

Dearomative Indole (3 + 2) Reactions with Azaoxyallyl Cations – New Method for the Synthesis of Pyrroloindolines

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S Supporting Information

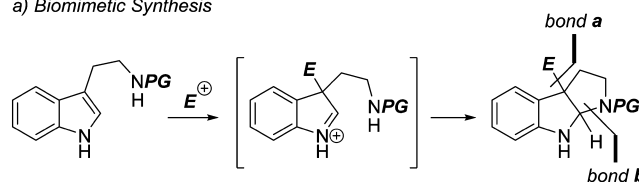
ABSTRACT: Herein, we report the first examples of the synthesis of pyrroloindolines by means of (3 + 2) dearomative annulation reactions between 3-substituted indoles and highly reactive azaoxyallyl cations. Computational studies using density functional theory (DFT) (B3LYP-D3/6-311G**++) support a stepwise reaction pathway in which initial C–C bond formation takes place at C3 of indole, followed by ring closure to give the observed products. Insights gleaned from these calculations indicate that the solvent, either TFE or HFIP, can stabilize the transition state through H-bonding interactions with oxygen of the azaoxyallyl cation and other relevant intermediates, thereby increasing the rates of these reactions.

Pyrroloindolines are important structural motifs found in numerous families of biorelevant alkaloid natural products. As a result, considerable resources have been expended to develop new and improved methods for their syntheses. By far, the most common way to prepare pyrroloindolines is through biomimetic pathways starting with either tryptophan, tryptamine, or derivatives thereof.^{1–20} Such a strategy involves the formation of bonds **a** and **b** (Scheme 1a) by alkylation at C3 with various electrophiles to generate an iminium intermediate, followed by ring closure to give the desired products. The alternative retrosynthetic disconnection at bonds **b** and **c** (Scheme 1b) would require 3-substituted indole **1** and 1,3-dipole **2** as synthons. In the forward direction, this approach constitutes a dearomative indole (3 + 2) annulation reaction and has been a relatively underexplored option for preparing pyrroloindolines as compared to the biomimetic strategy described above. Notable recent examples include Reisman's use of 2-amidoacrylates,^{21–23} Davies' reports of Rh-catalyzed annulation reactions,^{24,25} and annulations with aziridines by Chai.²⁶

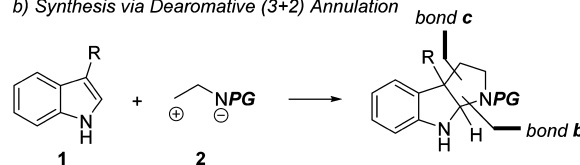
Consistent with our continuing interest in indole annulation²⁷ and alkylation reactions,²⁸ we recently disclosed a new method for carrying out formal (3 + 2) cycloadditions between 3-substituted indoles and oxyallyl cations **5** (Scheme 1c).²⁹ We were, therefore, intrigued by Jeffrey and co-workers' report in which they described the (4 + 3) cycloaddition reaction between azaoxyallyl cations and dienes such as furan and cyclopentadiene,^{30–32} later expanded to include diaminations.^{33,34} We postulated that azaoxyallyl cations **9** may also react with 3-substituted indoles in a fashion analogous to oxyallyl cations (Scheme 1d).²⁹ In this manuscript and in the

Scheme 1. Synthesis of Pyrroloindolines

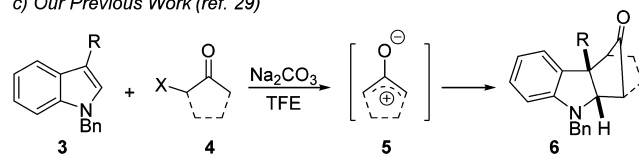
a) Biomimetic Synthesis



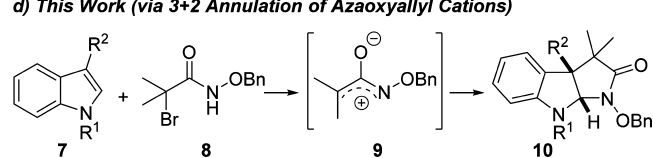
b) Synthesis via Dearomative (3+2) Annulation



c) Our Previous Work (ref. 29)



d) This Work (via 3+2 Annulation of Azaoxyallyl Cations)



