Iodoindole Synthesis

IPy_2BF_4-Promoted Intramolecular Addition of Masked and Unmasked Anilines to Alkynes: Direct Assembly of 3-Iodoindole Cores**

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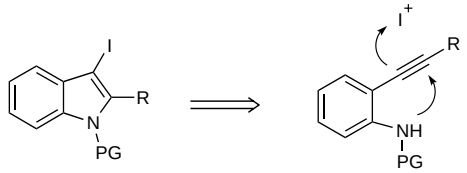
Recently, organometallic transformations have been pursued with renewed interest to approach the elusive addition reaction of the N–H bond across alkynes.[1] As a cleaner alternative to the use of metal-containing reagents and catalysts we have developed useful reactions for C–C bond formation and cleavage, based on the iodinating reagent bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4).[2] Herein, we present a powerful intramolecular addition of aniline and of several of its N-derivatives to alkynes, which relies on a simple iodination process. This new reaction entails a novel approach, and results in a general and valuable entry to the biological and synthetically relevant indole core.[3,4]

We have previously established a robust iodination of anilines that leads to the synthesis of substituted indoles via CuI-mediated cyclization of the corresponding *o*-((trimethylsilyl)ethynyl)aniline derivatives.[5] Certainly, new processes that selectively place additional functionality at the time of assembling the indole core are highly desirable.[6] Now, we illustrate a direct and clean entry to valuable 2-substituted-3-iodoindoles from readily available precursors. Thus, N-protected *o*-(alkynyl)anilines **1** furnish N-protected 3-iodoindoles **2** upon reaction with IPy_2BF_4,[2] the iodinating agent of choice to promote this process[7] (Scheme 1).

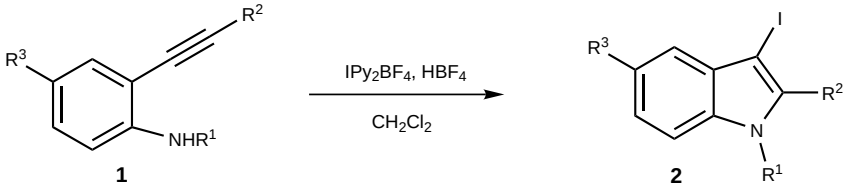


2 **1**

Scheme 1. 3-Iodoindole as a target from the iodocyclization of 2-alkynylaniline derivatives. PG = protecting group.

This C–N bond-formation reaction, which requires only a simple activation of the iodinating agent (namely, the addition of HBF_4 (1 equiv) to the reaction media), results in a versatile entry into 3-iodo-functionalised indoles (Table 1).[8] *N*-Boc derivatives gave satisfactory results when R^2 was an aryl or heteroaryl substituent (entries 1, 2, and 5).[9] However, when R^2 was an alkyl or 1-alkenyl group (entries 6, 7, and 10), the desired cyclization was very poor. Alternatively, for these functionalities, the related methanesulfonate derivative furnished indoles in moderate-to-good yield (entries 8, 9, and 11).

Table 1: Synthesis of indoles **2** from *o*-alkynyl aniline derivatives **1**, promoted by IPy_2BF_4.[a,b]



1 **2**

Entry	**1**	R^1	R^2	R^3	*t* [h][c]	*T* [°C]	**2**	Yield [%][d]
1	**1a**	CO_2tBu	Ph	H	15	−60	**2a**	68
2	**1b**	CO_2tBu	Ph	Me	8	−60	**2b**	76
3	**1c**	CO_2Me	Ph	H	24	−60	**2c**	53[e]
4	**1d**	*p*-$MeC_6H_4SO_2$	Ph	H	36	−60	**2d**	87
5	**1e**	CO_2tBu	3-thienyl	H	12	−20	**2e**	71
6	**1f**	CO_2tBu	1-cyclohexenyl	H	24	−60	**2f**	17[f]
7	**1g**	CO_2tBu	1-cyclopentenyl	H	15	−20	**2g**	10[f]
8	**1h**	$MeSO_2$	1-cyclopentenyl	H	15	−60	**2h**	61
9	**1i**	$MeSO_2$	Bn	H	15	−20	**2i**	54
10	**1j**	CO_2tBu	Bu	H	15	−20	**2g**	10[e]
11	**1k**	$MeSO_2$	Bu	H	24	−60	**2k**	84
12	**1l**	$MeSO_2$	Ph	H	48	−40	**2l**	74

