Abstract: The indoxyl unit is a common structural motif in alkaloid natural products and bioactive compounds. Here, we report a general method that transforms readily available 2-substituted indoles into 2,2-disubstituted indoxyls via nucleophile coupling with a 2-alkoxyindoxyl intermediate and showcase its utility in short total syntheses of the alkaloids brevianamide A (7 steps) and trigonoliimine C (6 steps). The developed method is operationally simple and demonstrates broad scope in terms of nucleophile identity and indole substitution, tolerating 2-alkyl substituents and free indole N–H groups, elements beyond the scope of most prior approaches. Spirocyclic indoxyl products are also accessible via intramolecular nucleophilic trapping.

Introduction

Indoxyls, also known as indolin-3-ones, are important structural units in biologically active small molecules and natural alkaloids (1–5, indoxyl highlighted in red, Figure 1A), and serve as versatile precursors to related \( N \) heterocyclic compounds (e.g., 6). These include the highly cytotoxic duocarmycins (e.g., 3) and the potent \( \mu \)-opioid receptor agonist mitrogyrine pseudoindoxyl (4), which have received interest from the medical community as payloads in antibody-drug conjugates or potential analogues, respectively. 2,2-Disubstituted indoxyls bear a fully substituted center at the C-2 position and represent a core challenge in the synthesis of targets such as ibotutene (1) and brevianamide A (2). While many creative methods toward 2,2-disubstituted indoxyls have been reported from the synthetic community, including cyclization/trapping of 2-alkynyl arylazides or -nitroarenes, aryne heteroannulation, interrupted Ugi reactions, and many others, challenges still remain in accessing such motifs bearing two alkyl substituents at C-2, as would be required for 1–2.

One of the most convenient ways to access 2,2-disubstituted indoxyls (8) is via deaeromatization of readily available indole starting materials. Broadly speaking, such reactions fall into two classes: those that begin with (or proceed via) a 2,3-disubstituted indole (7), and those that begin with a 2-substituted indole (9) and introduce the second substituent through an additional nucleophilic component (Figure 1B). The former approach proceeds via oxidation of the substituted indole 7 to a 3-hydroxyindolenine (10), followed by Wagner–Meerwein-type 1,2-shift of the C-3 substituent to C-2 with concomitant formation of the indoxyl ketone. Indeed, this approach has been widely explored, including in alkaloid total synthesis, but can suffer from competing rearrangement into the 3,3-disubstituted oxindole isomer 12 (via transient epoxide 11) in a manner that can be highly substrate- and condition-specific. Additionally, the preparation of the required 2,3-disubstituted indole can often be step-intensive. Alternatively, from a 2-substituted indole (9), oxidation can yield an electrophič 3-oxoindolenine (13) or its equivalent (14) prior to trapping with a nucleophile. Aside from being complementary to the prior rearrangement approach, this strategy offers the advantage of being convergent, provided sufficient generality is available for the nucleophilic and electrophilic components. This approach has been explored, proceeding via either an imine (13) or 2-hydroxy/2-alkoxyindoxyl intermediate (14) which reacts with nucleophiles, typically mediated by Lewis or Brønsted acids. A key issue in such reactions is avoiding simple dimerization of the indole fragment via attack of the nucleophilic indole starting material onto 13 during oxidation to yield an adduct like 15; in fact, many methods explicitly target such dimers (or trimers) because of this problem. Additionally, where cross-couplings are possible, the overwhelming majority of such methods are only suitable for 2-aryl substituted systems and/or require N-substitution, likely due to the instability of the corresponding 2-alkylamine/iminium intermediates (vide infra). Though a handful of exceptions exist, these approaches also typically require highly nucleophilic coupling partners like indoles or pyroles (Mayr nucleophilicity parameter, \( N = 5.5–7 \)) presumably to ensure efficient iminium trapping. Among these methods, You and coworkers reported a notable asymmetric coupling of indoles with spiroindoxyls that relies on a hydroxyalkyl chain as reversible iminium trap (see 16, Scheme 1B, bottom), building off of racemic work by Kobayashi which necessarily limits the scope to specific 2-(hydroxyalkyl) substrates.

