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Cyclopropylazetoindolines as Precursors to C(3)-Quaternary-Substituted Indolines

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In light of their presence in a wide variety of structurally complex and biologically active substrates, including those shown in Figure 1,[1−3] it is not surprising that C(3)-quaternary-substituted pyrroloindolines have received a significant amount of attention from the synthetic and medicinal chemistry communities.[4,5] While a number of very elegant approaches to these structures have been described,[6] new and especially more general routes are still needed. Outlined here are our efforts to help to address this problem through the use of a new class of fused heterocycles, cyclopropylazetoindolines, as useful electrophiles in the synthesis of C(3)-quaternary-substituted pyrroloindolines.

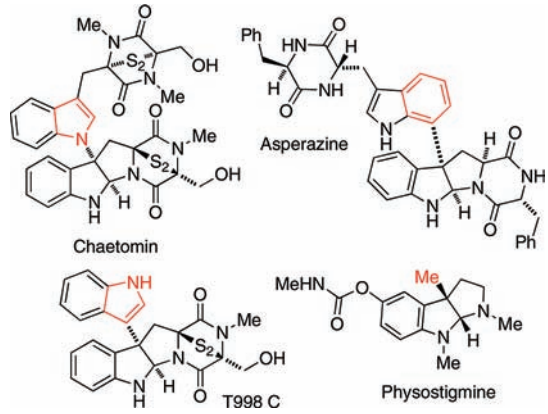
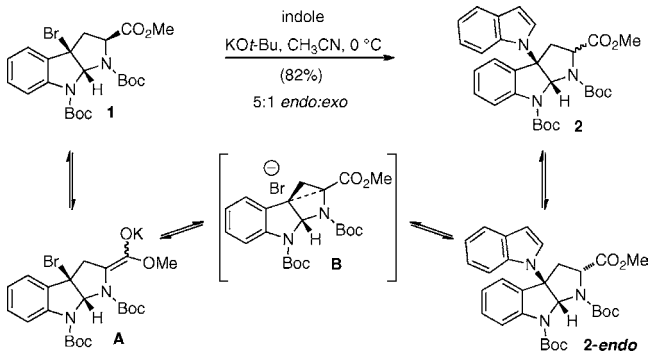


Figure 1. C(3)-quaternary-substituted pyrroloindoline natural products.

Scheme 1. Mechanistic Hypothesis for the Coupling Chemistry of **1**



As part of our synthesis of C(3)−N(1′) indoline dimers, including members of the kapakahine family, we recently reported that bromopyrroloindoline **1**, which is readily available in a single step in high diastereoselectivity from the corresponding tryptophan derivative,[7] undergoes a novel anionic coupling reaction with indoles that leads to the stereoselective generation of C(3)-quaternary-substituted pyrroloindolines such as **2** (Scheme 1).[8] During preliminary mechanistic studies, we found that the success

Scheme 2. Hall's Synthesis of Bicyclo[2.1.0] Analogue **4**

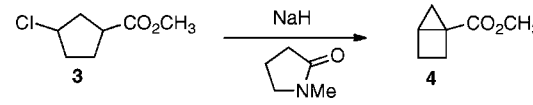
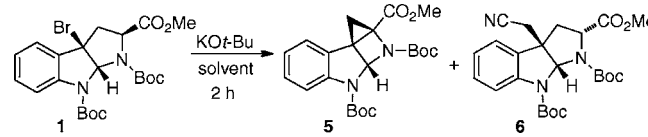


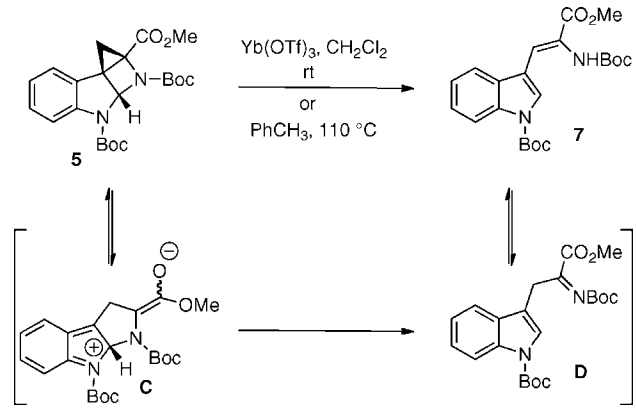
Table 1. Cyclopropylazetoindoline Formation



entry	equiv of KO*t*-Bu	solvent	yield of **5**[a]	**5**:**6**:**1**[b]
1	1.0	CH_3CN	45%	1:0:1
2	1.2	CH_3CN	55%	11:3:5
3	1.5	CH_3CN	20%	1:2:1
4	2.0	CH_3CN	0%	0:1:0[c]
5	***1.2***	***THF***	***89−95%***	***1:0:0***

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] **6** was isolated in 42% yield.

