Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX–XXX
Letter
pubs.acs.org/OrgLett

Access to 3-Prenylated Oxindoles by α-Regioselective Prenylation: Application to the Synthesis of (±)-Debromoflustramine E

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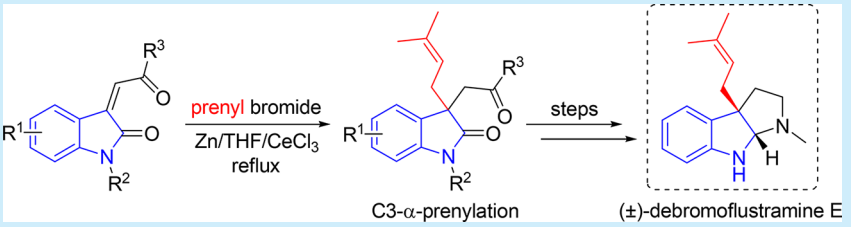
Supporting Information



ABSTRACT: The development of a rapid, highly efficient, and one-pot synthesis of C3-α-prenylated oxindoles with simple reagents is described. The process is based on zinc-mediated α-regioselective prenylation of 3-acylidene-oxindole with commercially available prenyl bromide using inexpensive $CeCl_3$ as the catalyst. The new transformation tolerates a wide range of 3-acylidene-oxindoles, providing easy access to a variety of functionalized 3-prenylated oxindoles. The synthetic utility of the approach is verified by formal synthesis of the flustramine family alkaloid (±)-debromoflustramine E.

Prenylated indole alkaloids are present in a large number of natural products and bioactive molecules (Figure 1).[1] They

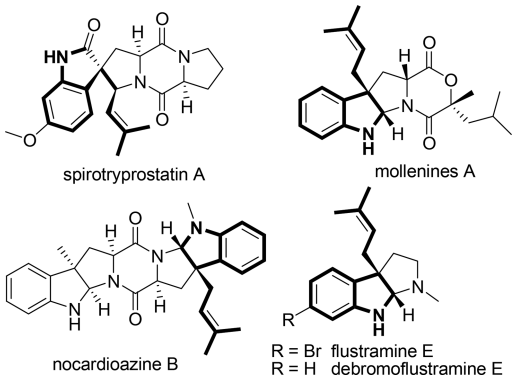
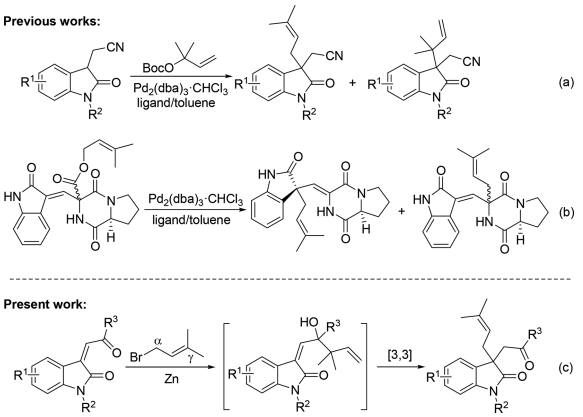


Figure 1. Biologically active 3-prenylated indole alkaloids.

display a variety of interesting biological and pharmacological properties. 3-Prenylated oxindoles are key intermediates for the synthesis of those indole alkaloids such as the flustramine family of natural products.[2] In principle, the direct incorporation of a prenyl group into the 3-position of the oxindoles represents the most reliable method to prepare 3-prenylated oxindoles. However, a major problem in direct prenylation can be the formation of two regioisomeric products, i.e., α-product and γ-product.[3] In particular, the selective formation of a α-product has proven to be challenging.[4]

In 2011, the Trost group investigated an elegant approach to 3-prenylated oxindoles via palladium-catalyzed asymmetric prenylation of oxindoles (Scheme 1a).[5a] Another approach to access 3-prenylated oxindoles was palladium-catalyzed decarboxylation−alkylation of prenyl-β-ketoester, which was presented by the same group in 2007 (Scheme 1b).[5b] Despite great innovation, the formation of regioisomeric mixtures in these reactions remains the inherent limitation. Meanwhile, both a presynthesis of the $Pd_2dba_3{\cdot}CHCl_3$ complex and an additional step to access the prenyl source are required in those transformations, which is not ideal from a practical perspective. To achieve "ideal synthesis",[6] the use of simple reagents and an easily available prenyl source for the preparation of 3-prenylated oxindoles with high regioselectivity is highly desirable.