Thus, a general approach which can tolerate a range of 2-alkyl substituents, a broader selection of nucleophiles, and not require N-protection would be highly desirable. This should expedite the synthesis of complex targets such as trigonoliimine C (6) and is especially evident when considering application to indoxyl alkaloids such as ibotutene (1) or brevianamide A (2), neither of which incorporate a 2-aryl unit or N-substitution. Herein, we describe the development of a general approach that transforms readily available 2-substituted indoles into 2,2-disubstituted indoxyls via nucleophile coupling with a 2-alkoxyindoxyl intermediate. The method demonstrates broad scope in terms of nucleophile identity and indole substitution, tolerating 2-alkyl substituents and free indole N–H groups. The utility of our approach is highlighted in concise syntheses of the alkaloids brevianamide A (2) and trigonoliimine C (6).
Results and Discussion

To begin these efforts, we sought a robust, alkyl-group-tolerant entry to an activated intermediate such as 13 or 14 from 2-alkylindoles, which are either commercially available or accessible in one step using the C–H alkylation method developed by Bach and coworkers. Out of these options, we considered 2-alkoxynoxindoxyl intermediates to be the most feasible precursors. Although we screened several potential methods for their preparation, we found that the most user-friendly and scalable option was to treat the indole substrate with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH, 22, 2.0 equiv) in a mixture of CH₂Cl₂ and EtOH at room temperature. Similar oxodiperoxymolybdenum(VI) complexes had been reported for N-acylindole oxidations by Sakamoto[17a,b] and later by Jimenez[17c] along with a single example of the use of 22 with a free N–H 2-alkylindole substrate.[17d] Using these mild oxidation conditions, phthalimide-containing model substrate 23[18] was converted to N-H 2-ethoxyindoxyl 24 in 74% after rapid chromatographic purification on triethylamine-deactivated silica gel (Table 1). In general, however, N-H 2-ethoxyindoxyl compounds displayed variable stability to chromatographic purification (often more severe than 24), which led us to develop a two-step, one-purification protocol from indole to final indoxyl product (vide infra); for the purpose of optimizing the nucleophile coupling part of that sequence, however, we chose to utilize pure 24.

Table 1. Optimization of Nucleophile Coupling

| Entry | Deviation from above | 25 (%) | 26 (%) |
|-------|----------------------|--------|--------|
| 1     | None                 | 98 (95)* | 0      |
| 2     | HFIP as solvent      | 99 (88)* | 0      |
| 3     | CH₂Cl₂ as solvent    | 19 27   |        |
| 4     | THF as solvent       | 0 85    |        |
| 5     | CH₂CN as solvent     | 6 14    |        |
| 6     | TFA as catalyst      | 81 0    |        |
| 7     | TMSOTf as catalyst   | 56 0    |        |
| 8     | TMSCl as catalyst    | 58 0    |        |
| 9     | TiCl₄ as catalyst    | 94 0    |        |
| 10    | BF₃·OEt₂ as catalyst | 86 0    |        |
| 11    | 5.0 mol% p-TsOH·H₂O  | 56 0    |        |
| 12    | 3.0 equiv nucleophile | 80* 0   |        |
| 13    | 1.5 equiv nucleophile | 72 (83)* | 0      |

*aReactions conducted on 0.1 mmol of 24. ¹H NMR yields with 1,3,5-trimethoxybenzene as internal standard. ²Isolated yield.
We began by screening conditions for coupling 24 with 1,3-dimethoxybenzene (5 equiv) as a moderately nucleophilic partner (N = 2.48). Initial efforts to employ a catalytic amount of p-toluenesulfonic acid (p-TsOH, 10 mol%) in several common solvents (entries 3–5) at 0 °C to room temperature showed that a key issue was simple elimination of the ethoxy group (presumably via an iminium ion) to give (Z)-enamine 26. We found, however, that the fluorooalcohol solvents 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which are known to stabilize cationic intermediates, gave none of the elimination byproduct and provided excellent yields of the desired aryl coupling product 25 (HFIP: 99%; TFE: 98%; entries 1–2). In fact, screening different acids in TFE, we found that acid identity was not especially important, with several Lewis acids and Lewis acids (entries 6–10) all providing product to varying degrees (e.g., trifluoroacetic acid: 81%; TiCl4: 94%). In the case of Lewis acids in TFE, we consider these as likely precursors of the corresponding Brønsted acid (e.g., TIOH from TMSOTf) or perhaps able to engage in Lewis acid-assisted Brønsted acid catalysis with the protic solvent (e.g., BF3·OEt2). To assess whether p-TsOH in TFE was simply able to reprotonate any enamine 26 that formed to the iminium ion in order to funnel it to product 25, we subjected 26 to the standard reaction conditions (entry 1). Only decomposition of 26 was noted with no 25 formed, suggesting that the TFE solvent either stabilizes the intermediate iminium ion or increases the rate of its reaction with the aryl nucleophile (or both). Efforts to employ a lower loading of nucleophile and acid catalyst (entries 11–13) showed a moderate reduction in yield with 3 equivalents of arene (80%) but a more significant drop with 1.5 equivalents of nucleophile (72%) or 5 mol% p-TsOH (56%). Ultimately, we settled on the use of 10 mol% p-TsOH in TFE as a mild, user-friendly, and relatively inexpensive set of conditions with which to explore the generality of this method.

