Published in final edited form as:

Org Lett. 2016 August 19; 18(16): 4100–4103. doi:10.1021/acs.orglett.6b02024.

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

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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, 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.

Graphical abstract

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 towards flexible intermediates that allow for the rapid variation of functionality at this position. This expedites diversity-oriented approaches to both natural

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:xxx. Included are full experimental procedures (including the synthesis of indole **36**) and copies of NMR spectra.

Notes

The authors declare no competing financial interest.

and unnatural pyrroloindolines, allowing for rapid synthesis and facilitating biological evaluation. While selenides⁸ and sulfonium salts⁹ 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.¹

Our recent interest in the substitution chemistry of trichloroacetimidates with oxygen, sulfur and nitrogen nucleophiles¹³ 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-hydroxy furoindoline 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-hydroxy pyrroloindolines,^{8e,8f,12a,16} the oxidation reported by Takayama and co-workers¹⁷ which 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 then provided the C3a-trichloroacetimidate pyrroloindoline **9**.

With an efficient route to imidate **9** established, the nucleophilic substitution at the C3a position of the pyrroloindoline (Table 1) 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 ¹H 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 BF₃•OEt₂ 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.

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. Dimethoxy benzene (**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 hours 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.

Nitrogen based nucleophiles were also evaluated (Table 3). The displacement of imide **9** with electron poor anilines was rapid and high yielding at room temperature using $\text{BF}_3 \cdot \text{OEt}_2$ (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 imide provided an improved yield. Anilines with an *ortho*-halogen substitution or an *ortho*-nitro group were well tolerated. *N*-Methyl aniline **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 or 5,7-dibromoindoline (**24a**) were 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 $\text{Cu}(\text{OTf})_2$ was used as the catalyst in mesitylene solvent. The improved yield using $\text{Cu}(\text{OTf})_2$ may be attributed to a more selective reaction with the weaker Lewis acid.

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 imide **9** provides a more expeditious route.

This new methodology 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 imide **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 imide **9** utilizing $\text{BF}_3 \cdot \text{OEt}_2$ gave only trace amounts of product due to side reactions. Evidently the *N*s group was not effective at deactivating the indole towards

electrophilic side reactions. Better results were obtained with Cu(OTf)₂, 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 arundinine **5** was completed by removal of the Cbz group and reduction of the methyl carbamate. 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 methodology. 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 complex structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Financial support was provided by the National Institute of General Medical Sciences (R15-GM116054). NMR spectra were obtained at Syracuse University using instrumentation acquired with the assistance of the National Science Foundation (CHE-1229345).

REFERENCES

- (1). (a) Hino, T.; Nakagawa, M. *The Alkaloids : Chemistry and Pharmacology*. Brossi, A., editor. Vol. 34. Academic Press; New York: 1988. p. 1-75.(b) Anthoni, U.; Christophersen, C.; Nielsen, PH. *Alkaloids: Chemical and Biological Perspectives*. Pelletier, SW., editor. Vol. 13. Pergamon Press; London: 1999. p. 163-236.(c) Ruiz-Sanchis P, Savina SA, Albericio F, Alvarez M. *Chem. Eur. J.* 2011; 17:1388. [PubMed: 21268138]
- (2). (a) Steven A, Overman LE. *Angew. Chem., Int. Ed.* 2007; 46:5488.(b) Crich D, Banerjee A. *Acc. Chem. Res.* 2007; 40:151. [PubMed: 17309195] (c) Repka LM, Reisman SE. *J. Org. Chem.* 2013; 78:12314. [PubMed: 24295135] (d) Kim J, Movassaghi M. *Acc. Chem. Res.* 2015; 48:1159. [PubMed: 25843276]
- (3). Carle JS, Christophersen C. *J. Am. Chem. Soc.* 1979; 101:4012.
- (4). Varoglu M, Corbett TH, Valeriote FA, Crews P. *J. Org. Chem.* 1997; 62:7078. [PubMed: 11671801]
- (5). Zhou H, He H-P, Wang Y-H, Hao X-J. *Helv. Chim. Acta.* 2010; 93:1650.
- (6). Yeung BKS, Nakao Y, Kinnel RB, Carney JR, Yoshida WY, Scheuer PJ, Kelly-Borges M. *J. Org. Chem.* 1996; 61:7168. [PubMed: 11667621]
- (7). Zhalolov I, Khuzhaev VU, Tashkhodzhaev B, Levkovich MG, Aripova SF, Abdullaev ND. *Chem. Nat. Compd.* 1998; 34:706.
- (8). (a) Marsden SP, Depew KM, Danishefsky SJ. *J. Am. Chem. Soc.* 1994; 116:11143.(b) Depew KM, Marsden SP, Zatorska D, Zatorski A, Bornmann WG, Danishefsky SJ. *J. Am. Chem. Soc.* 1999; 121:11953.(c) Crich D, Huang X. *J. Org. Chem.* 1999; 64:7218.(d) Schiavi BM, Richard DJ, Joulie MM. *J. Org. Chem.* 2002; 67:620. [PubMed: 11855998] (e) Ley SV, Cleator E, Hewitt PR. *Org. Biomol. Chem.* 2003; 1:3492. [PubMed: 14599007] (f) Hewitt PR, Cleator E, Ley SV. *Org. Biomol. Chem.* 2004; 2:2415. [PubMed: 15326519]