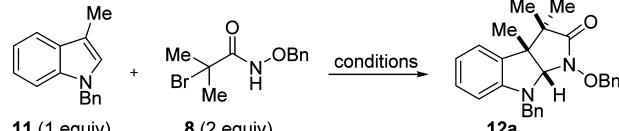
previous paper of this issue,³⁸ the first examples of dearomative (3 + 2) annulation reactions between indoles and azaoxyallyl cations is described as a novel means to prepare pyrroloindolines.

We initiated our studies by examining the reaction between *N*-benzyl-3-methylindole (**11**) and bromohaloamide **8** under conditions we originally developed for the (3 + 2) annulation reaction of oxyallyl cations.²⁹ Gratifyingly, this led to the formation of the desired product **12** in 94% isolated yield (Table 1, entry 1). Under these conditions (first reported by Föhlich and co-workers for generating oxyallyl cations),³⁵ formation of the azaoxyallyl cation likely occurs by hydrogen-bond-mediated tautomerization followed by unimolecular ionization of bromide. Despite this success, we later discovered that the use of TFE (2,2,2-trifluoroethanol) leads to competitive decomposition of haloamide **8** by solvolysis. By

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Table 1. Optimization Reactions

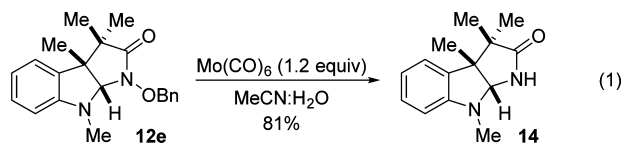


entry	base	solvent	concn (M)	temp (°C)	time (h)	yield ^a (%)
1	Na ₂ CO ₃	TFE	0.25	rt	4	94
2	Na ₂ CO ₃	TFE	0.25	0	6	61
3 ^b	Na ₂ CO ₃	TFE	0.25	rt	6	91
4	Na ₂ CO ₃	THF	0.25	rt	18	no rxn
5	NEt ₃	HFIP	0.25	rt	16	42
6	K ₂ CO ₃	HFIP	0.25	rt	8	40
7	Cs ₂ CO ₃	HFIP	0.25	rt	12	46
8	Na ₂ CO ₃	HFIP	0.25	rt	4	89
9 ^b	Na ₂ CO ₃	HFIP	0.25	rt	18	66
10	Na ₂ CO ₃	HFIP	0.50	rt	6	39

^aIsolated yield. ^b2 equiv of indole, 1 equiv of haloamide.

switching to the more sterically hindered solvent hexafluoroisopropanol (HFIP), we were able to minimize these solvolysis byproducts while maintaining high yields of the desired pyrroloindolines (entry 8).