We initiated such studies by exploring the nucleophile scope using purified 24 as the iminium precursor (Table 2). Pleasingly, the reaction tolerated a range of arene and n-nucleophiles. For highly nucleophilic arene partners (N > 5) like indoles and pyrrole, we found that 3 equivalents of nucleophile could be employed, while maintaining high yields (77–88%, 27–30). Other heteroarene partners like 2-methylfurran (82%, 31) and 2-methylthiophene (81%, 32) were also competent under such conditions. A variety of allylations could be conducted with allylsilane, allylstannane, or nucleophilic alkene partners to give olefin-containing products (34–37, 75–93%). The coupling efficiency with functionalized nucleophilic partners yielding 35 bearing an allylic acetoxyl group (75%) or highly hindered ones which forge vicinal fully-substituted centers (75%, 36) is noteworthy. Additionally, we found that carbonyl nucleophiles in the form of silyl enol ethers could couple efficiently, while a relatively acidic β-diketone was also a viable substrate; the products from these couplings provide versatile ketone (38, 40) or enal (39) functionalities for further elaboration. Finally, although the nucleophile scope is greater than that observed for related indoxyl syntheses, we did note that less nucleophilic coupling partners such as anisole (N = -1.18) and 2-methylanisole gave either no observed product or only a moderate yield (31%, 33), respectively. Based on our experience, nucleophiles with N > 1 tended to react effectively unless steric factors became dominant (see SI for unsuccessful partners).

Next, we explored the tolerance of the method toward different indole substituents using 1,3-dimethoxybenzene and allyl-
trimethylsilylamine as representative nucleophiles (Table 3). As mentioned above, the stability of the intermediate 2-ethoxyindoxyl to purification was variable, so the nucleophile coupling reaction was performed on this crude intermediate following work-up to provide a convenient two-step, one-purification transformation. Using an n-butyl group as a model 2-alkyl substituent, the method tolerated a range of substituents on the indole nucleus, including electron-withdrawing (e.g., CN, NO₂, CF₃, halogen, 41–52, 56–77, 2 steps) and electron-donating (Me, OMe, 53, 62–63), though the efficiency for the latter systems was lower (37–50%, 2 steps). Substrates bearing N-substitution in the form of benzyl or methyl groups also performed well in the chemistry (62–67, 70–72, 37–78%, 2 steps), and were on average higher yielding compared to their N-H congeners. Side-chains containing benzzyloxy (54, 66–67), acetoxy (57), phenyl (56), cyclopropane (64–65), and fluoro (72) functionality were well tolerated, as was a simple 2-methyl substituent (58–59, 37–96%, 2 steps). A substrate containing an acid sensitive Boc-protected amino acid moiety also survived coupling conditions, providing products 68 and 69 in good yields (65–67%, 2 steps) but with low diastereoselectivity (dr = 1.3:1). Although not extensively explored here, given our focus on 2-alkylindole systems, we did demonstrate that 2-phenylindole could be converted to indoxyls 60 and 61 in moderate yield (34–65%, 2 steps) using our protocol. Additionally, more complex spirocyclic products (73–74) could be generated in good yield (69–70%, 2 steps) by incorporating nucleophilic amines into the side-chain, while a fused 7-membered indoxyl was formed via cyclization of an N-tethered methoxyarene (75, 58%).

With the scope of the method defined, we returned to our original goal of its application to complex molecule synthesis (Scheme 1). As an initial test, we targeted the preparation of the core structure of indoxyl-containing Itoga alkaloids like iboluteine (1)⁹puted by spirocyclic Boc-amine 76. We were able to access this poly cyclic indoxyl from cyclohexanone adduct 38 via a deprotection/reductive amination/protection sequence (Scheme 1A). The two initial steps appeared to converge the mixture of diastereomers of 38 to one observable product, presumably via epimerization α- to the ketone or imine. The final structure and stereochemistry of 76 were confirmed by X-ray crystallographic analysis.

Next, we set our sights on the synthesis of trigonolimine C (6), an indole alkaloid isolated from the leaves of Trigonostemon liii⁴⁴ that displays moderate anticancer activity (Scheme 1B).⁵² Trigonolimine C (6) has been the subject of three prior total syntheses by the groups of Tambar, Movassaghi, and Ramana, wherein its imine motif was accessed via intramolecular indoxyl condensation.⁵² Our synthesis of 6 began with the advancement of indole 77 (prepared in two steps from commercial materials, see SI) to 2-ethoxyindoxyl intermediate 78, followed by coupling with protected tryptamine 79⁵⁶ (3 equiv). This provided the indole addition product 80, a known precursor to 6 in 60% yield over the two steps (0.5 mmol scale). Thus, following the
reported 2-step sequence,[26b,c] we completed our synthesis of trigonolimine C (6) in a total of 6 steps (longest linear sequence).

