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Synthetic Methods |*Hot Paper*|

Indole Synthesis through Sequential Electrophilic N–H and C–H Bond Activation Using Iodine(III) Reactivity

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Dedicated to Professor Ángel R. de Lera on the occasion of his 60th birthday

Abstract: An intramolecular approach towards the regioselective construction of 2,3-diarylated indoles is reported. The reaction follows an intramolecular electrophilic N–H and C–H bond functionalization between the aniline and acetylene. This methodology employs the concept of a traceless tether to provide access to the free 2,3-diarylated indole products comprising a total of 18 examples. Hypervalent iodine reagents were identified as suitable promoters and four different protocols are provided, including stoichiometric and catalytic transformations.

Over a century after Emil Fischer's landmark achievement of the first synthesis of the indole core,[1] new techniques for their preparation remains an active field of research. The widespread occurrence of indoles in molecules of pharmaceutical and biological interest[2] has triggered paramount synthetic efforts towards their construction.[3]

We recently reported a metal-free oxidative approach using a modified Koser reagent for the intramolecular cyclization of 2-vinyl anilines.[4] This approach allowed unprecedented access to the 2,3-unsubstituted indole core; all different kinds of substituents at the arene were tolerated. Generally, the complimentary synthesis of indole derivatives with predictable 2,3-substitution pattern meets with certain restrictions. For the case of 2,3-diarylated derivatives, the use of transition-metal catalysis has enabled some elegant solutions to this problem (Figure 1, top).[5,6] To establish an alternative approach, we decided to explore this synthetic challenge from the perspective of an intramolecular reaction using a removable tether (Figure 1, bottom). In order to provide suitable conditions for the application in pharmaceutical and biological sciences, we anticipated an iodine(III) compound to be the reagent of choice, since residual contamination by toxic metals is not an issue with this type of reagents.[7,8] An iodine(III)-based oxidant should be able to promote the required sequential N–H and C–H bond activation at the aniline component for oxidative fusion of the two respective centers with the acetylene to construct the indole core.[9] This overall process can be conceptually understood as a formal oxidative [3+2] cycloaddition.[10] Traceless removal of the tether group would then generate the 2,3-diarylated indole with complete selectivity regarding the individual aryl group positioning.

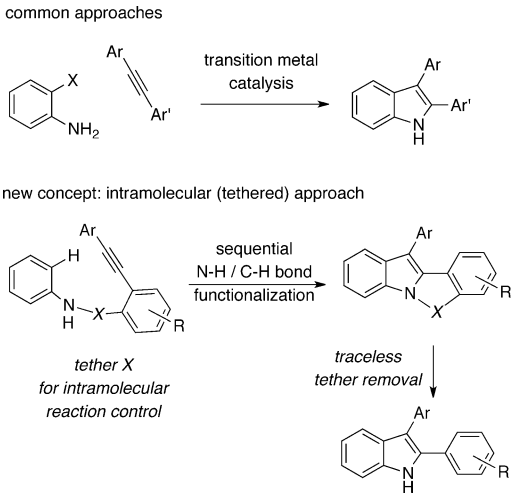
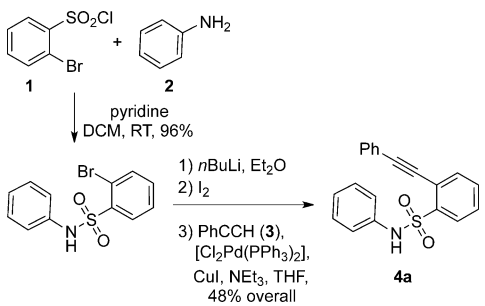


Figure 1. Conceptual approach for tethered 2,3-diaryl indole synthesis.

The viability of this approach was pursued using a sulfonyl group as the tether.[11] A modular synthesis of starting materials could be carried out from commercially available 2-bromobenzene sulfonylchloride **1**. Scheme 1 exemplifies the synthesis of the unsubstituted cyclization precursor **4a**. It starts with the



Scheme 1. Synthesis of cyclization precursor **4a**.

