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Lewis Acid Catalyzed Displacement of Trichloroacetimidates in the Synthesis of Functionalized Pyrroloindolines

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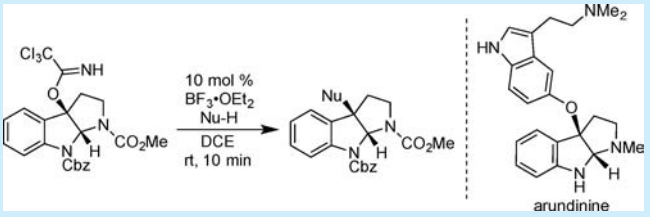
Supporting Information

ABSTRACT: The pyrroloindoline core is found in many natural products. These structures often differ at the C3a position, which may be substituted with an oxygen, nitrogen, or sp^3- or sp^2-hybridized carbon. Utilizing a trichloroacetimidate leaving group, a diversity-oriented approach to these structures has been developed. The trichloroacetimidate intermediate allows for the rapid incorporation of anilines, alcohols, thiols, and carbon nucleophiles. This method was applied in the synthesis of arundinine and a formal synthesis of psychotriasine.



The pyrroloindoline ring system is found in many well-known alkaloids and cyclic peptides.[1] These systems have become popular targets for total synthesis efforts that are driven by the unusual structures and promising bioactivity presented in many of these natural products.[2] In assessing pyrroloindoline natural products, the structures may be classified by the substituent at the C3a position, which may be an sp^3- or an sp^2-hybridized carbon (as in flustramine B (**1**)[3] or asperazine (**2**)[4]), an indole or indoline nitrogen (as in psychotriasine (**3**)[5] or kapakahine C (**4**)[6]) or the oxygen of an ether (like arundinine **5**[7]) (Figure 1).

Given that the C3a position is an important point of diversity in these structures, significant effort has been directed toward flexible intermediates that allow for the rapid variation of functionality at this position. This expedites diversity-oriented approaches to both natural and unnatural pyrroloindolines, allowing for rapid synthesis and facilitating biological evaluation. While selenides[8] and sulfonium salts[9] have been employed, the bromide is most commonly utilized as a leaving group at the C3a position with a number of approaches to pyrroloindoline natural products taking advantage of this leaving group. Displacement of C3a-bromo pyrroloindolines can be achieved with the use of stoichiometric base, but these reactions typically only function well when an ester is present at C2.[10] Otherwise, silver salts are often utilized,[11] but these conditions often require the use of superstoichiometric amounts of these expensive reagents. Single-electron-transfer conditions have also been explored for substitution of the bromide with carbon nucleophiles.[12]

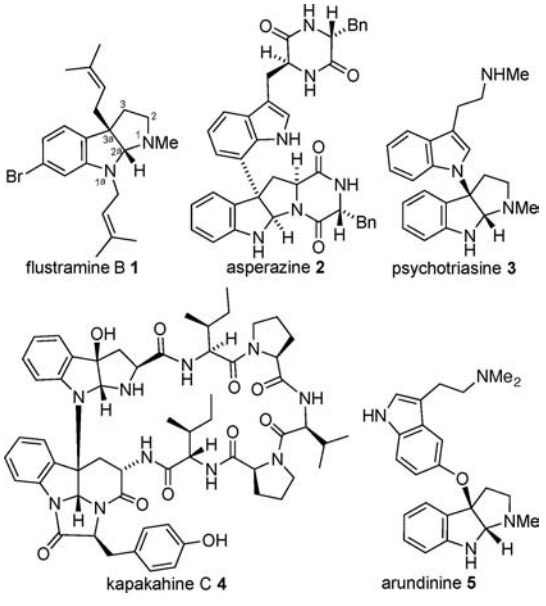


Figure 1. Some representative pyrroloindoline natural products.

Our recent interest in the substitution chemistry of trichloroacetimidates with oxygen, sulfur, and nitrogen nucleophiles[13] led to the hypothesis that a C3a-trichloroacetimidate pyrroloindoline could be utilized to synthesize a diverse library of pyrroloindoline-based structures from a common starting material.[14] Relevant to this hypothesis, Sunazuka has recently shown that a C3a-hydroxyfuroindoline trichloroacetimidate was a competent electrophile under Lewis acid promoted conditions.[15] In order to explore this chemistry, a C3a-hydroxy pyrroloindoline was required. While a number of methods have been reported for the synthesis of C3a-hydroxypyrroloindolines,[8e,f,12a,16] the oxidation reported by Takayama and co-workers[17] that employs *m*-CPBA and TFA seemed to provide the most direct access. When protected tryptamine **6** was exposed to these conditions, a 59% yield of pyrroloindoline **7** was obtained. Protection of the indoline nitrogen and formation of the trichloroacetimidate provided the C3a-trichloroacetimidate pyrroloindoline **9** (Scheme 1).

