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Oxidative (3 + 2) Cycloaddition Reactions of Diaza-Oxyallyl Cationic Intermediates and Indoles for the Synthesis of Imidazoloindolines

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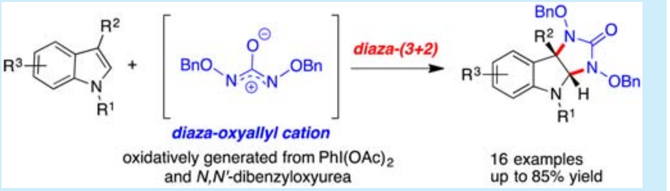
Supporting Information

ABSTRACT: An oxidative diaza-(3 + 2) cycloaddition reaction of simple urea derivatives with substituted indoles has been developed. This transformation provides rapid access to highly functionalized imidazoloindolines that are represented in bioactive compounds. The reported method is compatible with a wide variety of functional groups and directly provides unique heterocyclic scaffolds from indoles and a simple urea derivative.



The indole core is broadly represented in numerous biologically active natural products such as alkaloids and pharmaceuticals.[1−6] 2,3-Diamino indole analogues have demonstrated promising biological activity, bringing significant motivation to develop methods to construct this heterocyclic motif. Imidazo[4,5-*b*]indole derivatives exhibit significant anti-inflammatory, antibacterial, and antifungal activities (Figure 1).[7−9] 6*H*-Indolo[2,3-*b*]quinoxaline analogues comprise an important class of DNA intercalating agents[10−12] and possess a broad spectrum of pharmacological activities that includes antiviral, anticancer, antimutagenic, and antiarthritic activities.

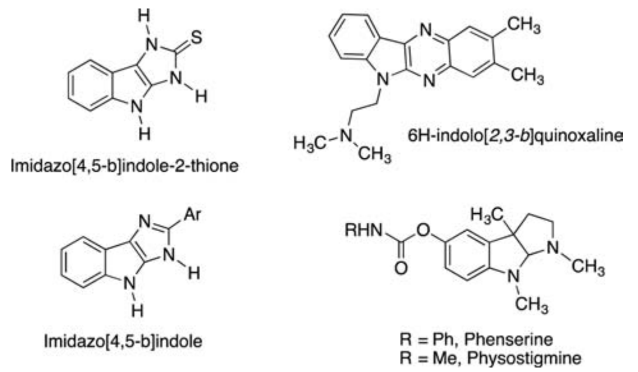


Figure 1. Examples of biologically active [2,3-*b*]- and [4,5-*b*]-indole compounds and natural products.

There are only a few reported methods to construct the diamino indoles, and these approaches often involve multistep processes using organoazide derivatives.[13−17] Despite the pharmacological importance of 2,3-diamino indole derivatives, a straightforward synthesis of 2,3-diamino indoles has yet to be realized. Dearomative (3 + 2) cycloaddition reactions provide direct means to 2,3-difunctionalize indole nuclei.[18,19,25] Recently, Wu and co-workers reported dearomative (3 + 2)-cycloaddition reactions of substituted indoles and oxyallylic cations to provide [2,3-*b*]-cyclopentanone fused indoline scaffolds.[19] Our group has reported a series of papers that describe the generation and the aza-(4 + 3) cycloaddition reaction of a putative aza-oxyallylic cation to provided highly functionalized caprolactam intermediates.[20−22] Later we found that diaza-oxyallylic cations could be generated by either dehydrodehalogenation of *N*-chlorourea derivatives or later by the direct oxidation of *N*,*N*′-dibenzyloxy urea and that these intermediates efficiently reacted with aromatic and nonaromatic cyclic dienes and, in the latter case, acyclic 1,3-dienes.[23,24] Recently, our group along with Wu and co-workers found that aza-oxyallyl cationic intermediates underwent a dearomative (3 + 2) annulation reaction with 1,3-disubstituted indoles **5**.[25] This discovery led us to consider the development of a dearomative (3 + 2)-heteroannulation reaction of a diaza-oxyallylic cation and substituted indoles **5** (Scheme 1). Building on our group's previous development of an oxidative 1,4-diamination of 1,3-dienes, we envisioned that dearomative cycloaddition of the indole **5** with oxidatively generated diaza-oxyallyl cation **3** would be a concise approach to access the 2,3-diaminoindoles **9**.