Scheme 1. Methods for the Preparation of 3-Prenylated Oxindoles



On the basis of our continuing interest in the regioselective prenylation and its application,[7] we envisioned that by using 3-

Received: January 5, 2018

DOI: 10.1021/acs.orglett.8b00045
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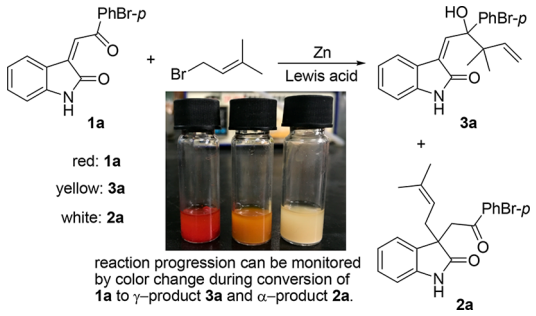
acylidene-oxindoles as a synthetic precursor, we might realize the introduction of a prenyl fragment into the 3-position of oxindoles with high regioselectivity using prenyl bromide as a prenyl source. It is expected that an initial addition of the C═O bond with prenylzinc would afford γ-intermediate, which might undergo subsequent [3,3] sigmatropic rearrangement to afford the target α-product (Scheme 1c). Herein, we report our efforts in achieving such a zinc-mediated α-regioselective prenylation using cheap and simple reagents without the need for prederivatization to prenyl sources, allowing for the expedient construction of a wide range of 3-prenylated oxindoles.

To assess the feasibility for the reaction outlined in Scheme 1c, compound **1a**[8] was initially selected as the model substrate to screen the reaction conditions (Table 1). Treatment of 3-acylidene-oxindole **1a** and prenyl bromide in the presence of zinc powder in THF at room temperature did not produce the desired product **2a** rather than 1,2-γ-adduct **3a** in almost quantitative yield (entry 1). Pleasingly, when the same reaction was carried out at reflux, the expected C3-α-prenylated product **2a** was observed, albeit with a low 26% yield (entry 2), indicating a pathway of [3,3] sigmatropic rearrangement. Encouraged by this result and taking into consideration the importance of a Lewis acid in [3,3] rearrangement,[9] we envisaged that a Lewis acid could coordinate to both the oxygen of oxindole and the side chain of **3a**, and this double activation would accelerate the reaction. Hence, various Lewis acids were screened under similar conditions. The results indicated that $ZnBr_2$ and $BF_3{\cdot}Et_2O$ exhibited moderate catalytic activity for the reaction (entries 3 and 4), whereas $CoCl_2$, $TiCl_4$, and $SnCl_4$ were less effective (entries 5−7). Other Lewis acids such as $AlCl_3$, $InCl_3$, and $CeCl_3$ showed higher activity to catalyze this reaction, among which $CeCl_3$ exhibited the highest catalytic potency (entries 8−10). Fe (III) catalysts such as $FeCl_3$, $FeBr_3$, and $Fe(caca)_3$ were also equally effective for the reaction (entries 11−13), but the corresponding workup and purification turned out to be inconvenient. Therefore, $CeCl_3$ was chosen as the optimal Lewis acid for further studies. Decreasing the catalyst loading to 15 mol % led to no loss in yield (entry 14). However, reduction in the yield was noticed when $CeCl_3$ was decreased to 10 mol % (entry 15). Conducting the reaction in other solvents such as dioxane (diox) led to no desired α-product formation and the recovery of the starting material **1a** (entry 16). Unlike previous allylations which usually require the removal of the excess active zinc powder in advance,[10] there is no additional separate step of prenylzinc reagent needed in all cases presented here and the excess zinc powder in the reaction system did not affect the reaction results. This one-pot procedure represents a practical advantage of the present methodology, which would greatly facilitate the operation. To demonstrate the synthetic utility of the one-pot method, the model procedure was successfully scaled up in comparable yield. The product **2a** (1.21 g, 76%) was prepared when the reaction was run on the 4 mmol scale.