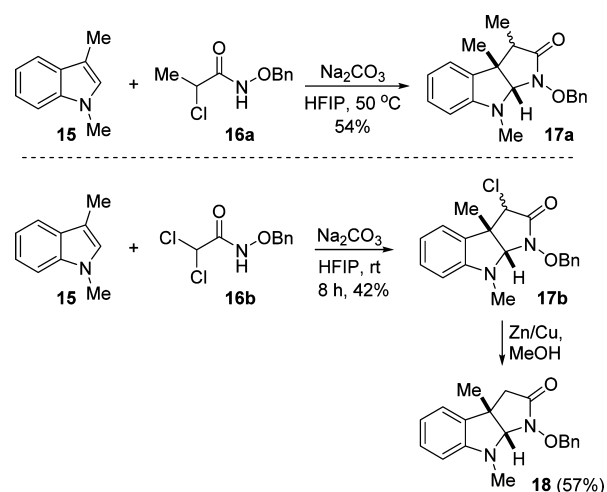
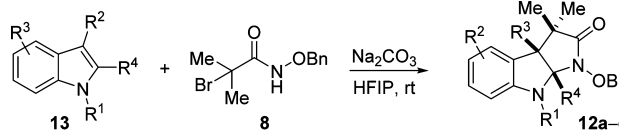
With optimized reaction conditions in hand, we sought to delineate the scope of the reaction. Alkylation on the indole nitrogen could be either methyl or benzyl. The reaction was compatible with a wide range of functional groups at the C3 position of indole. These include esters, free alcohols, esters, nitriles, phthalimide, isopropyl, and methyl. We also demonstrated that substitution at C2 (entry 6), electron-rich groups at C4/6 (entry 17), and electronegative groups at C5 are well tolerated (entry 15). For the electron-rich substrate, we observed significant amounts of byproducts resulting from electrophilic aromatic substitution with the azaoxyallyl cation at C7 (entry 17). We were able to overcome this problem by reversing the stoichiometry of the indole and haloamide starting materials. N–O bond cleavage could be achieved using Mo(CO)₆ to give 14 (eq 1).



When indole 15 was reacted with monomethyl-substituted α -haloamide 16a, the expected product 17a was generated in 54% yield as an inseparable mixture of diastereomers with respect to the stereocenter bearing the methyl group (Scheme 2). It was also possible to prepare unsubstituted pyrroloindolines such as 18. We accomplished this by carrying out the annulation reaction of 15 with dichlorohaloamide 16b to initially give 17b in a 1:1 diastereomeric ratio with respect to the stereocenter bearing the chloride. Protodehalogenation using the Zn/Cu couple provided the desired compound 18.

Several of the yields in Table 2 (entries 1, 7, 11, 12, 13, 15) and for compound 17 are slightly different from the corresponding reactions reported in the paper preceding this one.³⁸ These differences are likely attributable to a combination of higher reaction concentration (i.e., 1 M versus 0.25 M) and, in some instances, longer reaction times (entries 1, 11, 15) and

Scheme 2. Synthesis of Monosubstituted and Unsubstituted Pyrroloindolines

Table 2. Scope of Dearomative Indole (3 + 2) Reaction^a


Entry	R ¹	R ²	R ³	R ⁴	time (h)	Yield (%) ^b	pdt
1	Bn	Me	H	H	4	88	12a
2	Bn	EtO ₂ C	H	H	24	65	12b
3	Bn	HO	H	H	18	63	12c
4	Bn	BnO	H	H	36	62	12d
5	Me	Me	H	H	6	93	12e
6	Me	Me	H	Me	12	42 ^c	12f
7	Me	EtO ₂ C	H	H	48	68	12g
8	Me	BnO	H	H	48	76	12h
9	Me	MeO	H	H	48	66	12i
10	Me	MeO	H	H	48	63	12j
11	Me	PhthN	H	H	12	54	12k
12	Me	NC	H	H	18	75	12l
13	Me	<i>i</i> -Pr	H	H	48	54	12m
14	Bn	allyl	H	H	24	25 ^c	12n
15	Me	Me	5-Br	H	12	72	12o
16	Me	Me	5-Me	H	12	65	12p
17	Me	Me	4,6-OMe	H	18	72	12q

^aIndole (1 equiv), α -haloamide (2 equiv), Na₂CO₃ (4 equiv) in HFIP, 0.25 M. ^bIsolated yield. ^cSignificant decomposition products observed.

higher temperatures (50 °C versus room temperature for compound 17) that were utilized by Jeffrey.

The mechanism of this reaction was examined using Density Functional Theory (DFT) using the dispersion corrected B3LYP-D3 functional and the 6-311G**++ basis set; this

method and basis set have been demonstrated to be competent in predicting the energetics of reactions of oxyallyl cations with indoles.²⁹ The model starting materials used were indole **15** and azaoxyallyl cation **9-Me**. An implicit solvent correction for 2,2,2-trifluoroethanol (TFE) was used. Full details of all calculations are provided in the [Supporting Information](#).

