Dearomative Indole Cycloaddition Reactions of Aza-Oxyallyl Cationic Intermediates: Modular Access to Pyrroloindolines
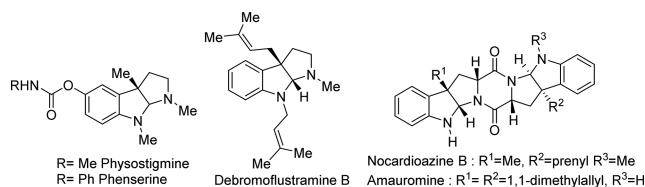
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S *Supporting Information*

ABSTRACT: A regioselective dearomative aza-(3 + 2) cycloaddition reaction of substituted indoles with α-halohydroxamates has been developed. This transformation provides rapid access to highly functionalized pyrroloindolines that are represented in large number of bioactive compounds. The natural product, physostigmine, has been concisely synthesized utilizing this method.

Heterocycle fused indolines are ubiquitous in natural products and exhibit a broad range of biological activities. Alkaloids with a hexahydropyrrolo[2,3-b]indole structural unit have demonstrated anticancer, antibacterial, and cholinesterase inhibition activities.[1−3] This promising biological activity has inspired the synthetic community to develop methods to access this heterocyclic unit (Figure 1).

R= Me Physostigmine
R= Ph Phenserine

Debromoflustramine B

Nocardioazine B : R[1]=Me, R[2]=prenyl R[3]=Me
Amauromine : R[1]= R[2]=1,1-dimethylallyl, R[3]=H

Figure 1. Examples of natural products containing pyrroloindole core.[4−8]

Our group has developed aza-(4 + 3) heterocycloaddition reactions of putative aza- and diaza-oxyallyl cation intermediates with dienes for the preparation of seven-membered nitrogen-containing heterocycles.[9−13] Exploration of the substrate scope of this reaction demonstrated that the attempted aza-(4 + 3)-cycloaddition of the α-halohydroxamate with 2-methylfuran provided the pyrrolidinone **3** as the major product instead of bicyclic caprolactam (Scheme 1). Presumably this 5-5 fused heterocyclic product was a formal (3 + 2)-annulation with the aza-oxyallylic cation intermediate. While observations of (3 + 2)-type reactivity have been described for all carbon oxyallylic

Scheme 1. Observation of a (3 + 2) Cycloaddition-Type Reaction of α-Halohydroxamate and 2-Methylfuran
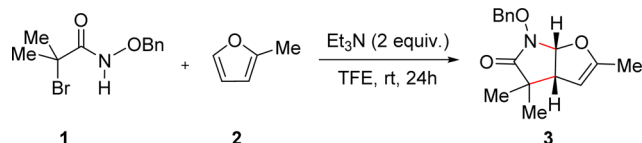
cations and alkene reactant,[14,15] such reactions of aza-oxyallylic cations have not been reported. Recently, Wu et al. have described a diastereoselective dearomative (3 + 2)-cycloaddition reaction of substituted indoles with α-haloketone to afford highly functionalized fused indoline compounds.[16,17] Given our previous observations of this mode of reactivity and the precedent of Wu et al., we pursued the development of a modular method to access pyrrolo[2,3-b] indoles scaffolds from the formal (3 + 2)-cycloaddition reaction of aza-oxyallylic cation intermediates with substituted indoles. This manuscript and a paper by Wu et al. (10.1021/jacs.5b10221) published later reports the first examples of a formal (3 + 2)-cycloaddition reaction between aza-oxyallylic cations and substituted indoles.

Our studies were initiated with reaction of 1,3-dimethylindole **4** with the α-halohydroxamate **1** under Föhlisch conditions [Et₃N, CF₃CH₂OH (TFE)].[18] Treatment of 1,3-dimethylindole with **1** under these conditions resulted in a 62% yield of the desired pyrroloindole along with the solvolysis of the α-halohydroxamate by TFE.[9] Further optimization of the reaction conditions, varying the base, solvent, and concentration, uncovered bulkier hexafluoroisopropanol (HFIP) as the best solvent for production of the desired product (Table 1). Hünig's base and proton sponge were found to afford the desired product in comparable yields, with Na₂CO₃ as the optimal base for the reaction.

