF at 140 °C for 20 h.

Table 1. Optimisation of reaction conditions

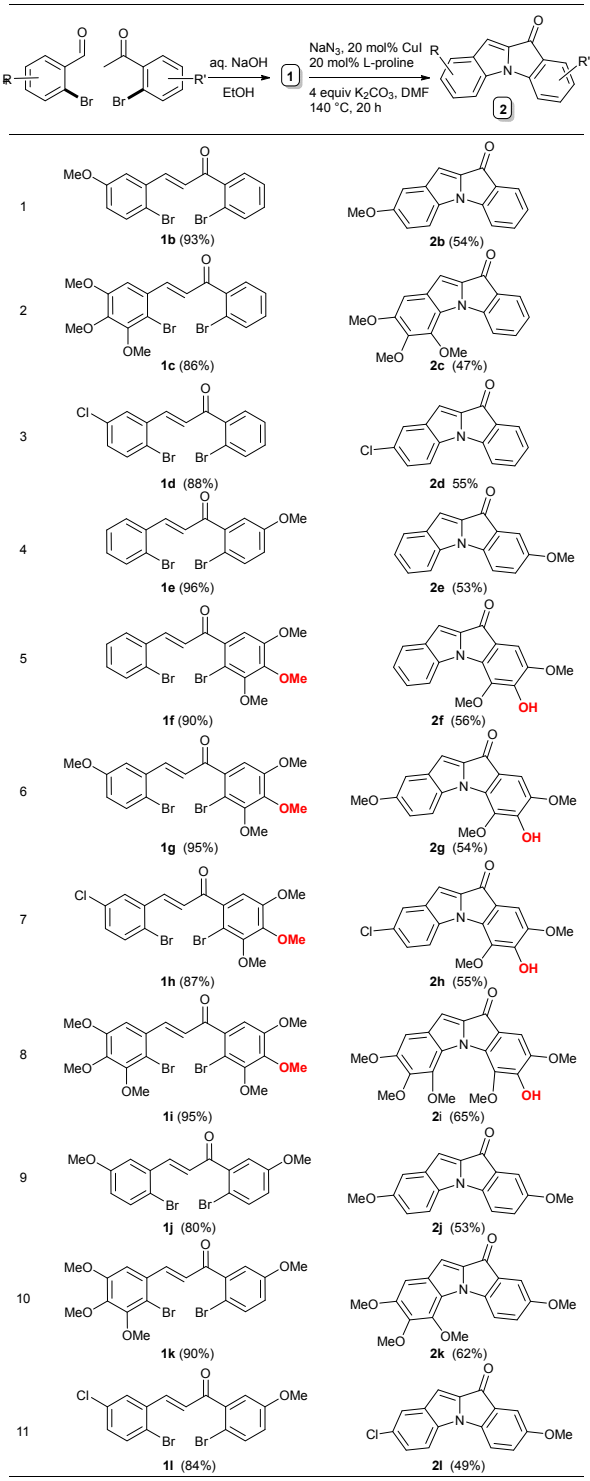


No.	Solvent	Catalyst (20 mol%)	Base (4 equiv)	NaN_3 (equiv)	Yield (%)
1	NMP	CuI	K_2CO_3	1.2	38
2	DMSO	CuI	K_2CO_3	1.2	30
3	DMA	CuI	K_2CO_3	1.2	35
4	**DMF**	**CuI**	**K_2CO_3**	**1.2**	**52**
5	DMF	CuBr	K_2CO_3	1.2	23
6	DMF	CuO	K_2CO_3	1.2	10
7	DMF	$CuSO_4$[a]	K_2CO_3	1.2	26
8	DMF	CuI	Cs_2CO_3	1.2	36
9	DMF	CuI	Na_2CO_3	1.2	2
10	DMF	CuI	NaOH	1.2	25
11	DMF	CuI	tBuOK	1.2	32
12	DMF	CuI	K_2CO_3	1.5	45
13	DMF	CuI	K_2CO_3	2	42
14	DMF	CuI	K_2CO_3	2.5	44

[a]Na-ascorbate used

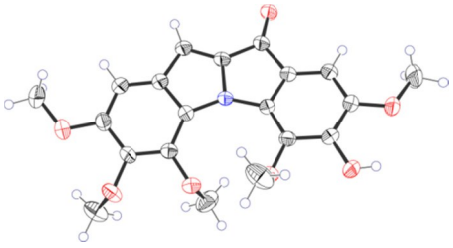
Next, the generality of the current reaction has been examined by keeping mainly electron donating groups and halogens on either of the rings. Initially, the substrates were selected where the nature of substituent on the 'A' ring was varied from methoxy to trimethoxy. With these substrates, the product yields improved marginally. Even the substrates with halogens groups were compatible under these conditions. In general, the yields are moderate for this one-pot three-step cascade (Table 2, entries 2b to 2d). Similarly, when the same electron donating groups were placed on the other aryl ring, the comparative yields of the products improved. Interestingly, with the substrate having the 3,4,5-trimehoxyaroyl unit (Table 2, entry 2f), the demethylation of one of the methoxy groups was seen to occur.[12] The symmetric ^1H spectral pattern observed for this aryl unit in the ^1H NMR spectrum of 2f revealed that the demethylation of the *p*-OMe occurred selectively. To check the generality of this demethylation, the scope of substrates by varying the groups on the ring "A" and by keeping the trimethoxy group on the ring "D'' has been examined.

Table 2. Synthesis of various bis-bromochalcones and scope of the Cu-catalyzed sequential 3 x C–N bond formation



The results were consistent with respect to demethylation.The single crystal X-ray analysis of one of the compounds **2i** (Figure 2) supported the assigned structure. In general, with these substrates having the trimethoxy groups present on the ring "D" the product yields are better than with the substrates where the trimethoxy groups are present on the ring A (Table 2 entries **2g**–**2i**). However, substrateswith trimethoxyaryl units took longer reaction times compared to the rest of the substrates. This may be due to the steric hindrance caused by one of the methoxy groups being ortho to bromine for the SNAr reaction or for the Ullmann coupling.

Figure 2. Single crystal X-ray structure of **2i** (the ellipsoids are drawn at 50% probability



Conclusions

In conclusion, a simple catalytic protocol for the preparation of the tetracyclic indoloindolone derivatives from easily accessible bis-bromochalcones has been developed. This Cu-catalyzed process presumably involves the following set of reactions – (i) SNAr with azide making the first C–N bond; (ii) The Cu-catalyzed conversion of azide to nitrene and subsequent intramolecular insertion of nitrene across the C–H bond with the net formation of second C–N bonds to give indole; and (iii) finally the intramolecular Ullmann reaction to form third C–N bond thus leading the formation of indol-3-one ring. More detailed investigations on understanding the complete course of this reaction, improving the yields by exploring the possible combination of leaving groups, are the objectives of our future exploration in this context.

Acknowledgements

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Graphical Abstract:

Cu–Catalyzed Sequential C–N Bond Formations: Expeditious Synthesis of Tetracyclic Indoloindol-3-ones

Anand M. Kulkarni, Kolluru Srinivas, Mukund V. Deshpande and Chepuri V. Ramana

A sequence of 3 reactions in one-pot; SNAr, nitrene C–H insertion and Ullmann coupling; three C–N bond formations