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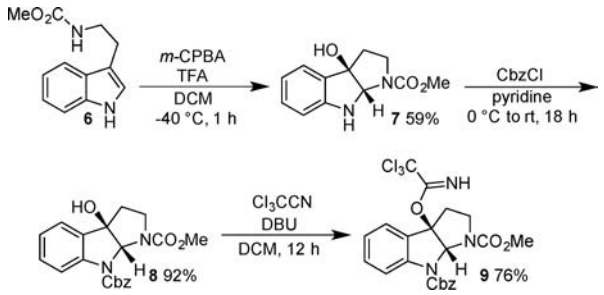
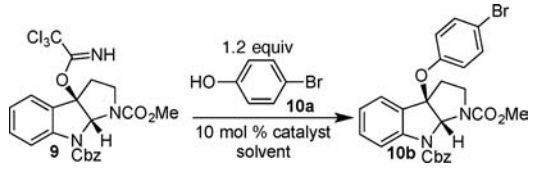
Scheme 1. Synthesis of Imidate Pyrroloindoline 9



With an efficient route to imidate **9** established, nucleophilic substitution at the C3a position of the pyrroloindoline (Table 1)

Table 1. Substitution of Imidate 9 with 4-Bromophenol 10a



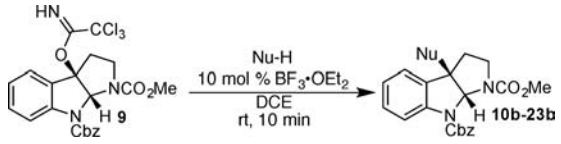
entry	conditions[a]	yield (%)
1	CSA, DCM, rt, 24 h	63
2	CSA, DCE, reflux, 1 h	75
3	TfOH, DCE, rt, 15 min	65
4	$Cu(OTf)_2$, DCE, rt, 15 min	71
5	$BF_3{\cdot}OEt_2$, DCE, rt, 10 min	75
6	$BF_3{\cdot}OEt_2$, THF, rt, 10 min	0
7	$BF_3{\cdot}OEt_2$, DME, rt, 10 min	31
8	$BF_3{\cdot}OEt_2$, CH_3CN, rt, 10 min	29
9	$BF_3{\cdot}OEt_2$, $MeNO_2$, rt, 10 min	47

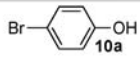
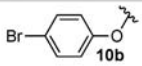
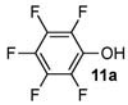
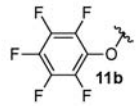
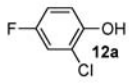
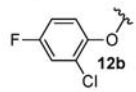
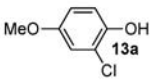
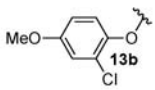
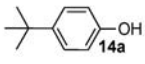
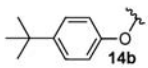
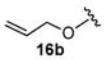
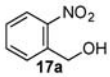
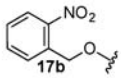
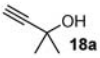
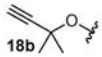
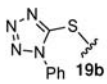
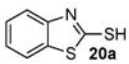
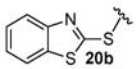
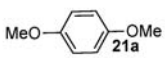
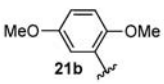
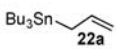
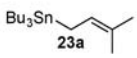
[a]10 mol % acid catalyst was used in all cases.

was explored. 4-Bromophenol (**10a**) was chosen as the nucleophile for optimizing the displacement conditions since it could serve as a model system for the synthesis of arundinine **5**. Brønsted acids were first utilized as catalysts for the displacement reaction. Use of CSA at room temperature provided a sluggish reaction, but heating to reflux in DCE provided 75% yield after 1 h. Using the more powerful TfOH provided an even faster reaction at rt, but numerous side products were seen in the crude ^{1}H NMR. The switch was then made to the Lewis acid $Cu(OTf)_2$, which was found to provide good yields of product. Moving to the more powerful Lewis acid $BF_3{\cdot}OEt_2$ provided an even more rapid reaction giving 75% isolated yield of the desired product, and these conditions were adopted for evaluating other nucleophiles. Other solvents proved to be less effective, providing lower yields of product.

Several other nucleophiles were then evaluated in substitution reactions with imidate **9** (Table 2). Electron-poor phenols were excellent substrates in this system, with more electron-rich phenols giving more side products. At least some of these side products were due to competing Friedel–Crafts alkylation reactions. Aliphatic alcohols like 2-nitrobenzyl alcohol, methanol, and allyl alcohol also proved to be excellent nucleophiles and provided the corresponding ethers with very high yields (Table 2, entries 6–8). Even the sterically encumbered dimethyl propargyl alcohol **18a** participated in the substitution, providing **18b** in excellent yield. Thiol-based nucleophiles **19a** and **20a** also yielded the corresponding thioethers with very high yields.

