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N-Indolyltriethylborate: A Useful Reagent for Synthesis of C3-Quaternary Indolenines

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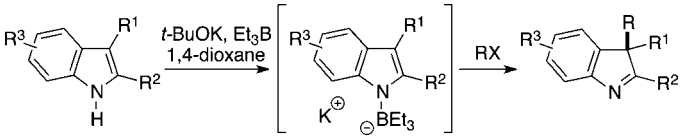
ABSTRACT



***N*-Indolyltriethylborate was found to be a useful reagent for dearomatizing C3-alkylation of 3-substituted indoles with both activated and nonactivated alkyl halides to give C3-quaternary indolenines, pyrroloindolines, furoindoline, and hexahydropyridoindoline under mild reaction conditions. The utility of these reagents was demonstrated in the syntheses of a pyrroloindoline-4-cholestene hybrid and debromoflustramine B.**

Indole alkaloids are widely distributed in both terrestrial and marine organisms and often show interesting biological and pharmacological properties.[1] Whereas Nature employs biosynthetic machineries to enzymatically synthesize indole alkaloids from tryptophan and other biosynthetic precursors,[2] dearomatization of simple indoles provides a convenient connection between the readily available aromatic heterobicycle and complex indole-containing structural motifs through chemical synthesis.[3] In particular, dearomatizing C3-alkylation/arylation of 3-substituted indoles leads to the formation of C3-quaternary indolenines, which are versatile building blocks for the synthesis of the alicyclic molecular frameworks found in complex indole alkaloids and related compounds.[4] A number of approaches have been developed for the synthesis of these compounds from electron-rich indoles and activated electrophiles, such as carbonyl, imine, Michael acceptors, transition metal complexes, etc., by Friedel–Crafts or similar transformations.[5] In order to overcome the thermodynamic cost associated with dearomatization of indoles and the relatively low π-nucleophilicity of 3-substituted indoles for formation of the quaternary center, these transformations are often executed intramolecularly to give spiro- or other polycyclic indolenines[6] or coupled with intramolecular N- or C-cyclization of the initial indolenine products to give pyrroloindolines,

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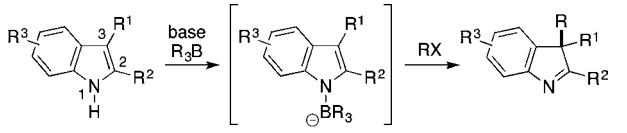
furoindoline, or hexahydrocarbazoles as the products.[7] Thus, it is not surprising that only a few examples exist for dearomatizing allylation/benzylation of 3-substituted indoles to give C3-quaternary indolenines,[8] and the corresponding alkylation reactions with nonactivated electrophiles have been rare.[9] The development of new approaches for the dearomatizing alkylation will significantly expand the scope of this process and could provide new synthetic strategies to complex indole alkaloids. Herein we report that *N*-indolytriethylborates are excellent reagents for synthesis of C3-quaternary indolenines through dearomatizing alkylation of indoles with, not only activated alkyl groups (such as allyl, benzyl, etc.) but also nonactivated primary and secondary alkyl halides.

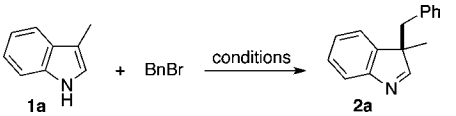
Scheme 1. C3-Alkylation of N-Indolyltrialkylborates



The N-deprotonation of indoles leads to the build up of electron density. However, this does not necessarily translate into increased π-nucleophilicity, as N1- and C2-alkylation may compete with the desired C3-alkylation of indolides.[10] Whereas magnesium, zinc, and some other metal indolides have been employed in C3-nucleophilic reactions to give 3-substituted indoles,[11] presumably because the relatively stable covalent metal−N bonds prevent the N-alkylation pathway, these metal indolides are only moderately nucleophilic, and low reactivity was observed when 3-substituted indolides were employed as the nucleophile. Our recent study of decarboxylative allylic alkylation of allyl indolenin-3-carboxylates suggests that *N*-indolyltrialkylborates are formed as reactive intermediates.[12] We envisioned that these species would be useful π-nucleophiles for the dearomatizing C3-alkylation of indoles because of the electron-rich nature of the aromatic system and the tight N−B association which would prevent not only the competing N-alkylation but also the C2-alkylation pathway, as well (Scheme 1).