Attempts to locate a transition state for a concerted reaction were unsuccessful, but energy surfaces for various stepwise processes were found. Formation of the expected product **12** could occur in a stepwise fashion by initial construction of the C–C bond at C3 of indole **15** to give intermediate **19a** as shown in [Figure 1](#). Alternatively, formation of a C–N bond at C2 of the indole could occur first to give intermediate **19b**. The energy profiles for these two reactions are illustrated in [Figure 2](#).

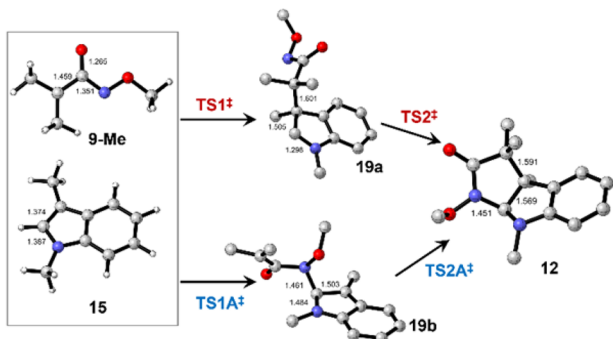


Figure 1. Calculated structures of starting materials, product and intermediates for the stepwise reaction of **15** with **9-Me** to give **12**. Except for **9-Me** and **15**, H atoms are not shown.

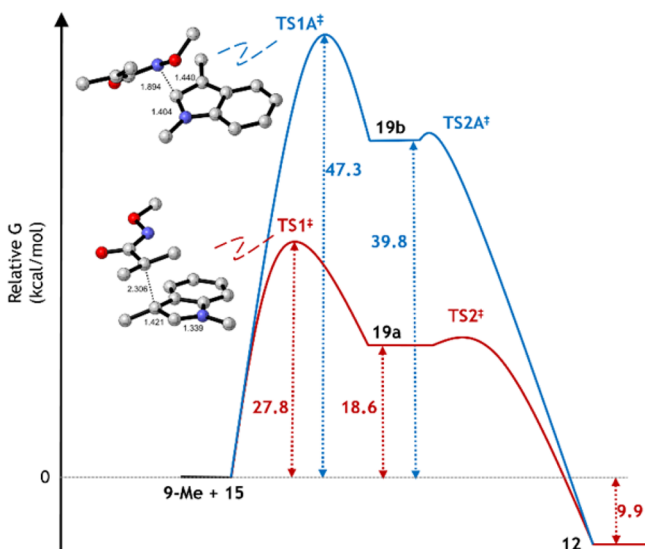


Figure 2. Free energy profiles for the stepwise formation of product **12** via intermediates **19a** (red) and **19b** (blue) with calculated structures of the transition states for the rate limiting steps. H atoms are not shown.

The lowest energy stepwise pathway is via intermediate **19a**, which is over 21 kcal/mol more stable than its regioisomer **19b**. Moreover, transition state TS1^\ddagger which leads to **19a** is almost 20 kcal/mol lower in energy than TS1A^\ddagger leading to **19b**. Formation of product **12** is downhill by almost 10 kcal/mol with respect to the starting materials. There are other conformers of intermediate **19a** with essentially equal energies,

none of which shows any interaction of N with C2 of the indole; likewise conformers essentially isoenergetic with TS1^\ddagger were also located. We were unable to find TS2^\ddagger , suggesting that it is a very low energy process that evolves smoothly during rotation of the newly formed C–C bond of intermediate **19a**.