Table 1. Optimization of Reaction Conditions[a]



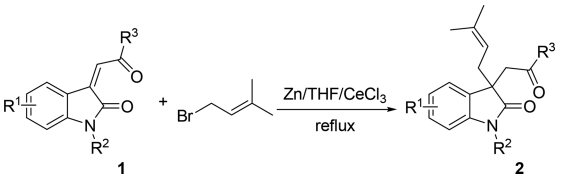
entry	Lewis acid (mol %)	solvent	temp (°C)	time (h)	**2a** (%)[b]	**3a** (%)[b]
1	none	THF	25	2	ND	>98
2	none	THF	reflux	12	26	49
3	$ZnBr_2$ (25)	THF	reflux	12	41	18
4	$BF_3{\cdot}Et_2O$ (25)	THF	reflux	12	37	27
5	$CoCl_2$ (25)	THF	reflux	12	31	56
6	$TiCl_4$ (25)	THF	reflux	16	26	40
7	$SnCl_4$ (25)	THF	reflux	16	20	44
8	$AlCl_3$ (25)	THF	reflux	12	69	trace
9	$InCl_3$ (25)	THF	reflux	12	68	ND
10	$CeCl_3$ (25)	THF	reflux	8	77	ND
11	$FeCl_3$ (25)	THF	reflux	12	70	ND
12	$FeBr_3$ (25)	THF	reflux	12	72	ND
13	$Fe(caca)_3$ (25)	THF	reflux	10	75	trace
14	$CeCl_3$ (15)	THF	reflux	8	79	ND
15	$CeCl_3$ (10)	THF	reflux	12	66	9
16	$CeCl_3$ (10)	diox	reflux	16	ND	ND

[a]Reactions were performed with **1a** (0.5 mmol), prenyl bromide (0.75 mmol), and zinc (1.0 mmol) in a one-pot manner. [b]Isolated yield.

Under the optimized conditions (Table 1, entry 14), the generality of this novel α-prenylation was investigated, as shown in Table 2. Initial investigation of the scope of the reaction was focused on varying the substituents (R^1) on the aromatic ring of oxindoles. The results show that the reaction took place efficiently using substrates that contain a variety of arene ring substituents (R^1). For instance, the substrates possessing −H (**1b**) as well as electron-donating groups such as −Me (**1c**) and −OMe (**1d**) are well compatible with this process, delivering the C3-α-prenylated products **2b−d** in good to excellent yields (entries 1−3). Furthermore, halogen functional groups such as −F (**1e**), −Cl (**1f**), and −Br (**1g**) are unaltered by and do not affect the process (entries 4−6). Altering the position of substituents on the phenyl ring of oxindoles did not significantly affect the reaction behaviors (entry 6, **1g** vs entries 7−9, **1h**, **1i**, and **1j**). Next, we investigated reactions of 3-acylidene-oxindoles that contain various R^3 groups attached to carbonyl carbon. 3-Acylidene-oxindoles bearing both electron-donating and -withdrawing functionalities (R^3) were found to be excellent substrates and gave the desired products in moderate to good yields, such as 4-MeC_6H_4 (**1k**), 4-$MeOC_6H_4$ (**1l**), 4-FC_6H_4 (**1m**), and 4-ClC_6H_4 (**1n**) groups (entries 10−13). Besides the para-substituted phenyl groups of R^3, the substrate bearing a meta substituent also exhibited good reactivity and resulted in the formation of **2o** in 72% yield (entry 14). However, no desired C3-α-product **2p** or 1,2-γ-adduct was observed when using the substrate possessing an ortho substituent at the phenyl ring of R^3 (entry 15), probably attributed to the ortho-position effect of the substituent. To our delight, the trifluoromethyl group ($-CF_3$), as a useful structural motif in many biologically active molecules, attached on the phenyl ring of R^3 gave the corresponding product **2q** in a reasonable yield (entry 16). 3-Acylidene-oxindole **1r** has been identified as a selective plasmodial cyclin dependent protein kinase (CDK) inhibitor.[11] We believe that the preparation of its analogue would be useful for structure−activity relationship studies. Hence, **1r** was subjected to the same reaction conditions and the corresponding product **2r** was obtained in 82% yield (entry 17). In addition to substrates with monosubstituted aryl groups, those bearing disubstituted aryl groups such as **1s** and **1t** were also reactive, producing the

DOI: 10.1021/acs.orglett.8b00045
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope[a]



