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A Unified Approach to Mono- and 2,3-Disubstituted *N*–H Indoles

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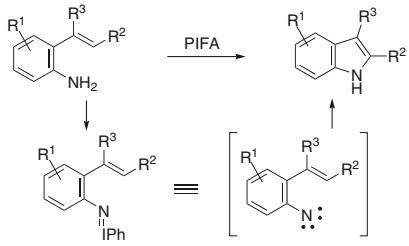

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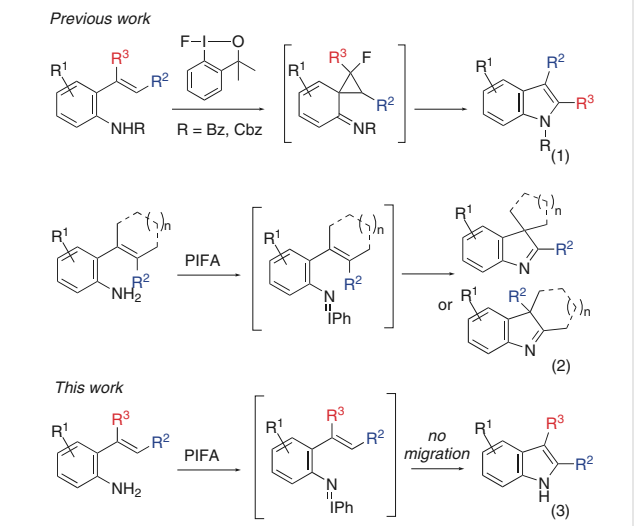
Abstract A unified approach to mono- and disubstituted *N*–H indoles is described by means of oxidative cyclization of 2-alkenyl anilines, which are prepared by cross-coupling of the corresponding *o*-bromoanilines. This procedure is operationally expedient and tolerant of common functional groups to allow regiospecific installation of the alkyl and aryl substituents.

Key words indoles, 2-alkenylanilines, hypervalent iodines, iminoiodinanes, phenylnitrenes

The indole ring motif is embedded in a large number of alkaloids and represents one of the most ubiquitous and important heterocycles in nature. The indole alkaloids possess a wide range of structural complexity and diversity, as well as interesting biological activity. The continuing importance of indoles to organic synthesis and medicinal chemistry has spurred the development of general synthetic methods, ever since the venerable Fischer indole synthesis. The preparation and functionalization of indoles has been an active area of research, resulting in a myriad of methods, as can be seen in many review articles.[1] Despite many powerful known methods, a new approach tolerant of common functional groups and broadly applicable to different substitution patterns under mild conditions is highly desirable. Recent indole syntheses make use of *o*-haloanilines, as exemplified by the Castro and Larock methods for the preparation of 2- and 2,3-disubstituted indoles, respectively.[1] Impressive advances in cross-coupling reactions provide easy access to *o*-alkynyl and *o*-alkenyl aniline derivatives that serve as versatile precursors to indoles.[2] Hypervalent iodine reagents were frequently employed for their oxidative functionalization reactions, including the indole synthesis.[3,4] A recent notable study of oxidation of 2-alkenylaniline derivatives with hypervalent *F*-iodanes afforded the regiodivergent synthesis of indoles:[4a] unlike *o*-alkenylanilines having *N*–H and *N*-Me (not shown), those bearing *N*–Bz and *N*–Cbz proceeded with the migration of substituents (i.e., the switch between R^2 and R^3, Scheme 1, eq. 1).[4a,4c–f] Also reported was an efficient preparation of 3*H*-indoles, when $R^2 \neq H$ (Scheme 1, eq. 2).[4b] These known examples were indicative of mechanistic intricacies, depending on activation of an alkene or nitrogen moiety by a hypervalent iodine. Surprisingly missing was a comprehensive examination of an operationally simple approach by $PhI(OCOCF_3)_2$ (PIFA) oxidative cyclization of 2-alkenyl anilines, leading to free *N*–H indoles without requiring *N*-protecting groups (Scheme 1, eq. 3). As part of projected total syntheses of structurally complex indole alkaloids,[5] we report herein a successful implementation of this strategy which is amenable to the preparation of indoles with all substitution patterns.