Table 2. Addition of Oxygen, Sulfur, and Carbon Nucleophiles to Imidate 9



entry	nucleophile	product	yield (%)
1			75
2			80
3			70
4			61[a]
5			50[a]
6	MeOH **15a**	 **15b**	97
7			91
8			88
9			89
10			78[b]
11			90
12			79
13			62[c]
14			48[c]

[a]Some apparent Friedel–Crafts products (~14% for **13b**, ~33% for **14b**) were observed in the crude ^{1}H NMR. [b]Reaction was performed at reflux for 30 min. [c]Reaction performed at reflux for 2 h.

Given the presence of aryl, prenyl, and *tert*-prenyl groups at the pyrroloindoline C3a position, some carbon nucleophiles that can provide similar functionality were also evaluated. Dimethoxybenzene (**21a**) provided the Friedel–Crafts alkylation product in 79% yield at room temperature in 10 min. Allyltributyltin **22a** had to be heated to reflux for 2 h to afford the alkylated product. Prenyltributyltin **23a** provided the reverse prenylated product **23b**, a common motif in pyrroloindoline natural products, in 48% yield under similar reaction conditions. The moderate yield in this case may be due to sterics, as the new carbon–carbon bond is formed between two quaternary centers.

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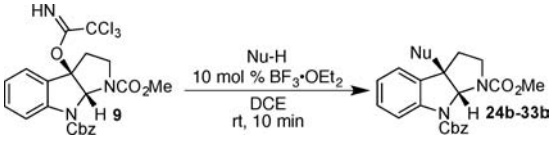
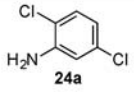
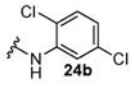
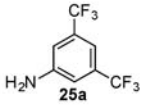
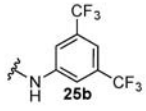
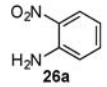
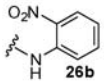
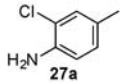
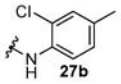
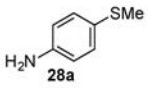
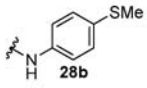
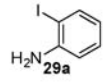
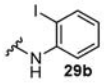
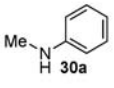
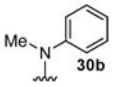
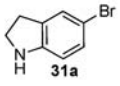
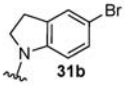
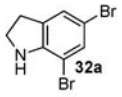
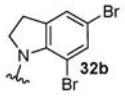
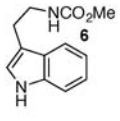
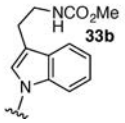
Nitrogen-based nucleophiles were also evaluated (Table 3). The displacement of imidate **9** with electron-poor anilines was rapid and high yielding at room temperature using $BF_3{\cdot}OEt_2$ (entries 1−3). More electron-rich anilines had to be refluxed in dichloroethane to provide the desired product, and the yields tended to be more moderate. In some cases, using a slight excess of the imidate provided an improved yield. Anilines with an *ortho*-halogen substitution or an *o*-nitro group were well tolerated. *N*-Methylaniline **30a** provided a moderate yield of the *N*-substituted product, with the *N*-substitution blocking the nitrogen and leading to competitive Friedel−Crafts alkylation reactions. Indoline was a competent nucleophile under these conditions; however, the product decomposed readily and was difficult to purify. Similar systems have been reported to be unstable by other researchers.[9a] However, when 5-bromoindoline **31a** or 5,7-dibromoindoline **32a** was employed, satisfactory yields were obtained (entries 8 and 9), as the bromine atoms block the undesired alkylation of the aromatic ring and slow oxidation of the indoline to the indole. Employing an indole instead of the indoline provided a complex mixture of products. After significant reoptimization, a 25% yield of the *N*-alkylated product **33b** could be isolated from the reaction mixture when $Cu(OTf)_2$ was used as the catalyst in mesitylene solvent. The improved yield using $Cu(OTf)_2$ may be attributed to a more selective reaction with the weaker Lewis acid.