Scheme 3. Decomposition of **5**



of this reaction was contingent upon the generation of enolate **A** and proposed that **A** is involved in assisting the bromide in leaving via cyclopropylazetoindoline transient **B** (Scheme 1).

In spite of the extensive use of pyrroloindolines in synthetic chemistry,[9] to the best of our knowledge, cyclopropylazetoindolines such as **B** are unique. Thus, we became intrigued with the question of whether cyclopropylazetoindolines are isolable, and if they are, whether their subsequent reactivity would match the reactivity of bromopyrroloindoline **1**. We were at least partly driven to answer these questions by an earlier report from Hall describing the synthesis, isolation, and use of bicyclo[2.1.0]pentane **4** in anionic polymerization reactions (Scheme 2).[10,11]

With the isolation of the cyclopropylazetoindoline as our target, we studied the behavior of bromopyrroloindoline **1** when it was subjected to KO*t*-Bu in the absence of nucleophile. Our initial

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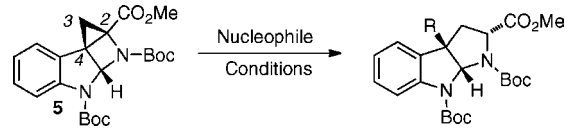
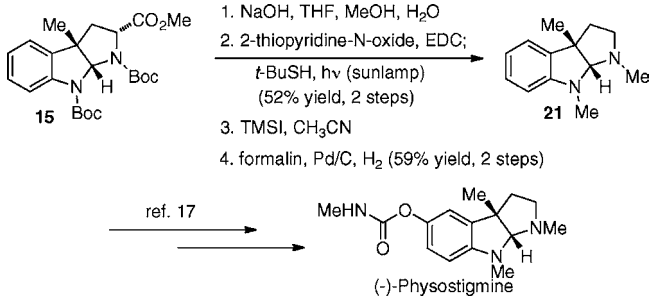
Table 2. Reactions of Cyclopropylazetoindoline **5** with Nucleophiles



entry	nucleophile (equiv)	conditions	R	product	yield
1	indole (1.5)	KO*t*-Bu, CH_3CN, 0 °C, 5 min	*N*-indolyl	**2-*endo***	70%
2	$NaBH_4$ (10)	THF, rt, 2 h	H	**8**	75%
3	NaN_3 (10)	PPTS, DMF, rt, 2 h	N_3	**9**	72%
4	C_6H_5OH (5)	DBU, THF, rt, 6 h	C_6H_5O	**10**	70%
5	*p*-$MeOC_6H_4OH$ (5)	DBU, THF, rt, 10 h	*p*-$MeOC_6H_4O$	**11**	76%
6	*p*-$NO_2C_6H_4OH$ (5)	DBU, THF, rt, 48 h	*p*-$NO_2C_6H_4O$	**12**	70%
7	C_6H_5SH (5)	DBU, THF, rt, 5 h	C_6H_5S	**13**	84%
8	*p*-$NO_2C_6H_4SH$ (5)	DBU, THF, rt, 1 h	*p*-$NO_2C_6H_4S$	**14**	80%
9	$AlMe_3$ (2)	CH_2Cl_2, −40 to 0 °C, 0.5 h	Me	**15**	76%
10	KCN (10)	PPTS, 18-crown-6, THF, rt, 4 h	CN	**16**	70%
11	CH_3NO_2	DBU, THF:CH_3NO_2 (4:1), rt, 2 h	CH_2NO_2	**17**	50%
12	$CNCH_2CN$ (10)	DBU, THF, rt, 2 h	CNCHCN	**18**	60%
13	methyl acetoacetate (5)	DBU, THF, rt, 2 h	$CH_3C(O)CHCO_2CH_3$	**19**	75%
14	*p*-MeC_6H_4MgBr, CuCN (5)	THF, −78 °C, 15 min	*p*-MeC_6H_4	**20**	70%

Scheme 4. Enantioselective Formal Synthesis of (−)-Physostigmine



experiments were run in CH_3CN and utilized 1.2 equiv of KO*t*-Bu, and they resulted in a mixture of products that included acetonitrile adduct **6**, recovered starting material **1**, and, to our delight, cyclopropylazetoindoline **5** in 55% yield (Table 1, entry 2). The structure of **5** was elucidated both spectroscopically (see the Supporting Information) and chemically (see below).