We tested this hypothesis using benzylation of 3-methylindole. Indeed, in the presence of Et_3B, benzylation of lithium 3-methylindolide, prepared by N-deprotonation of the indole with *n*-BuLi, led to formation of indolenine **2a** (Table 1, entry 1). Encouraged by this result, other trialkylboranes were briefly surveyed. The sterically bulky *n*-hexyl-9-BBN gave a reasonable reaction yield (entry 2), while only less than 10% of **2a** was formed in the presence of Ph_3B (entry 3). The reaction did not proceed at all when the more Lewis acidic $(F_5C_6)_3B$ was used as the additive and 3-methylindole was recovered (entry 4). Various bases were also tested for the reaction. While NaH (entry 5) and KH (entry 6) gave results similar to that of *n*-BuLi, improved reaction efficiency was obtained when *t*-BuOK was used (entry 7). On the other hand, NaOMe was found to be significantly less effective for the reaction (entry 8). Also ineffective were K_2CO_3 and Et_3N (entries 9 and 10), which gave **2a** in low yields only. A number of solvents were screened, and 1,4-dioxane was found to give the highest yield of **2a** (entries 11−15). In order to evaluate if the reaction could be executed under catalytic conditions, the benzylation was also tested using substoichiometric amount of Et_3B. While only C3-benzylation was observed under these conditions, this was accompanied by reduced reaction efficiency under otherwise identical reaction conditions (entries 16 and 17).

Table 1. Screening of Reaction Conditions[a]



entry	additive	base	solvent	**2a** (%)
1	Et_3B	*n*-BuLi	THF	74
2	hexyl-9-BBN	*n*-BuLi	THF	62
3	Ph_3B	*n*-BuLi	THF	<10
4	$(F_5C_6)_3B$	*n*-BuLi	THF	NR
5	Et_3B	NaH	THF	78
6	Et_3B	KH	THF	75
7	Et_3B	*t*-BuOK	THF	81
8	Et_3B	NaOMe	THF	20
9	Et_3B	K_2CO_3	THF	<10
10	Et_3B	Et_3N	THF	23
11	Et_3B	*t*-BuOK	Et_2O	68
12	**Et_3B**	***t*-BuOK**	**1,4-dioxane**	**94**
13	Et_3B	*t*-BuOK	DMF	70
14	Et_3B	*t*-BuOK	toluene	82
15	Et_3B	*t*-BuOK	CH_2Cl_2	80
16	Et_3B[b]	*t*-BuOK	1,4-dioxane	78
17	Et_3B[c]	*t*-BuOK	1,4-dioxane	53
18		*t*-BuOK	1,4-dioxane	17

[a] Reactions carried out with 0.50 mmol of **1a**, 1.1 equiv of the base, 1.1 equiv of the borane additive, and 1.1 equiv of benzyl bromide at room temperature. [b] 0.55 equiv of Et_3B. [c] 0.30 equiv of Et_3B.

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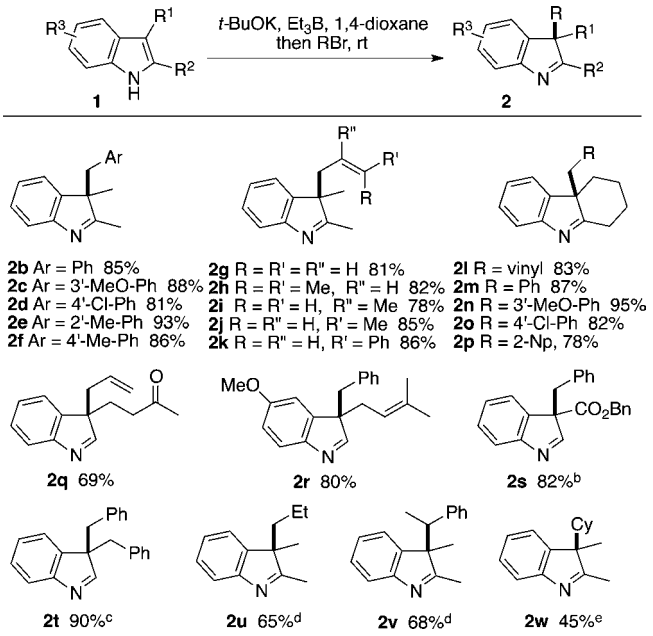
Scheme 2. Scope of the Reaction[a]



[a] Unless noted otherwise, the reaction was carried out with 0.50 mmol of **1**, 1.1 equiv of *t*-BuOK, 1.1 equiv of Et_3B, and 1.1 equiv of alkyl halides at room temperature for 12 h. [b] 60−65 °C. [c] 3.0 equiv of benzyl bromide, 2.5 equiv of *t*-BuOK, and 1.5 equiv of Et_3B. [d] 2.0 equiv of alkyl halide, 60−65 °C, 36 h. [e] 3.0 equiv of cyclohexyl bromide, 90−95 °C, 36 h.