[a] Indoles **2** were characterized by NMR spectroscopy, mass spectrometry, and gave analytical and/or HRMS data in agreement with the given structure. [b] IPy_2BF_4 (1.1 equiv), HBF_4 (1 equiv). [c] Determined as a function of the disappearance of **1**. [d] Based on the isolated indole **2**. [e] A cyclic urethane derivative was formed and isolated from the crude reaction mixture. [f] An allene structure was formed as major reaction product.

The feasibility of accomplishing a clean and efficient biscyclization process was satisfactorily tested with model compounds **3a** and **3b**. Upon iodination, **3a** provided a facile route to an interesting 1,4-phenyl-linked bisindole **4a**, as depicted in Scheme 2.

The butadiyne **3b**, readily accessible from the parent terminal alkyne, offers an attractive route to iodinated 2,2′-bisindolyl scaffolds **4b**, which have great potential in the preparation of naturally occurring bioactive compounds of

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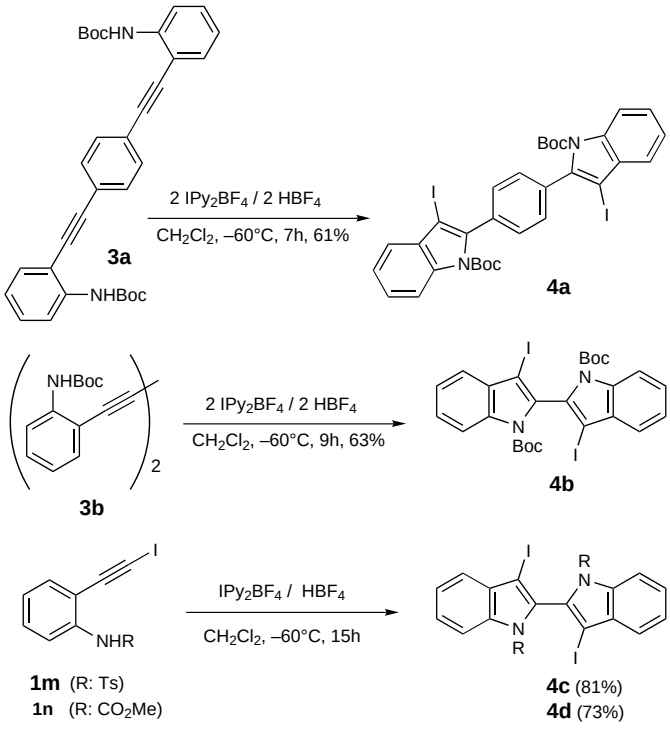
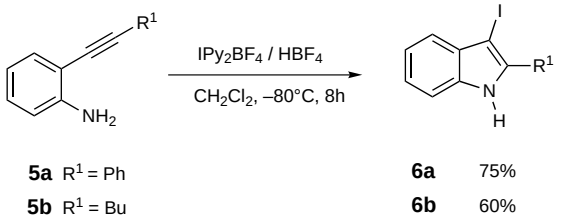


Scheme 2. Biscyclization reactions. Boc = 1-butyloxycarbonyl; Ts = tosyl.

the indolocarbazole family, such as rebeccamycin.[10] With regard to these important building blocks, we have found that simple 2-iodoalkynylanilines **1m** and **1n** smoothly afford bisindole cores **4c** and **4d**. This remarkable result opens a short and valuable synthetic entry to complex indole frameworks.