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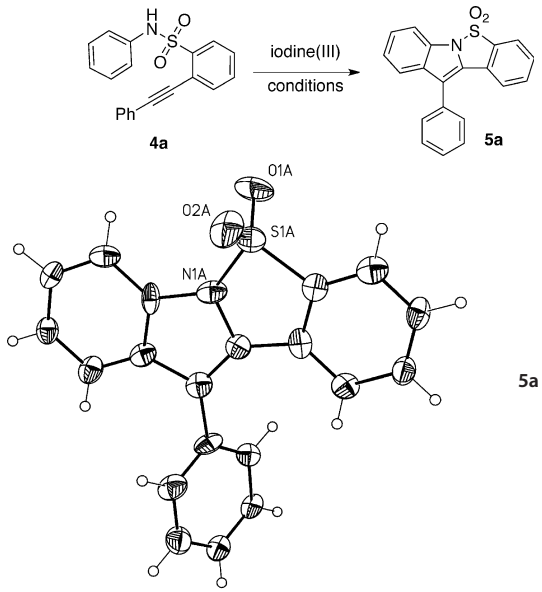
condensation of **1** with aniline **2** followed by a bromine/iodine exchange and Sonogashira coupling with phenyl acetylene **3**. In this way, compound **4a** was obtained in a straightforward manner. Functionalized derivatives of **4a** are also accessible through incorporation of the corresponding substituted derivatives of **1**, **2** and/or **3**.[12]

With the required precursor **4a** in hand, the intramolecular indole synthesis was investigated for standard hypervalent iodine(III) reagents as promoters (Table 1). Initially, [bis(trifluoroacetoxy)iodo]benzene (PIFA) was tested. Validating our assumption, this reagent readily converted **4a** into **5a** in 57% isolated yield (entry 1). The structure of **5a** was unambiguously assured by X-ray analysis at this stage.[13] Lowering the temperature to 0 °C led to a significant increase in yield, whereas a further decrease in temperature had no beneficial effect (entries 2 and 3). The related reaction with diacetoxy iodobenzene (PIDA) led to almost no conversion (entry 4); however, upon changing the solvent to hexafluoroisopropanol (HFIP),[14] complete conversion within 45 min was observed (85% isolated yield; entry 5).

Table 1. Optimization for preformed iodine(III) reagents.

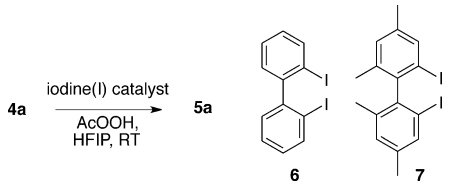


Entry	Reagent	Solvent	*T* [°C]	*t*	Yield [%][a]
1	PIFA	CH_2Cl_2	25	10 min	57
2	PIFA	CH_2Cl_2	0	6 h	78
3	PIFA	CH_2Cl_2	−15	10 h	64
4	PIDA	CH_2Cl_2	25	12 h	<10[b]
5	PIDA	HFIP	25	45 min	85

[a] Isolated yield after purification. [b] Based on crude reaction mixture (^{1}H NMR spectroscopy).

With established conditions for the formation of indole **5a** under stoichiometric conditions available, the possibility of a reaction using catalytic amounts of the aryliodine was explored (Table 2).[15] Initially, the PIDA/HFIP system was employed. Peracetic acid was chosen as benign terminal oxidant together with the iodobenzene as potential catalyst. Some reactivity was accomplished, but isolated yields of **5a** remained low (entries 1 and 2). Changing the catalyst to 2,2′-diiodobiphenyl **6** resulted in improved yields (64% at 20 mol% loading; entry 3). Lowering the catalyst loadings led to diminished yields (entries 4 and 5) together with the formation of unidentified degradation products. To reduce the latter, the oxidant was employed as limiting agent, which increased the yield to 65% (at 5 mol% catalyst; entry 6). Surprisingly, at increased catalyst loading of 10 mol%, product formation again became less selective (entry 7). The same context was initially observed for Kita's catalyst **7**[16] (entries 8 and 9). However, in this case an increase in oxidant resulted also in improved yields (entries 10 and 11). Finally, the introduction of dichloroethane as solvent component and two consecutive additions of the oxidant at 0 °C resulted in a protocol that provided **5a** in 78% isolated yield (entries 12 and 13).

Table 2. Optimization for reactions under iodine(III) catalysis.