- (9). (a) Tayu M, Ishizaki T, Higuchi K, Kawasaki T. *Org. Biomol. Chem.* 2015; 13:3863. [PubMed: 25714899] (b) Tayu M, Suzuki Y, Higuchi K, Kawasaki T. *Synlett.* 2016; 27:941.
- (10). (a) Espejo VR, Rainier JD. *J. Am. Chem. Soc.* 2008; 130:12894. [PubMed: 18774822] (b) Espejo VR, Li X-B, Rainier JD. *J. Am. Chem. Soc.* 2010; 132:8282. [PubMed: 20518467] (c) Villanueva-Margalef I, Thurston DE, Zinzalla G. *Org. Biomol. Chem.* 2010; 8:5294. [PubMed: 20856944] (d) Ruiz-Sanchis P, Savina SA, Acosta GA, Albericio F, Alvarez M. *Eur. J. Org. Chem.* 2012; 2012:67.
- (11). (a) Wang Y, Kong C, Du Y, Song H, Zhang D, Qin Y. *Org. Biomol. Chem.* 2012; 10:2793. [PubMed: 22383065] (b) Kim J, Movassaghi M. *J. Am. Chem. Soc.* 2011; 133:14940. [PubMed: 21875056] (c) Xie W, Jiang G, Liu H, Hu J, Pan X, Zhang H, Wan X, Lai Y, Ma D. *Angew. Chem. Int. Ed.* 2013; 52:12924.
- (12). (a) Bruncko M, Crich D, Samy R. *J. Org. Chem.* 1994; 59:5543. (b) Movassaghi M, Schmidt MA. *Angew. Chem. Int. Ed. Engl.* 2007; 46:3725. [PubMed: 17415735] (c) Ventosa-Andres P, Gonzalez-Vera JA, Valdivielso AM, Teresa Garcia-Lopez M, Herranz R. *Bioorg. Med. Chem.* 2008; 16:9313. [PubMed: 18818089] (d) Furst L, Narayanam JMR, Stephenson CRJ. *Angew. Chem., Int. Ed.* 2011; 50:9655. (e) Sun Y, Li R, Zhang W, Li A. *Angew. Chem., Int. Ed.* 2013; 52:9201.
- (13). (a) Howard KT, Duffy BC, Linaburg MR, Chisholm JD. *Org. Biomol. Chem.* 2016; 14:1623. [PubMed: 26691695] (b) Wallach DR, Stege PC, Shah JP, Chisholm JD. *J. Org. Chem.* 2015; 80:1993. [PubMed: 25568933] (c) Duffy BC, Howard KT, Chisholm JD. *Tetrahedron Lett.* 2015; 56:3301. (d) Shah JP, Russo CM, Howard KT, Chisholm JD. *Tetrahedron Lett.* 2014; 55:1740. (e) Adhikari AA, Shah JP, Howard KT, Russo CM, Wallach DR, Linaburg MR, Chisholm JD. *Synlett.* 2014:283.
- (14). (a) Nickel S, Nickel P, Hellmert M, Ernst S, Jewell R, Pearce CA, Jones G, Hamza D, Kaiser M. *Bioorg. Med. Chem.* 2015; 23:2636. For the development of pyrroloindoline libraries, see. [PubMed: 25907365] (b) Piemontesi C, Wang Q, Zhu J. *Org. Biomol. Chem.* 2013; 11:1533. For a similar strategy with oxindole-based trichloroacetimidates, see. [PubMed: 23348749]
- (15). (a) Ideguchi T, Yamada T, Shirahata T, Hirose T, Sugawara A, Kobayashi Y, Omura S, Sunazuka T. *J. Am. Chem. Soc.* 2013; 135:12568. [PubMed: 23957424] (b) Yamada T, Ideguchi-Matsushita T, Hirose T, Shirahata T, Hokari R, Ishiyama A, Iwatsuki M, Sugawara A, Kobayashi Y, Otaguro K, Omura S, Sunazuka T. *Chem. - Eur. J.* 2015; 21:11855. [PubMed: 26147398]
- (16). (a) Sakai A, Tani H, Aoyama T, Shioiri T. *Synlett.* 1998:257. (b) Kamenecka TM, Danishefsky SJ. *Angew. Chem., Int. Ed.* 1998; 37:2993. (c) Kamenecka TM, Danishefsky SJ. *Angew. Chem., Int. Ed.* 1998; 37:2995. (d) Kamenecka TM, Danishefsky SJ. *Chem. - Eur. J.* 2001; 7:41. [PubMed: 11205026] (e) Baran PS, Guerrero CA, Corey EJ. *J. Am. Chem. Soc.* 2003; 125:5628. [PubMed: 12733890] (f) Didier C, Critcher DJ, Walshe ND, Kojima Y, Yamauchi Y, Barrett AGM. *J. Org. Chem.* 2004; 69:7875. [PubMed: 15527264] (g) Iwaki T, Yamada F, Funaki S, Somei M. *Heterocycles.* 2005; 65:1811. (h) Yamada F, Fukui Y, Iwaki T, Ogasawara S, Okigawa M, Tanaka S, Somei M. *Heterocycles.* 2006; 67:129. (i) Kajiyama D, Saitoh T, Yamaguchi S, Nishiyama S. *Synthesis.* 2012; 44:1667. (j) Deng X, Liang K, Tong X, Ding M, Li D, Xia C. *Org. Lett.* 2014; 16:3276. [PubMed: 24922604]
- (17). Kitajima M, Mori I, Arai K, Kogure N, Takayama H. *Tetrahedron Lett.* 2006; 47:3199.
- (18). Newhouse T, Lewis CA, Eastman KJ, Baran PS. *J. Am. Chem. Soc.* 2010; 132:7119. [PubMed: 20426477]