Our previous investigations identified that the desired diaza-oxyallyl cationic intermediate **3** could be oxidatively generated from urea **1** by using (diacetoxyiodo)benzene in the presence of a base and the diene reactant. Likewise, oxidative (3 + 2) reactions of 1,3-dimethylindole **10** with *N*,*N*-dibenzyloxy urea **1** and PhI(OAc)2 (BAIB) in 2,2,3,3-tetrafluoropropanol (TFP) furnished the desired cycloadduct in 21% yield. Further optimization of this reaction revealed that the addition of the oxidant (BAIB) in CH$_3$CN improved the yield to 58%, likely due to competitive oxidation of the indole by BAIB.[26] Upon extensive screening of reaction conditions, the slow addition of BAIB (1.5 equiv) in CH$_3$CN to the mixture of base (TFP-Na, 1.2 equiv), indole (1.0 equiv), and urea (2.0 equiv) in TFP over 3 h at 0 °C was found to be the optimal reaction conditions,

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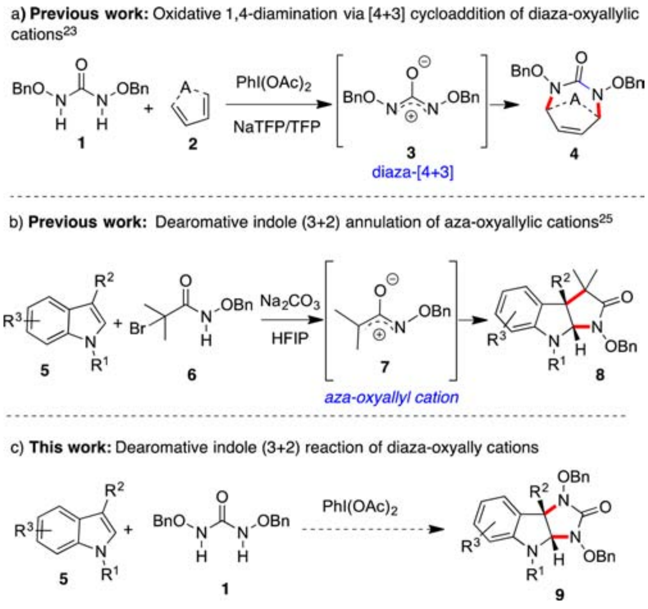
Scheme 1. Cycloaddition Reactions of 1,3-Dienes and Indoles with aza-Oxyallyl Cations



affording 79% of the desired cycloadduct (Table 1, entry 7). A similar yield (71%) was achieved by performing the oxidative (3 + 2) reaction of **10** at a 10-fold higher scale.

With the optimized conditions in hand we further evaluated the substrate scope of the oxidative (3 + 2)-reactions of various substituted indoles. All C-3 alkyl substituted indoles provided high yields of the desired products. Substitution with bulky C-1 and C-3 substituents only slightly diminished the yield of the desired cycloadduct (Figure 2, **9c**, **9d**, **9f**, **9k**, and **9l**). Reactions of C-3 and C-5 substituted indoles provided good yields of the desired product (Figure 2, **9b**, **9i**, **9j**). However, reaction of the *N*-TBS protected skatole provided a moderate yield (Figure 2, **9o**) along with 12% of a TBS deprotected cycloadduct, presumably due to the instability of the *N*-silyl group under the reaction conditions.

Table 1. Optimization of the Oxidative Cycloaddition of 1,3-Dimethyl Indole 10 with *N*,*N*′-Bis(phenylmethoxy)urea 1[a]

entry	$PhI(OAc)_2$ (equiv)	urea (equiv)	NaTFP (equiv)	yield (%)
1	2	1.2	2	46
2	1.2	1.2	1.2	58
3	1	1.2	1.2	65
4	1	1.5	1.2	68
5	1.2	1.5	1.2	75
6	1.3	1.5	1.2	77
7	1.5	2	1.2	79
8	1	1	–	28
9	1	1	1	58
10[b]	1	1	1	46
11	1.5	2	2	79
12	2	2	2	70
13[c]	1	1	1	21
14[d]	1.5	2	2	71

[a] All reactions were conducted by slow addition of BAIB in CH_3CN to a solution of the urea, base (TFP-Na), and indole (1 equiv), in tetrafluoropropanol over 3 h at 0 °C on 100 mg (0.35 mmol) scale. [b] Na_2CO_3 used as the base. [c] Addition of BAIB over 1 min. [d] The reaction was performed using 3.7 mmol of 1,3-dimethylindole.