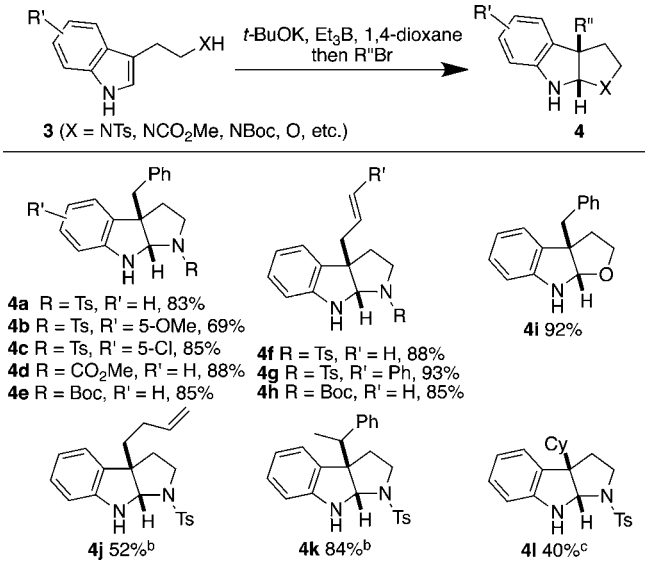
Unsurprisingly, in the absence of Et_3B, *N*-benzylindole (not shown) was generated as the major product (40%) while **2a** was formed in 17% yield only (entry 18).

We examined the scope of the reaction using various substituted indoles and alkyl halides (Scheme 2). C2,C3-Disubstitution was found to be compatible with the reaction as **2b** was formed in 85% yield upon reaction of 2,3-dimethylindole and benzyl bromide. Benzyl bromides substituted with π-donating methoxyl, electron-withdrawing chloride, or simple methyl groups all reacted with 2,3-dimethylindole to give the corresponding C3-benzylation products **2c**−**2f** in high yields. Reactions of 2,3-dimethylindole and various substituted allyl bromides proceeded smoothly as well under the optimized reaction conditions to give the C3-allylation products in unanimously good yields (**2g**−**2k**). Hexahydrocarbazole readily reacted with benzyl and allyl bromides to give the corresponding C3-quaternary indolenines (**2l**−**2p**) with good efficiency. Indoles with various C3-substitutions were also compatible with the reaction conditions to give the corresponding allylation and benzylation products in good yields. Benzylation of unsubstituted indole under the optimized reaction conditions gave a mixture of 3-benzyl indole (not shown) and 3,3-dibenzyl indolenine **2t** (1:1, 37%). The latter was exclusively formed when unsubstituted indole reacted with excess of *t*-BuOK and Et_3B.

C3-Alkylation of 3-substituted indoles with less reactive electrophiles is challenging and rarely reported.[9] Thus, even though an elevated reaction temperature (60−65 °C) was necessary, we were pleased to observe that 2,3-dimethylindole combined with *n*PrBr to give **2u** in 65% yield under otherwise identical reaction conditions. This alkylation reaction could also be extended to secondary alkyl halides such as (1-bromoethyl)benzene to give **2v** as a mixture of diastereomers (1.5:1). Cyclohexylbromide, a nonactivated secondary alkyl halide, also smoothly combined with 2,3-dimethylindole to give **2w** in 45% yield. Unsurprisingly, the reaction of 2,3-dimethylindole and *t*-butyl bromide did not proceed under the reaction conditions (not shown).

This reaction protocol was also effective for dearomatizing alkylation of tryptamine derivatives, and the initial C3-quaternary indolenine products underwent spontaneous cyclization to give pyrroloindolines (Scheme 3). Thus, the reaction of tryptamine derivatives (*N*-tosyl, *N*-CO_2Me, and *N*-Boc) and benzyl or allyl bromides led to formation of the corresponding pyrroloindolines (**4a**−**4h**) in high yields. N-Alkylation of the starting tryptamine derivatives or the pyrroloindoline products was not observed. Interestingly, furoindoline **4i** was obtained as the sole product when 1*H*-indole-3-ethanol was used, indicating that free hydroxyl groups are also compatible with the reaction conditions. The excellent π-nucleophilicity of indoles

Scheme 3. Reaction of Tryptamine Derivatives[a]



[a] Unless noted otherwise, the reaction was carried out with 0.50 mmol of **3**, 1.1 equiv of *t*-BuOK, 1.1 equiv of Et_3B, and 1.1 equiv of alkyl halide at room temperature for 12 h. [b] 2.0 equiv of alkyl halides, 60−65 °C, 36 h. [c] 3.0 equiv of cyclohexyl bromide, 90−95 °C, 36 h.