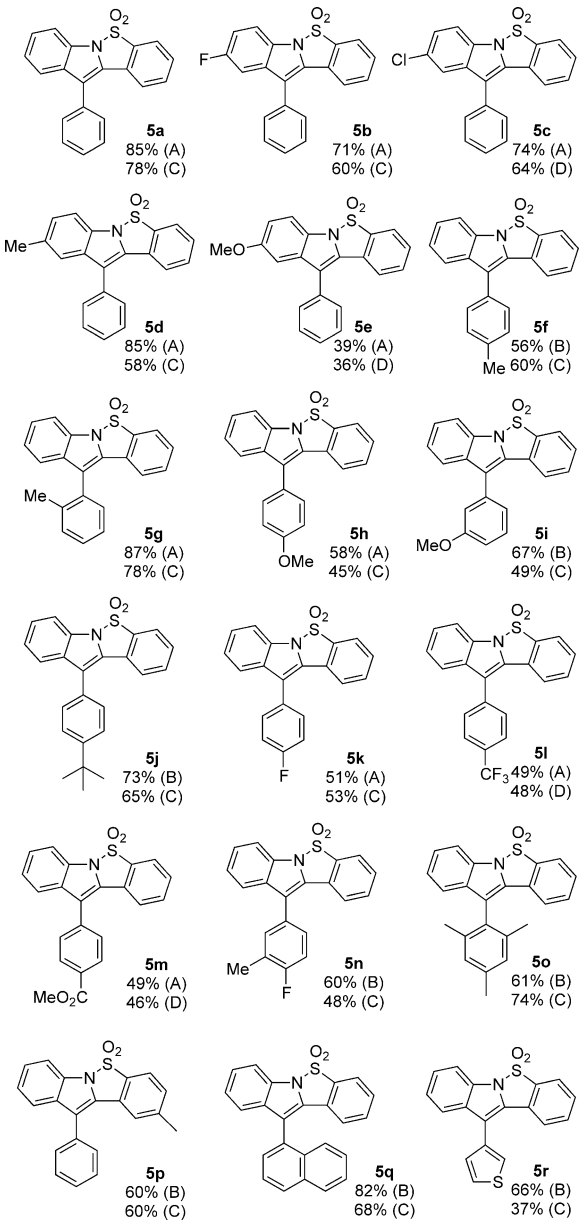


Entry	Catalyst ([mol%])	Oxidant [equiv]	Yield [%][a]
1	PhI (20)	1.1	33
2[b]	PhI (20)	1.1	38
3	**6** (20)	2.2	64
4	**6** (10)	2.2	47
5	**6** (5)	2.2	35
6	**6** (5)	0.95	65
7	**6** (10)	0.95	55
8	**7** (5)	0.95	44
9	**7** (10)	0.95	35
10	**7** (10)	1.1	57
11	**7** (20)	1.5	61
12[c]	**7** (20)	1.5	69
13[c]	**7** (20)	1.8	78

[a] Isolated yield after purification. [b] With one equivalent of acetic acid. [c] In HFIP/$(CH_2Cl)_2$, 1/1 (v/v), and with sequential addition of the oxidant in two portions (second one after 15 min reaction time) at 0 °C.

Examples demonstrating the general scope of the present reaction are presented in Scheme 2. For each compound, conditions are given for one stoichiometric and one catalytic transformation, demonstrating that the cyclization reactions to compounds **5** can be conducted both with equimolar amounts of a preformed iodine(III) reagent (protocols A,B) or under conditions of a homogeneous aryliodine(I/III) catalysis (protocols C,D).[12] A total of 18 successful examples with different substitution pattern at all three arene rings exemplifies the capacity of the present transformation to act as a general route towards indole synthesis.

A reasonable mechanistic context is depicted in Figure 2. The reaction is initiated by interaction between the hypervalent iodine reagent and substrate **4**, most probably through



Scheme 2. Substrate scope. Procedures: (A) sulfonamide **4** (0.1 mmol), PIDA (0.15 mmol) in HFIP (1 mL) at RT; (B) sulfonamide **4** (0.085 mmol), PIFA (0.094 mmol) in DCM (1 mL) at 0 °C; (C) sulfonamide **4** (0.1 mmol), **7** (20 mol %), AcOOH (0.18 mmol) in HFIP/DCE (1/1, v/v, 1 mL) from 0 °C to RT; (D) sulfonamide **4** (0.1 mmol), **6** (5 mol %), AcOOH (0.095 mmol) in HFIP (1 mL) at RT.