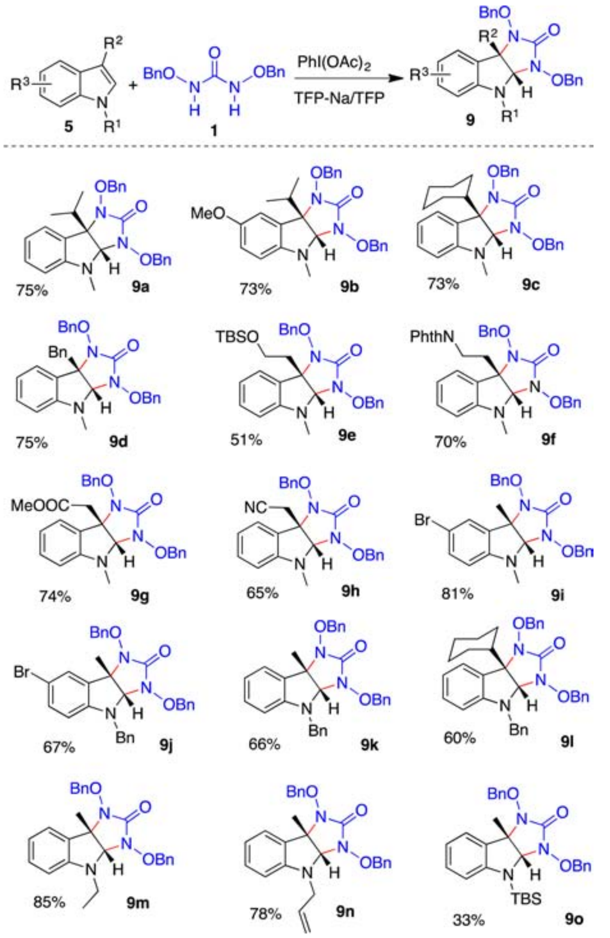
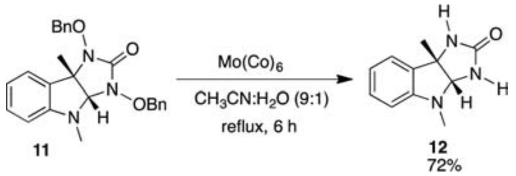


Figure 2. Oxidative cycloaddition reactions of 1,3-disubstituted indoles **5** with *N*,*N*′-bis(phenylmethoxy)urea **1**. All of the reactions were conducted by slow addition of a solution of BAIB (1.5 equiv) over 3 h to a solution of the base (1.2 equiv), indole (1.0 equiv), and urea (2.0 equiv) over 3 h at 0 °C. The yield of the reaction is calculated based upon the isolated mass of the pyrroloindoline **9**.

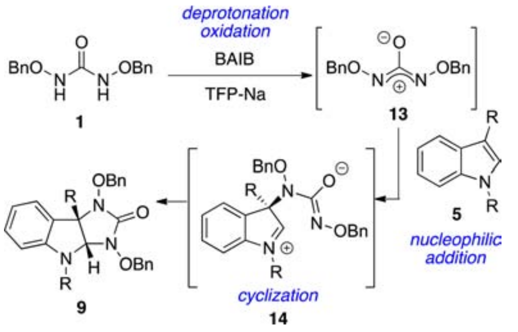
Cycloadducts derived from this annulation method could serve as precursors to conveniently access a variety of imidazoloindoline compounds. One necessary step to this functionalization requires the cleavage of the N−OBn bond from the cyclic urea. We found that both N−O bonds could be efficiently cleaved using $Mo(CO)_6$ to afford imidazolo[4,5-*b*]indole **12** in 72% yield (Scheme 2).

Scheme 2. N−O bond Cleavage Reaction of Cycloadduct 10



Our mechanistic hypothesis for the formal (3 + 2) reaction of the urea and indole is presented in Scheme 3. Deprotonation and oxidation of the urea provide a diazaoxyallylic cation **13**, analogous to what we have proposed for the oxidative diaza-(4 + 3) reaction of dienes.[23] It is established that hydroxamate esters efficiently undergo oxidation to an *N*-acyl nitrenium ion using hypervalent iodide reagents.[27] Nucleophilic addition of the indole **5** at the C-3 position to the diaza-oxyallylic cation **13** provides the zwitterionic intermediate **14**. Intramolecular nucleophilic capture of the iminium ion by the imidate nitrogen atom would provide the imidazoloindole product **9**. This stepwise annulation mechanism has been supported by the computational analysis carried out by Wu and co-workers for the analogous reaction of an aza-oxyallylic cation and 1,3-dimethylindole.[25b] Alternatively, the imidate could undergo O-addition to the iminium, which could rearrange to the final product; however, there is no definitive experimental evidence supporting either pathway.

Scheme 3. Mechanistic Hypothesis for the Formation of 9 from the Reaction of an Oxidatively Generated Diaza-oxyallylic Cation with the 1,3-Disubstituted Indole



In conclusion, we have developed a first dearomative indole (3 + 2) cycloaddition reaction of a putative diaza-oxyallyl cationic intermediate for the synthesis of imidazoloindolines using a simple urea derivative and (diacetoxyiodo)benzene as the oxidant. This reaction is compatible with various functional groups, demonstrates a broad substrate scope, and provides building blocks for the synthesis of 2,3-diamino indoles and related heterocyclic scaffolds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03527.

Experimental procedures, tabulated characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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