Scheme 1 Indole and 3*H*-indole syntheses

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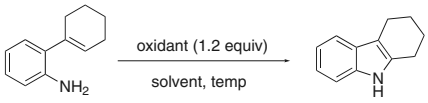
We were primarily interested in the preparation of more challenging 2,3-disubstituted indoles, a common structural motif in structurally complex indole alkaloids. Treatment of aniline **1a**[2b,6] with $PhI(OCOCF_3)_2$ (PIFA) afforded the indole product **2a** (Table 1). Screening of solvent and reaction temperature revealed that a satisfactory (73%) yield was obtained at room temperature in THF (entry 8). Slightly lower yields of **2a** were obtained with $PhI(OAc)_2$ (PIDA) in THF (entry 9).

Table 1 Oxidative Cyclization of Aniline **1a** with PIFA



1a **2a**

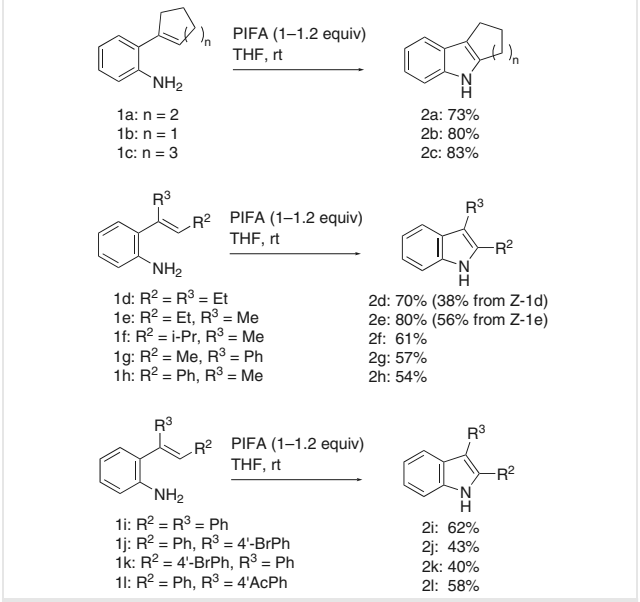
Entry	Solvent[a]	Conditions[b]	Yield (%)
1	dioxane	PIFA, rt	45
2	DMF	PIFA, rt	43
3	CH_2Cl_2	PIFA, rt	NR
4	CH_3CN	PIFA, rt	8
5	THF	PIFA, rt	60
6	THF	PIFA, –78 °C	20
7	THF	PIFA, 60 °C	53
8	THF	PIFA (1 equiv), rt[c]	73
9	THF	PIDA, rt	61

[a] 0.15 M concentration.
[b] 30 min to 1 h.
[c] 10 min.

The substrate scope was broad, and alkyl- and/or aryl-2,3-disubstituted indoles were obtained in 40–83% yields (Scheme 2).[2b,6,7] Most importantly, the indole formation proceeded with no scrambling of R^2 and R^3, which was unequivocally established by careful comparison of the spectral data for **2e–h** and **2j–l** with the literature data; the latter indoles possess the differently substituted phenyl moieties and their regiospecific syntheses are made possible by no scrambling. Distinctively different spectra of **2g** vs **2h**; and **2j** vs **2k** confirmed no scrambling of R^2 and R^3. The formation of free *N*–H indoles is a noteworthy advantage of this method, whereas many known methods required protecting groups at the indole nitrogen.[1] As expected, this protocol is tolerant of common functional groups such as bromo and keto substituents in the side chains.

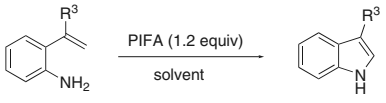
Indoles **2g** and **2i** were prepared from a mixture of *E*- and *Z*-alkenyl anilines (8:1 and 1:2.8, respectively) for convenience, indicating the indole formation from both *E*- and *Z*-alkenes. In the case of **2d** and **2e**, an *E*- and *Z*-mixture of the starting substrates was separated by column chromatography. Each geometrical isomer was subjected to indole formation: both isomers afforded the identical indoles, where higher yields (70% and 80% for **2d** and **2e**) were obtained from the *E*-alkenes than the *Z*-isomers (38% and 56%, respectively). This method thus offers a regioselective alternative to the Larock indole synthesis.[1]