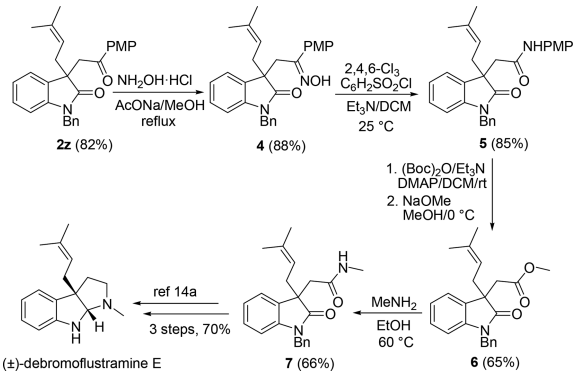
entry	1	R^1, R^2, R^3	2	yield (%)[b]
1	**1b**	H, H, Ph	**2b**	89
2	**1c**	5-Me, H, Ph	**2c**	81
3	**1d**	5-MeO, H, Ph	**2d**	83
4	**1e**	5-F, H, Ph	**2e**	83
5	**1f**	5-Cl, H, Ph	**2f**	88
6	**1g**	5-Br, H, Ph	**2g**	90
7	**1h**	4-Br, H, Ph	**2h**	80
8	**1i**	6-Br, H, Ph	**2i**	83 (82)[c]
9	**1j**	7-Br, H, Ph	**2j**	86
10	**1k**	H, H, 4-MeC_6H_4	**2k**	85 (83)[d]
11	**1l**	H, H, 4-MeOC_6H_4	**2l**	78
12	**1m**	H, H, 4-FC_6H_4	**2m**	76
13	**1n**	H, H, 4-ClC_6H_4	**2n**	80
14	**1o**	H, H, 3-BrC_6H_4	**2o**	72
15	**1p**	H, H, 2-BrC_6H_4	**2p**	0
16	**1q**	H, H, 4-$CF_3C_6H_4$	**2q**	50
17	**1r**	5-Br, H, 4-FC_6H_4	**2r**	82
18	**1s**	H, H, 3,4-(OCH_2O)C_6H_3	**2s**	77
19	**1t**	H, H, 3,4-$Cl_2C_6H_3$	**2t**	72
20	**1u**	H, H, 2-naphthyl	**2u**	80
21	**1v**	H, H, 2-thienyl	**2v**	42
22	**1w**	H, H, Me	**2w**	0
23	**1x**	H, Bn, Ph	**2x**	85 (82)[e]
24	**1y**	H, Bn, 4-BrC_6H_4	**2y**	84
25	**1z**	H, Bn, 4-MeOC_6H_4	**2z**	86 (82)[f]

[a]Reactions were performed with **1** (0.5 mmol), prenyl bromide (0.75 mmol), 15 mol % $CeCl_3$, and zinc (1.0 mmol) in THF at reflux under N_2 for 8 h. [b]Isolated yield. [c]Gram-scale reaction, **1i** (1.15 g) was used. [d]Gram-scale reaction, **1k** (1.05 g) was used. [e]Gram-scale reaction, **1x** (1.02 g) was used. [f]Gram-scale reaction, **1z** (1.10 g) was used.

corresponding C3-α-prenylated products **2s** and **2t** in 77% and 72% yields (entries 18 and 19), respectively. More bulky 2-naphthyl also survived well to afford the desired product **2u** in 80% yield (entry 20). The reaction also worked with the heteroaromatic substrates such as **1v** albeit with low yields (entry 21). The low yield of product **2v** might be due primarily to the detrimental interaction between the sulfur atom of the thiophene ring and the Lewis acid. Unfortunately, the reaction failed to afford the desired product **2w** and only a 1,2-γ-adduct intermediate was observed when R^3 was substituted with an aliphatic methyl group (entry 22). It is noteworthy that all the cases mentioned above use N-unprotected 3-acylidene-oxindoles as the substrate. This is particularly advantageous because the introduction and removal of protecting groups usually results in a reduced overall yield.[12] Finally, to explore the substrate scope further, we tested N-protected substrates (R^2). Just as expected, those N-protected substrates such as N-Bn protected ones **1x**, **1y**, and **1z** were well tolerated in this process, and the corresponding products **2x**, **2y**, and **2z** were obtained in 85%, 84%, and 86% yields, respectively (entries 23−25). The syntheses of products **2i**, **2k**, **2x**, and **2z** were accomplished on a gram scale with yields almost identical to those obtained in experiments on a smaller scale (entries 8, 10, 23, and 25), showing the robustness of this protocol.