The substrate scope using α-halohydroxamate **1** and various substituted indoles **9** was explored. Bulky alkyl substituents on C-3 position were found to slow the overall rate of reaction and lower the yield (Table 2, entries 1−3) of the cycloadduct due to competitive substitution at the indole C-7 position. Reactions of protected alcohol and amine groups at C-3 provided good yield of the desired products (Table 2, entries 5−6). Substitution of the indole with electron-withdrawing groups at the C-3 position (−COOMe and −CN) diminished the reactivity and resulted in no observed cycloadduct. However, these groups were tolerated by the reaction when not directly conjugated to the indole (Table 2, entries 7, 8). N-alkyl, -benzyl, -allyl, and -TBS protected indoles were found to produce the desired product. However, unprotected and N-Cbz protected indoles failed to provide desired cycloadducts. Additionally, reaction of indoles unsubstituted at the C-3 position exclusively provided the C-2 substituted product **7** (Scheme 2) along with a trace amount of cycloadduct only observed by crude NMR analysis.

The diminshed reactivity was observed during the reaction of α-halohydroxamate **1** with indole having bulky substitution at C-

Table 1. Optimization of the Reaction Conditions for the Reaction of α-Bromohydroxamate 1 and 1,3-dimethylindole 4[a]

| entry	solvent	base	conc. (M)	time (h)	% yield[b]
1	TFE	Et₃N	1.0	12	62
2	TFE	Na₂CO₃	1.0	20	63
3	HFIP	Et₃N	1.0	12	68
4	HFIP	DIPEA	1.0	12	72
5	HFIP	Na₂CO₃	0.5	20	80
6	HFIP	Na₂CO₃	1.0	20	84
7	HFIP	proton sponge	1.0	12	75
8	TFP	NaTFP	1.0	12	55
9	TFP	Na₂CO₃	1.0	30	58
10	ACN	Na₂CO₃	1.0	36	38

[a]All reactions were carried out with 1,3-dimethylindole (1 equiv), 2-bromo-2-methyl-*N*-(phenylmethoxy)propanamide (1 equiv), and base (2 equiv) dissolved in solvent (1 M) at room temperature. [b]Isolated yield.

**Table 2. Cycloaddition Reactions of 1,3-Disubstituted Indoles with 2-Bromo-2-methyl-*N*-(phenylmethoxy) Propanamide**[a]

entry	R¹	R²	R³	time	% yield[b]	pdt
1	Me	*i*-Pr	H	3 h	50	10a
2	Me	*i*-Pr	OMe	12 h	63	10b
3	Me	cyclohexyl	H	16 h	57	10c
4	Me	Bn	H	3 h	76	10d
5	Me	CH₂CH₂OTBS	H	60 h	73	10e
6	Me	CH₂CH₂NPhth	H	6 d	87	10f
7	Me	CH₂COOMe	H	16 h	83	10g
8	Me	CH₂CN	H	16 h	81	10h
9	Me	Me	Br	20 h	80	10i
10	Bn	Me	Br	20 h	85	10j
11	Bn	Me	H	20 h	76	10k
12	Bn	cyclohexyl	H	16 h	61	10l
13	Et	Me	H	16 h	79	10m
14	allyl	Me	H	16 h	83	10n
15	TBS	Me	H	36 h	92	10o

[a]All reactions were carried out with indole (1 equiv), 2-bromo-2-methyl-*N*-(phenylmethoxy)propanamide (1 or 1.2 equiv, see SI) and Na₂CO₃ (2 equiv) dissolved in solvent (1 M) at room temperature. [b]Isolated yield.

Scheme 2. Observation of a C-2 Substituted Product from Indole Unsubstituted at C-3 Position and α-Halohydroxamate
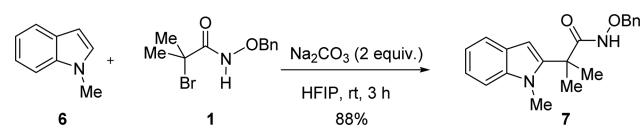
3 (Table 2, entries 1, 3, 12) due to competative electrophilic aromatic substitution (EAS) at C-7 position of indole. In order to

understand the reactivity of the cycloadduct **5** to electrophilic aromatic substitution, we treated indole **4** with excess of halohydroxamate **1** (3 equiv), which exclusively provided EAS product **8**. This was presumably due to the further reaction of cycloadduct with α-halohydroxamate. To evaluate the hypothesis, we further treated the cycloadduct **5** with α-halohydroxamate **1** to the cycloaddition conditions, which exclusively provided electrophilic aromatic substitution on at C-7 position of indole (Scheme 3).