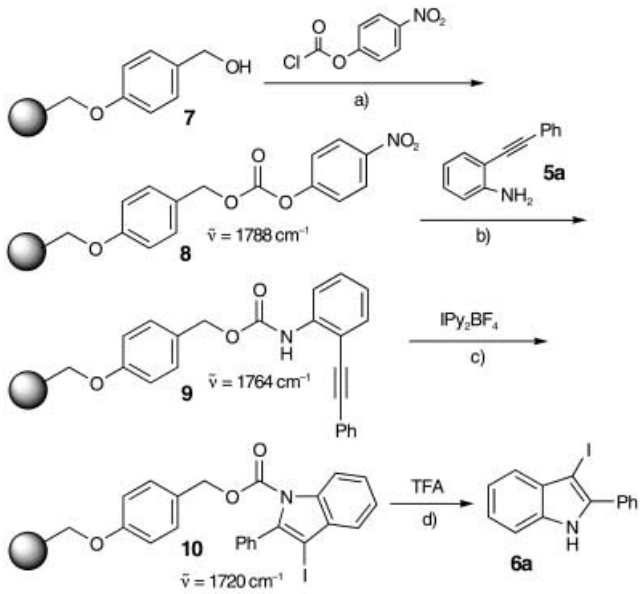
Protection of the N–H bond allows for efficient synthesis and handling of the target indoles. However, as depicted in Scheme 3, some unprotected anilines **5** were also efficient partners in this type of cyclization, which leads to the



Scheme 3. Cyclization of anilines; IPy_2BF_4 (1.1 equiv), HBF_4 (1 equiv).

corresponding free indoles.[11,12] To the best of our knowledge, these reactions represent the first examples of the addition of protected and unprotected anilines to internal alkynes, facilitated by a simple iodination reaction.

The solution chemistry reported above might be an interesting alternative pathway towards the first direct use of the key 3-iodoindole skeleton on a solid support. Thus, the binding of a carbamate group to the resin provides a convenient alternative for accomplishing the desired solid-



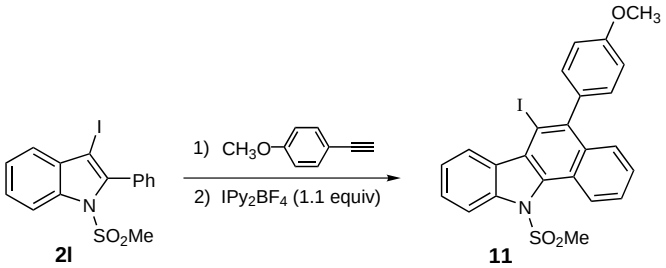
Scheme 4. a) Py, CH_2Cl_2, RT, 12 h; b) *N*,*N*-diisopropylethylamine (DIEA), HOBt·H_2O, DMF, CH_2Cl_2, 15 h; c) IPy_2BF_4 (2.2 equiv), HBF_4 (2.2 equiv), CH_2Cl_2, −20 °C, 24 h; d) trifluoroacetic acid (TFA)/CH_2Cl_2 (20 %), 1 h, RT. (31 % overall yield for four reaction steps).

phase indole synthesis (Scheme 4).[13] The approach of binding the resin to the moiety responsible for the N–C cyclization step has rarely been reported for the preparation of indoles.[14] A *p*-nitrophenyl-carbonate-modified Wang resin was used to prepare the desired carbamates from *o*-alkynylaniline.[15]

This system offers the first example of the solid-phase synthesis of an indole, promoted by a iodination process. As the versatile iodine functionality can be transformed on the resin using organometallic chemistry, this direct assembly of 3-iodoindole offers additional synthetic potential.[16]