Figure 1.
Some representative pyrroloindoline natural products.

Scheme 1.
Synthesis of imidate pyrroloindoline 9.

Scheme 2.
Formal synthesis of psychotriasine 3.

Scheme 3.
Synthesis of arundinine 5.

Table 1

Substitution of imideate 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 •OEt ₂ , DCE, rt, 10 min	75%
6	BF ₃ •OEt ₂ , THF, rt, 10 min	0%
7	BF ₃ •OEt ₂ , DME, rt, 10 min	31%
8	BF ₃ •OEt ₂ , CH ₃ CN, rt, 10 min	29%
9	BF ₃ •OEt ₂ , MeNO ₂ , rt, 10 min	47%

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

Table 2

Addition of oxygen, sulfur and carbon nucleophiles to imidate 9.

Entry	Nucleophile	Product	Yield
1			75%
2			80%
3			70%
4			61%
5			50%
6			97%
7			91%
8			88%
9			89%
10 ^a			78%

11			90%
12			79%
13 ^b			62%
14 ^b			48%

^aReaction was performed at reflux for 30 min.^bReaction performed at reflux for 2 h.

Table 3

Addition of nitrogen nucleophiles to imide 9.

Entry	Nucleophile	Product	Yield
1			80%
2			84%
3			84%
4 ^a			86%
5 ^a			44%
6 ^b			71%
7 ^{a,c}			46%
8 ^{a,b}			45%
9 ^b			71%
10 ^d			25%

^a Reaction was performed at reflux for 30 min.^b Excess imide **9** was used (1.3 equiv).^c Some Freidel-Crafts products were also observed.

^dCopper(II) triflate (30 mol %) was used in mesitylene solvent for 22 h at rt.

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