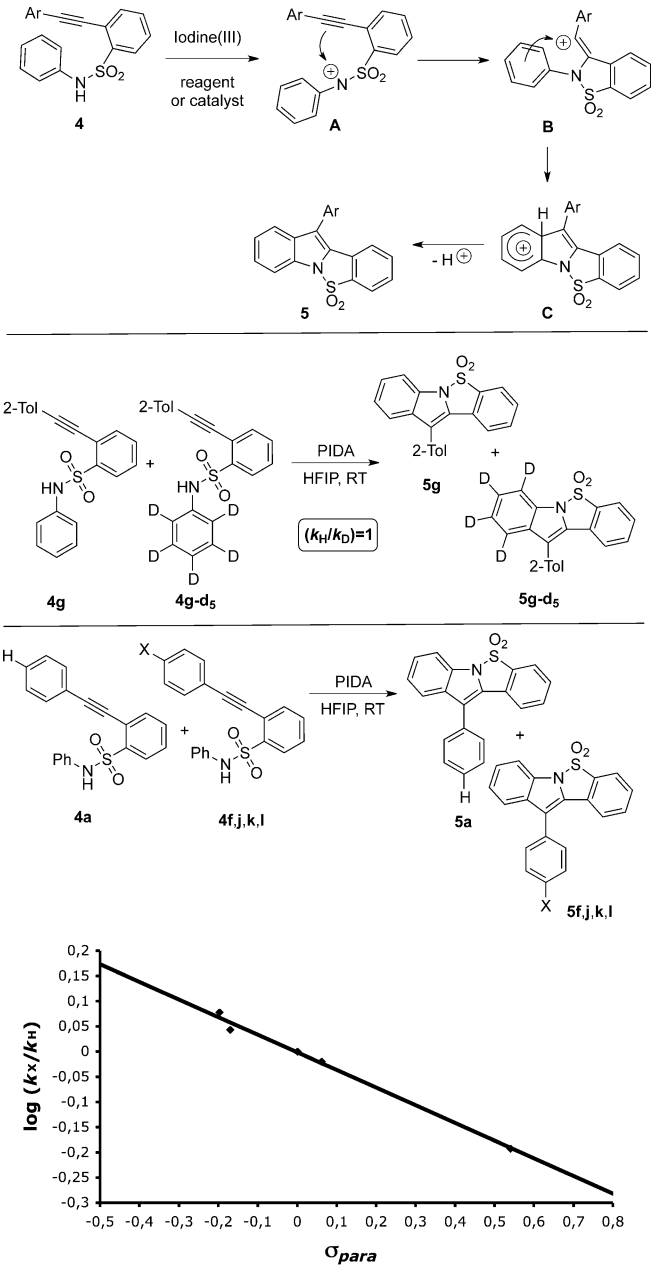
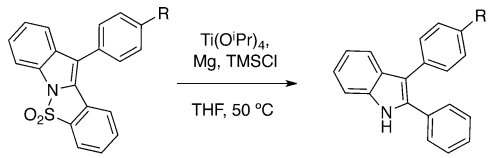


Figure 2. Mechanistic context and control experiments.

the formation of I–N bond.[17] The heterolytic cleavage of this bond results in the generation of an electrophilic nitrogen (stage **A**),[18,19] which upon attack by the acetylene moiety triggers a 5-*exo*-dig cyclization to **B**. This intermediary vinylic cation **B** undergoes further cyclization by nucleophilic attack of the aromatic ring of the aniline[20] followed by rearomatization of the resulting cationic intermediate **C**. Rearomatization to the final product **5** is accomplished upon loss of a proton. This step is comparably fast as demonstrated by a kinetic competition experiment between **4g** and **4g-d$_5$**, which gave no observable kinetic isotope effect ($k_H/k_D = 1.0$). A Hammett correlation using electronic information at the remote aryl group of the toluene core resulted in a ρ-value of −0.35, which indicated that the slow step of the overall reaction belongs to one of the electrophilic cyclization events at stages **A** or **B**.

In the final step, the sulfonyl tether is tracelessly removed upon treatment of the cyclization products **4** with titanium tetraisopropoxide, magnesium, and TMSCl (Scheme 3).[21] Under these conditions, the desired free 2,3-diarylated indoles **8** can be generated in good yields as demonstrated for the four derivatives **8a**,**f**,**k**,**l**.

In summary, we have developed an environmentally benign variant for the iodine(III)-mediated or -catalyzed construction of indoles through a new sequential N–H/C–H oxidation reaction. The reaction is of high scope and is based on the initial



5a (R = H)
5f (R = Me)
5k (R = F)
5l (R = CF_3)

8a (92%)
8f (75%)
8k (66%)
8l (84%)

Scheme 3. Deprotection of **5** to generate free 2,3-diaryl indoles.

presence of a sulfonyl tether, which can be readily removed in a traceless manner to provide regioselective access to 2,3-diarylated indoles.

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Keywords: hypervalent compounds · indoles · iodine · oxidation · tether

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[12] See the Supporting Information for details.

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