Table 3. Addition of Nitrogen Nucleophiles to Imidate 9

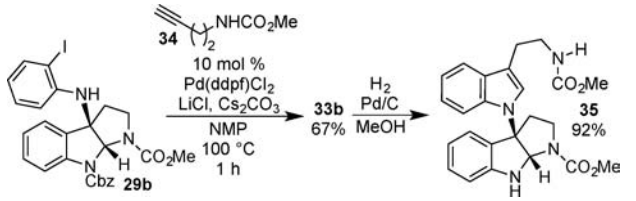


entry	nucleophile	product	yield (%)
1	 **24a**	 **24b**	80
2	 **25a**	 **25b**	84
3	 **26a**	 **26b**	84
4	 **27a**	 **27b**	86[a]
5	 **28a**	 **28b**	44[a,b]
6	 **29a**	 **29b**	71[c]
7	 **30a**	 **30b**	46[a,b]
8	 **31a**	 **31b**	45[a,b,c]
9	 **32a**	 **32b**	71[c]
10	 **6**	 **33b**	25[d]

[a]Reaction was performed at reflux for 30 min. [b]Some apparent Friedel−Crafts products were observed in the crude ^{1}H NMR (~20% for **28b**, ~26% for **30b**, ~19% for **31b**). [c]Excess imidate **9** was used (1.3 equiv). [d]Copper(II) triflate (30 mol %) was used in mesitylene solvent for 22 h at rt.

Access to aniline **29b** and indole **33b** led to a formal synthesis of psychotriasine (**3**, Figure 1). Following a route similar to that of Baran,[18] aniline **29b** was subjected to the Larock indole synthesis affording indole **33b** in 67% yield (Scheme 2). Removal of the Cbz group then provided indoline **35**, which intersected Baran's route to psychotriasine, completing a formal synthesis. While utilizing the 2-iodoaniline as a nucleophile followed by Larock indole synthesis results in higher yields, the direct addition of indole **33a** to imidate **9** provides a more expeditious route.

Scheme 2. Formal Synthesis of Psychotriasine 3



This new method was also utilized in a synthesis of arunidinine. Arunidinine (**5**) was first isolated by Abdullaev and co-workers in 1998 from the giant reed *Arundo donax*.[7] Key to the synthesis of arunidinine is the formation of the ether linkage at the C3a position of the pyrroloindoline, which may be formed from imidate **9**. As electron-poor phenols provided higher yields, protected indole **36** was synthesized as the phenol coupling partner (see the Supporting Information for the synthesis of **36**). Protection of the both tryptamine nitrogens as 2-nitrophenylsulfonamides was anticipated to prevent *N*-alkylation and deactivate the aromatic system, limiting side products from Friedel−Crafts-type reactions. Reaction of phenol **36** with imidate **9** utilizing $BF_3{\cdot}OEt_2$ gave only trace amounts of product due to side reactions. Evidently, the Ns group was not effective at deactivating the indole toward electrophilic side reactions. Better results were obtained with $Cu(OTf)_2$, and this afforded the etherified product **37** in 47% yield. The nosyl groups were then removed, with methylation of the aliphatic nitrogen to providing **38** in 75% yield over two steps. Conversion of **38** into arunidinine **5** was completed by removal of the Cbz group and reduction of the methyl carbamate (Scheme 3). The product of these transformations provided material that matched data reported for the natural product.

In summary, a convenient route to differentially substituted pyrroloindolines at the C3a position using a common trichloroacetimidate precursor has been demonstrated. Anilines, alcohols, thiols, phenols, and carbon-based nucleophiles provided moderate to high yields using only a catalytic amount of a Lewis acid. A formal synthesis of psychotriasine and a total synthesis of arundinine were also achieved using this new

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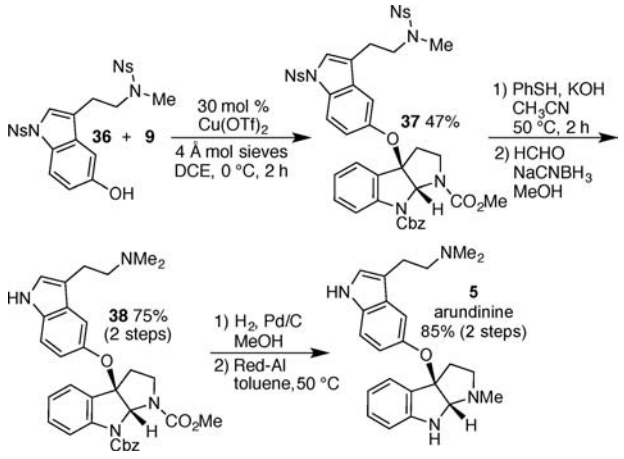
Scheme 3. Synthesis of Arundinine 5



method. Importantly, this technique can be utilized to rapidly synthesize a variety of pyrroloindoline structures and will be useful in a diversity-oriented approach for exploring the biological properties of these molecules. Future studies will focus on the exploration of more complex systems (including the effects of substitution on the indoline aromatic ring of imidate **9**) and additional applications in natural products synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02024.

Full experimental procedures (including the synthesis of indole **36**) and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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