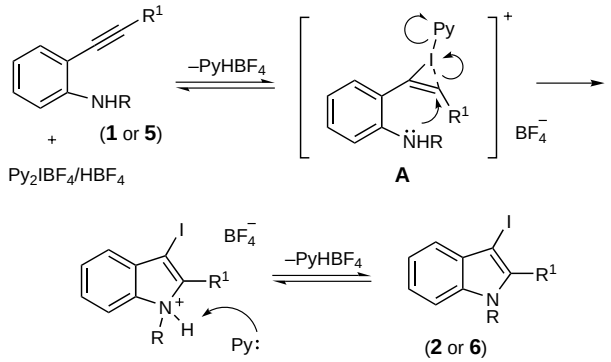
Interestingly, this strategy of indole skeleton preparation yields iodinated compounds upon the cyclization step. Thus, it provides a unique entry to further build-related heterocyclic cores using the same reaction sequence. For instance, by following this approach, compound **2l** can be rapidly transformed into carbazole derivative **11** in two steps (Scheme 5).[17]

A tentative mechanistic interpretation to explain the formation of the observed indoles might reasonably assume a reaction path that implies an initial interaction of electro-



Scheme 5. Conversion of indole to carbazole skeleton. 1) $[PdCl_2(PPh_3)_2]$ (10 mol %), CuI (20 mol %), Et_2NH, RT, 15 h, 47 %; 2) HBF_4 (1 equiv), CH_2Cl_2, −80 °C, 15 h, 17 %.

philic iodine with the alkynyl residue, to give the intermediate **A** (Scheme 6). Subsequent nucleophilic attack of nitrogen would lead to ring-closure. Only one equivalent of acid was used to activate the reagent in these reactions, therefore the second pyridine molecule might help to remove a proton from



Scheme 6. Proposed reaction mechanism.

the nitrogen atom, and result in the observed indole species.

In summary, both solution- and solid-phase strategies have been developed that result in an addition reaction of nitrogen to alkynes, which opens clean and synthetically competitive alternatives to the already established use of metal complexes. The reaction has been applied to the challenging field of the construction of the biologically relevant indole frame, where it proves to be the method of choice. Further studies on the scope of this method, and to gain insight into the unconventional formal cyclization–dimerization of 2-iodoalkynylanilines are in progress.

Experimental Section

All reactions were carried out under a positive pressure of nitrogen. Synthesis of **2a**: IPy_2BF_4 (0.41 g, 1.1 mmol, 1.1 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and stirred for 5 min at room temperature. The solution was cooled to −60 °C, and HBF_4 (137 μL, 54 % solution in Et_2O, 1.0 mmol, 1.0 equiv) was added. After 10 min, **1a** (293 mg, 1 mmol, 1 equiv) was added, and the solution was stirred (15 h) until the complete disappearance of **1a** was revealed by thin-layer chromatography (TLC). The reaction mixture was poured into 100 g of crushed ice and vigorously stirred, and then allowed to warm to room temperature. The organic layer was washed with a 5 % aqueous solution of $Na_2S_2O_3$ (50 mL), dried over sodium sulfate, and then concentrated. The product was purified by column chromatography (silica gel, hexane/EtOAc 20:1) to give 285 mg of compound **2a**, as a white solid (mp 67–69 °C); $R_f = 0.71$ (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 2$ Hz, 1 H), 7.51–7.33 (m, 8 H), 1.23 ppm (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.2$ (s), 130.3 (s), 136.5 (s), 134.9 (s), 130.1 (s), 129.9 (d), 128.1 (d), 127.8 (d), 125.5 (d), 123.5 (d), 121.7 (d), 115.2 (d), 83.7 (s), 72.3 (s), 27.3 ppm (q); IR: ν_{max} (KBr): $\tilde{\nu}$1723 cm^{-1}; MS (70 eV, EI): m/z (%) = 419 (M^+, 59), 363 (100), 320 (49), 237 (47). Elemental analysis (%) calcd for $C_{19}H_{18}INO_2$: C 54.43, H 4.33, N 3.34; found: C 54.42, H 4.30, N 3.35.

Experimental procedures, spectral and analytical data for indoles **2**, **4**, **6**,and carbazole **11**, and solid-phase transformations are given in the Supporting Information.

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Keywords: alkynes · cyclization · electrophilic addition · halogenation · nitrogen heterocycles

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[11] In this case, the reaction is more substrate dependent. Further studies are in progress to investigate alternative reaction paths.

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