We next examined the synthesis of 3-substituted indoles by the identical strategy to substantiate the full substrate scope (Table 2). Treatment of commercially available **3a** with PIFA afforded the desired indole **4a** in 78% yield (entry 5), where prolonged reaction times resulted in lower yields, presumably due to further oxidation of the latter.[8] When PIDA was employed in place of PIFA, the reaction was



Scheme 2 Additional indole syntheses

Table 2 Oxidative Cyclization of Aniline **3a**



3a: R^3 = Me **4a**: R^3 = Me

Entry	Solvent[a]	Conditions	Yield (%)
1	dioxane	rt, 5 h	60
2	dioxane	rt, 30 min	70
3	dioxane	rt, 10 min	74
4	dioxane	40 °C, 3 h	52
5	THF	rt, 10 min[b]	78
6	CH_3CN	rt, 5 h	55
7	TFE	rt, 1 h[c]	–

[a] 0.15 M concentration.
[b] 1.0 equiv of PIFA was used.
[c] 0.2 equiv of TFA was added.

incomplete to make separation of **4a** from unreacted **3a** onerous. Similarly, 3-phenylindole (**4b**) (R^3 = Ph, structure not shown) was obtained in 60% yield.[9] Overall, the cyclization reactions proceed rapidly, which in turn necessitates careful monitoring of reaction progress to achieve clean indole formation in synthetically useful yields. The latter can be attributed to subsequent over-oxidation of the desired indole products on prolonged exposure.[10] Interestingly, reaction solvents also affected yields (Tables 1 and 2).

Since 2-monosubstituted indoles (via 2-alkynylanilines starting from 2-haloanilines) are readily available by the Castro annulation and related variants,[1,11] no studies of the respective application to the formation of 2-substituted indoles were undertaken.

There are the two limiting reaction mechanisms that are predicated on activation of a nitrogen or alkene functionality by PIFA. The activation site is likely influenced by the nature of the *N*-substituent and the alkenyl group. Amides or carbamates would likely favor preferential activation of the 2-alkenyl moiety by hypervalent iodine reagents such as PIFA or PhIO, opening up the possibility of a formal switch of the R^2 and R^3 substituents via a cyclopropyl phenonium ion intermediate.[3c,4a,f] 1,2-Aryl migration was first reported in PIFA oxidation of α-substituted styrenes to the corresponding ketones.[3c] Partial migration (deuterium scrambling) was also observed for oxidation of 2-alkenyl aniline *N*-tosylates and carbamates with different hypervalent iodines.[4a,4f] In contrast, PIFA oxidation of 2-aryl aniline derivatives likely proceeds with *N*-oxidation, since oxidation of the 2-aryl group seems improbable.[12]

In the case of electron-rich NH_2 or NHR groups (i.e., with no electron-withdrawing *N*-protecting group), the preferential site of attack by PIFA is ambiguous in view of the juxtaposition of the two functional groups. Formation of iminoiodinane intermediates could be the predominant pathway.[13] The latter then undergo stepwise cyclization leading to the indoles with no migration of R^2 and R^3 substituents. An alternative manifold involves an intriguing possibility of 6π-electrocyclization of the corresponding nitrene intermediates. Additional studies are necessary to elucidate the mechanism.[14]

Mechanistic intricacies notwithstanding, this operationally simple method provides a unified approach to mono- and disubstituted *N*–H indoles, which allows the regiospecific installation of a wide range of the (alkyl and aryl) R^2 and R^3 substituents. Application in total synthesis of indole alkaloid natural products, as well as further refinement and optimization, is in progress.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1752656.

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(8) We thank Assia Chebieb and Dr. Mahesh Sandakonda for carrying out studies in Table 2.

(9) One example of the indole synthesis by the same procedure (with PIFA) was reported to afford **4b** in 78% yield. Interestingly, the corresponding cyclization of **1g** was reported to provide

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(14) Neither TFA nor 4 Å MS, which was employed for related reactions (ref. 4b and 4a, respectively), was necessary for this indole formation.