Scheme 1. (A) Synthesis of iboluteine core structure (76). (B) Formal synthesis of trigonolimine C (6).

Finally, we targeted the preparation of the more challenging brevianamide A (2) (Scheme 2), a bicyclo[2.2.2]diazaoctane alkaloid isolated from the fungus *Penicillium brevicompactum* in 1969 and shown to possess antifeedant activity against a number of crop pests.[27] Though many illuminating biogenetic studies and syntheses of targets in this family have been reported over the last four decades,[28] the total synthesis of brevianamide A has only very recently been achieved by Lawrence and coworkers.[29] These authors described an elegant biomimetic approach to 2, involving a 1,2-shift to putative indoxyl 90 from a transient 3-hydroxyindolenine intermediate (cf. 10 → 8, Fig. 1B), followed by a tautomerization/intramolecular [4+2] sequence. Overall, their approach provides a short 7-step synthesis of this natural product and its minor diastereomer, brevianamide B. For our part, we hoped to access 90 in a complementary fashion without the need for C-3/C-2-migration by utilizing a 2-substituted indole precursor. Thus, beginning with N-protected amino acid 81[30] (one step from commercial L-propargylglycine), we could couple its carboxylic acid with imine 83[20,31] via activation with Ghoose’s reagent[32] (82) under modified literature conditions[33] in 63% yield; here, heating the mixture of imine 83 and putative acid chloride proved crucial to achieving reasonable yields of enamide 84. Next, a Sonogashira coupling with 2-iodoaniline delivered aniline-alkyne 85 (70%), which could be smoothly cyclized to indole 87 using JohnPhosAu(MeCN)2SnF6 (86) in CH2Cl2 at room temperature in 80% yield.[34] With 87 in hand, the stage was set for our key transformation to indoxyl 89. In the event, oxidation yielded the expected 2-ethoxyindoxyl intermediate which was stable enough for partial chromatographic purification in this case. Subsequent treatment with prenylstannane 88 under the usual conditions generated the desired product 89 as a mixture of diastereomers (dr = 1.2:1) in 45% yield over the two steps. It is noteworthy that our method is able to tolerate the presence of multiple functionalities in 87 and that reverse prenylation occurs efficiently despite forming two adjacent fully-substituted centers. Although separation of each diastereomer could in principle lead to a single enantiomer of brevianamide A, we elected to advance the diastereomeric mixture together since, in a racemic sense, the diastereomers would converge to the same intermediate at the stage of heterodiene 91. Thus, treatment with NH3 in MeOH[29] was able to deprotect the pthalimide and cyclize to diketopiperazine 90, which was stable enough to be purified on silica gel if desired.[35] We found, however, that simply concentrating the reaction mixture and subjection to Lawrence’s conditions[29] (LIOH in H2O) in the same pot was sufficient to deliver brevianamide A (2) in 54% yield, completing a 7-step total synthesis of this complex alkaloid. In our hands, we were unable to isolate any brevianamide B (formed via [4+2] on the opposite diene face), though we did note very small amounts by 1H NMR or LC-MS analysis of the crude reaction mixture. As expected, our final sample of 2 displayed only minor enantioenrichment on the basis of its optical rotation (~9% ee expected based on the 1.2:1 dr of 89).

Conclusion

In summary, we have developed an operationally simple method for the conversion of 2-substituted indoles to 2,2-disubstituted indoxyls that is characterized by a broad substrate scope in terms of both indole and nucleophile partners. Our method provides convenient and relatively unique access to such heterocycles with 2,2-dialkyl substitution and free N–H groups, properties which should make it appealing for medicinal chemistry applications. We have showcased its utility in concise total syntheses of trigonolimine C (6 steps) and brevianamide A (7 steps), being amongst the shortest approaches to these targets reported to date. Future studies will focus on the use of aerobic oxidation and asymmetric catalysis to provide an efficient, enantioselective route to such motifs. Our hope is that the tools communicated here will inspire further exploration of 2,2-disubstituted indoxyls as medicinal agents.

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*Keywords:* indoxyl • total synthesis • alkaloids • synthetic methods
Scheme 2. 7-step total synthesis of brevianamide A (2).
oxidation based on that reported by Jiang and co-workers was successful but did not prove scalable above 0.2 mmol, see ref. 12c.

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A general, user-friendly synthesis of 2,2-disubstituted indoxyls from readily available 2-substituted indoles has been developed, tolerating unprotected indoles and 2-alkyl substitution as well as a broad range of nucleophilic partners. This method provides a solution to the challenge of 2,2-dialkyl indoxyl synthesis and is showcased in total syntheses of the complex alkaloids brevianamide A and trigonoliimine C in only 6–7 steps overall.