**Scheme 3. Observation of a C-7 Substituted Product from the Reaction of Indoles with 1**
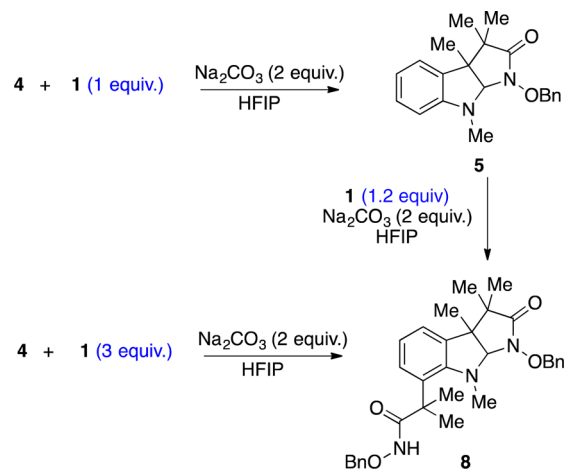
The scope of the reaction using various α-halo-hydroxamate reactants was explored. As established in our investigations of the aza-(4 + 3) reaction, α-alkyl substitution on the α-halohydroxamate was found to be important to generate the aza-oxyallyl cation. This is presumably due to the stabilizing effect that alkyl groups have on the resulting cationic intermediates. Chloro- and monoalkyl substituted halohydroxamates provided the desired products as a 1:1 mixture of diastereoisomers and required elevated temperature in order to provide the fair to good yields of the cycloadducts **12** and **16**. The cyclohexyl substituted α-halohydroxamate was found to react rapidly with 1,3-dimethylindole **4** at room temperature to afford desired product **14** in good yield, and the reaction of 1,3-diprenyl indole with the α,α-dichlorohydroxamate **15** provided desired cycloadduct **18** in poor yield.

With the development of this powerful convergent approach to the synthesis of pyrrolodinone scaffolds, we decided to pursue its application to the synthesis of the bioactive alkaloid physostigmine (Scheme 4). Treatment of a diastereoisomeric mixture of the chloro-cycloadducts **16** with an excess of SmI₂ in THF afforded butyrolactam **19**, reductively cleaving both the C–Cl and N–OBn bonds. Additionally we found that the C–Cl and N–OBn bonds can be cleaved in separate steps using Zn/NH₄Cl reduction via unsubstituted pyrroloindoline **23** followed by refluxing with Mo(CO)₆ (Scheme 5). N-methylation and reduction of the lactam using LiAlH₄ provided (±)-desoxysyroline **21** only in four steps from 1,3-dimethylindole **4** and the α,α-dichlorohydroxamate **15**. This synthesis represents a concise synthesis of (±)-desoxyseroline, which can be efficiently converted to (±)-physostigmine **22** as reported in the literature and could serve as a new strategy for the concise synthesis of related biologically active natural products.[1,19] Additionally, SmI₂ reduction of the cycloadduct **18** (Table 3) provided a lactam,

Scheme 4. Formal Synthesis of Physostigmine from Cycloadduct 16
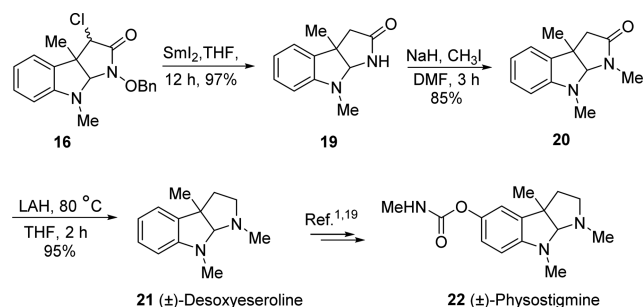
Scheme 5. Synthesis of Unsubstituted Pyrroloindolines from Cycloadduct 16
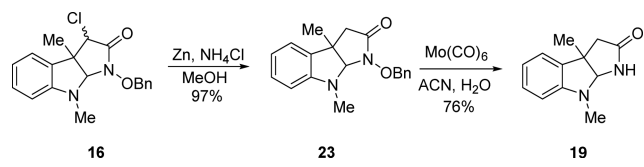
which can be easily transformed into debromofulstramine B (see Supporting Information (SI)) as reported in the literature.[20]

In summary, we have developed first dearomative indole (3 + 2) cycloaddition reactions of putative transient aza-oxyallyl cation intermediates for the synthesis of pyrroloindolines. This methodology is tolerant to various functionl groups with broad substrate scope. The versatility of this method has been

Table 3. Dearomative (3 + 2)-Cycloaddition Reactions of 1,3-Disubstituted Indoles with α-Halohydroxamates[a]

Entry	Indoles	α-Halo amides	Products	Time	% yield[b]
1	4	11	12	48 h[c]	51[d]
2	4	13	14	20 h	88
3	4	15	16	18 h[c]	67[d]
4	17 R = prenyl	15	18 R = prenyl	36 h	18

[a] All reactions were carried out with indole (1 equiv), α-halohydroxamate (1.2 equiv), and Na₂CO₃ (2 equiv) dissolved in solvent (1 M) at room temperature. [b] Isolated yield. [c] At 50 °C. [d] Diasteriomeric mixture.

demonstrated in the concise synthesis of physostigimine and debromoflustramine B.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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