As also indicated in Table 1, attempts to optimize the generation of **5** by modifying the amount of base were generally unsuccessful: the use of equimolar KO*t*-Bu led to the recovery of an increased amount of **1** (entry 1), while the use of larger amounts of KO*t*-Bu resulted in increased amounts of acetonitrile adduct **6** (entries 3 and 4). In an attempt to avoid the formation of **6**, we also examined the reaction in THF and were delighted to find that this modification had a dramatic effect on the reaction in that **5** could be generated in yields of 89−95% on a gram scale (entry 5). In addition to the efficiency of its synthesis, we were surprised by the stability of **5**, as it did not undergo noticeable decomposition when subjected to SiO_2 chromatography and was stable when stored for several weeks at 0 °C.

Having established conditions for the synthesis of **5**, we next carried out a study of its reactivity. We were hopeful that **5** would react with nucleophiles not only as a result of its inherent strain and its being a "donor−acceptor" cyclopropane[12] but also because of its proposed intermediacy in our earlier studies. As an indication of its reactivity, we found that **5** undergoes both a thermal and a Lewis acid-mediated decomposition to indole **7**.[13] This transformation presumably occurs via intermediates **C** and **D**, as illustrated in Scheme 3.

In addition to the decomposition studies outlined above, we were pleased to find that **5** reacts as an electrophile under relatively mild conditions with a wide range of hetero- and carbon nucleophiles. For example, **5** reacts with excess indole (1.5 equiv) in the presence of a substoichiometric quantity of KO*t*-Bu (0.5 equiv) to give heterodimer **2-*endo*** as the exclusive product in 70% yield (Table 2, entry 1). This result represents an improvement over the original heterodimerization reaction in that the original reaction required excess bromopyrroloindoline **1** and gave a mixture of **2-*endo*** and **2-*exo*** isomers. Other nucleophiles that react with **5** include inorganic salts [hydride, azide, and cyanide (Table 2, entries 2, 3, and 10)], phenols and thiophenols (entries 4−8), CH acids [nitromethane, malononitrile, and methyl acetoacetate (entries 11−13)], and carbon nucleophiles [$AlMe_3$ and aryl cuprate (entries 9 and 14)]. It is noteworthy that all of these reactions gave C(3)-substituted indolines with high diastereoselectivity (>95:5 endo:exo) and that bromopyrroloindoline **1** was inert under all of the reaction conditions except those used in entry 1.[14,15]

To demonstrate the applicability of this new methodology, we carried out a formal synthesis of the anticholinergic agent (−)-physostigmine (Scheme 4).[16] To this end, decarboxylation of the methyl adduct **15** resulted in the generation of pyrroloindoline **21** after removal of the Boc groups and bismethylamine formation (Scheme 4). The synthesis of **21** intercepts an intermediate used in the synthesis of (±)-physostigmine by Kulkarni and co-workers.[17]

In summary, this communication has described a unique and facile entry into quaternary-substituted indolines that takes advantage of the inherent reactivity of cyclopropylazetoindoline **5**, which represents a novel class of fused heterocycle. We intend to continue studying the reactivity profile of **5** and its application to the synthesis of biologically active indolines, including natural products.

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Supporting Information Available: General experimental procedure for the cyclization reaction and spectroscopic data for all new cyclic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Density functional theory (DFT)-calculated bond lengths for **5** matched the observed reactivity pattern (see Table 2 for the numbering scheme): C(2)−C(4) = 1.57 Å, C(3)−C(4) = 1.48 Å, and C(2)−C(3) = 1.51 Å. See the Supporting Information for details.

(15) Although we cannot rule out an S_N1 mechanism in which nucleophilic addition to an intermediate like **C** (Scheme 3) results in the observed products, an examination of the C(2)−C(4) bond in the minimized structure leads us to speculate that an S_N2 addition to the cyclopropane leads to product formation. A more detailed mechanistic investigation is a subject for future work. For a discussion of related cyclopropane ring-opening reactions in the CC-1065 and duocarmycin families, see: Boger, D. L.; Turnbull, P. *J. Org. Chem.* **1997**, *62*, 5849–5863.

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