Our calculations also reveal that the observed regiochemistry of addition to give **12** is kinetic in origin. The calculated intermediate **20a** en route to the formation of **21** (the regioisomer of **12**) is shown in [Figure 3](#). Product **21** is 1.8 kcal/mol

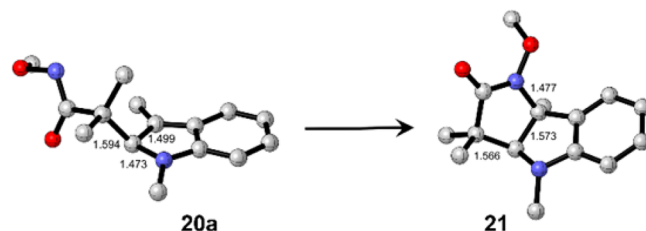


Figure 3. Calculated structures of starting materials, product, and intermediates for stepwise reaction of **15** with **9-Me** to give **21** (the regioisomer of **12**). H atoms are not shown.

mol more stable than **12**, and intermediate **20a** is also 1.8 kcal/mol more stable than the corresponding intermediate **19a**. However, the transition state leading to **20a** lies 2.9 kcal/mol higher in energy than TS1^\ddagger (leads to **19a**). From these data, we conclude that the preference for the formation of product **12** over **21** is governed by kinetic control.

The strong hydrogen-bonding solvents TFE and HFIP also play a significant role in this reaction. As an extreme limiting case, the effect of a very strong H-bonding solvent was modeled by calculating the energetics of the reaction between a fully O-protonated azaoxyallyl cation **22** and indole **15** with an implicit TFE solvent model. Key calculated structures are shown in [Figure 4](#). O-Protonation dramatically lowers the activation

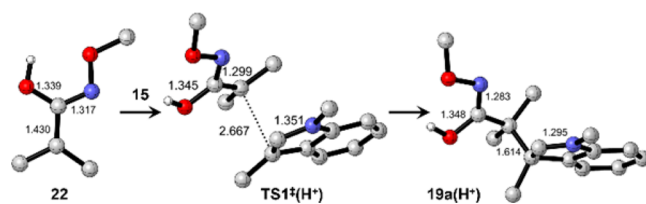


Figure 4. Calculated structures of protonated oxyallyl cation **22**, the protonated intermediate **19a(H⁺)**, and the protonated transition state $\text{TS1}^\ddagger(\text{H}^+)$ for its reaction with indole **15**. H atoms are not shown except for the OH.

barrier of the first step $\text{TS1}^\ddagger(\text{H}^+)$ (located 16.4 kcal/mol above reactants) and also strongly stabilizes the intermediate of the corresponding protonated intermediate **19a(H⁺)** which lies only 1.9 kcal/mol higher than the reactants. The energy of regioisomeric intermediate **20a(H⁺)** becomes 3.4 kcal/mol higher than that of **19a(H⁺)** with the transition state for formation of **20a(H⁺)** lying 4.3 kcal/mol above $\text{TS1}^\ddagger(\text{H}^+)$, thereby increasingly favoring the observed regioselectivity.

These calculations suggest that, when strong hydrogen bond-donor solvents are used, the actual energy of the transition state should be intermediate between that of TS1^\ddagger and $\text{TS1}^\ddagger(\text{H}^+)$. This should accelerate the rates of these reactions and also increase their regioselectivity. We and others have seen similar effects of protonation on the reaction energetics calculated for

the corresponding reactions between oxyallyl cations and **15**.^{29,36} Moreover, MacMillan and co-workers have empirically observed a similar phenomenon.³⁷ Collectively, these results offer the intriguing possibility that annulation reactions of azaoxyallyl or oxyallyl cations can be catalyzed with strong H-bond donor catalysts in aprotic solvents.

In summary, we have disclosed the first report of preparing pyrroloindolines by means of dearomative (3 + 2) annulation reactions between indoles and azaoxyallyl cations. DFT calculations indicate a stepwise reaction mechanism and that the hydrogen bond donor ability of the solvent plays an important role in the stabilization of transition states and intermediates.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.5b10221](https://doi.org/10.1021/jacs.5b10221).

Experimental details and characterization of all new compounds; selected NOESY, HMBC, HMQC, COSY data; details of DFT calculations; final geometry coordinates for all calculated structures; and larger scale graphics of Figures 1–4 (PDF)

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Notes

The authors declare no competing financial interest.

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