To demonstrate the strength of our method and how this approach can be very useful as a general method for preparing 3-prenylated indole alkaloids, we chose debromoflustramine E (a natural product of flustramine family alkaloids[13]) to show its formal synthesis (Scheme 2). To date, several syntheses of the

Scheme 2. Formal Synthesis of (±)-Debromoflustramine E

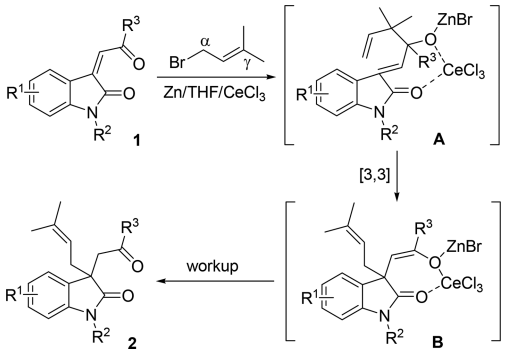


racemic and optically active forms have been reported.[3b,14] However, the reported routes to debromoflustramine E mainly rely on a multistep sequence to construct the prenyl moiety.[14a−d] Joseph-Nathan et al. developed a one-step Grignard alkylation to construct the prenyl moiety and with it as the key step accomplished the total synthesis of (±)-debromoflustramine E.[3b] However, a mixture of regioisomeric products was formed in the process, which is difficult to separate by column chromatography. Our formal synthesis of debromoflustramine E began with the gram-scale prenylation of 3-acylidene-oxindole **1z** with prenyl bromide in the presence of zinc powder and $CeCl_3$ to give C3-α-prenylated product **2z** in 82% yield (entry 25, Table 2). The treatment of **2z** with hydroxylamine hydrochloride in methanol in the presence of AcONa led to the formation of the desired ketoxime **4** in 88% yield. We screened numerous reaction conditions and found that 2,4,6-trichlorobenzenesulfonyl chloride promoted **4** to undergo a clean Beckmann rearrangement at 25 °C to produce amide **5** in 85% yield. After introducing a BOC group to the amide nitrogen atom, the resulting N-Boc derivative was treated with sodium methoxide in methanol to provide the ester **6**, which was then amidated using methylamine to the methyl amide **7**. Following the procedure reported by Kobayashi et al.,[14a] compound **7** could be transformed in a few steps, into indole alkaloid (±)-debromoflustramine E. While we did not attempt to assess other flustramine family alkaloids, we are confident that the method described here would be equally effective in the synthesis of debromoflustramine B[15] from compound **2l** and flustramine B[15] from compound **2i**, respectively.

On the basis of the experimental results shown in Table 1, together with the observation of an ortho-position effect in entry 15 of Table 2, a plausible reaction mechanism for the transformation is proposed in Scheme 3. Initially, a nucleophilic attack of the γ-carbon of the prenylzinc bromide on the carbonyl group attached to R^3 produces the γ-prenylated zinc alcoholate. This can be explained by the formation of the currently accepted six-membered cyclic transition state between the carbonyl compound and the prenylzinc moiety.[16] Then, $CeCl_3$ coordinates to both the oxygen of the zinc alcoholate and the oxindole as a

DOI: 10.1021/acs.orglett.8b00045
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Proposed Reaction Mechanism



bidentate Lewis acid promoter to form intermediate **A**.[17] Similarly to the copper(II)- and titanium(IV)-catalyzed Claisen rearrangement,[18] this two-point coordination would promote the subsequent [3,3] thermal rearrangement of **A**, which resulted in the formation of intermediate **B**. Final workup and enolization delivers the α-adduct **2**.

In conclusion, we have developed a conceptually new route for the introduction of a prenyl fragment at the C-3 position of oxindoles by the prenylation reaction of 3-acylidene-oxindole with prenyl bromide catalyzed by $CeCl_3$ in the presence of zinc powder, which provides easy access to a variety of functionalized 3-prenylated oxindoles. The protocol is direct and operationally simple, has high step economy and a broad substrate scope, uses simple materials, and is amenable to gram-scale synthesis of 3-prenylated oxindoles in high yields. Furthermore, this method holds great potential in the synthesis of prenylated indole alkaloid natural products. In this context, we employed this protocol to finish the formal synthesis of (±)-debromoflustramine E. Applications of this method toward other prenylated indole alkaloids are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00045.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Science and Technology Support Program of Jiangsu Province (BE2017643).

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DOI: 10.1021/acs.orglett.8b00045
Org. Lett. XXXX, XXX, XXX−XXX