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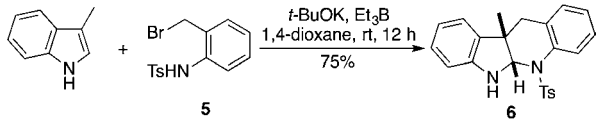
Scheme 4. Synthesis of Hexahydropyridoindoline **6**

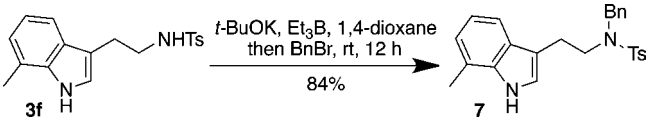


under this protocol was also demonstrated in reaction of *N*-tosyltryptamine with nonactivated primary and secondary alkyl halides to give the corresponding pyrroloindolines (**4j**–**4l**) that could not be synthesized by other means.

Hexahydropyridoindole, a structure motif found in complex indole alkaloids such as communesins and perophoramidine,[13] is also accessible through this method. Thus, reaction of 3-methylindole and **5** gave hexahydropyridoindoline **6** in 75% yield under the reaction conditions (Scheme 4).

We attribute the excellent indole π-nucleophilicity in the dearomatizing alkylation process to formation of the electron-rich *N*-indolyltriethylborates. These reagents are unlikely to form between 7-substituted indoles and trialkylboranes because of the resulting severe 1,3-interactions. Indeed, reaction of *N*-tosyl-7-methyltryptamine and benzyl bromide led to exclusive formation of **7** (Scheme 5), indicating that formation of *N*-indolyltriethylborate is necessary for enhanced π-nucleophilicity.[14] Formation of *N*-indolytriethylborate also serves to temporarily block the N1 and C2 positions so that regioselective C3-alkylation occurs exclusively.

Scheme 5. Benzylation of *N*-Tosyl-7-methyltryptamine

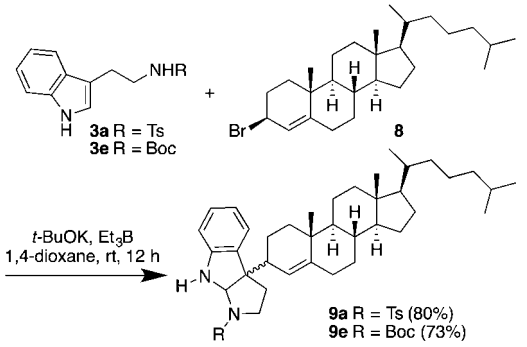


Prenylated indole alkaloids are hybrids of indole and isoprenoid units.[15] These natural products are found in a wide range of natural sources and often show interesting biological and pharmacological properties. In order to demonstrate the utility of this synthetic method, pyrroloindoline-4-cholestene hybrid **8** was synthesized as shown in Scheme 6 through alkylation of **3** with known 4-cholesten-3-bromide.[11b] Even though the hybrid was formed as a mixture of diasteromers, this method provides convenient access to these unique unnatural indole–isoprenoid hybrids which might be of potential biomedical value.

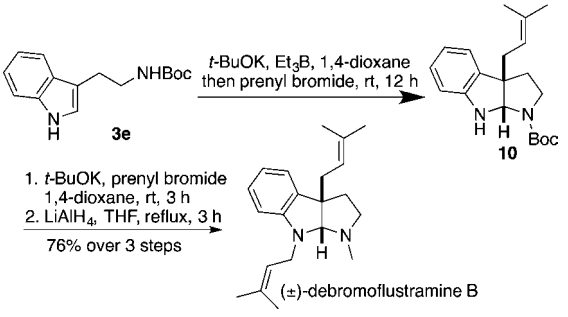
The utility of this synthetic method was further demonstrated in the total synthesis of debromoflustramine B, a prenylated indole alkaloid isolated from the marine briozoan *Flustra foliacea*, and the closely related pseudophyrnamines, such as pseudophrynaminol.[16] Thus, reaction

(16) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod.* **1994**, *57*, 997.

Scheme 6. Synthesis of Pyrroloindoline-4-cholestene Hybrid



Scheme 7. Synthesis of (±)-Debromoflustramine B



of *N*-Boc-tryptamine and prenyl bromide under the optimized reaction conditions led to the formation of **10** (Scheme 7), which was subjected to further prenylation and reduction with $LiAlH_4$ to give debromoflustramine B in 76% yield over three steps at 5.0 mmol scale.

In summary, *N*-indolyltriethylborate was found to be an excellent reagent for synthesis of C3-quaternary indolenines through dearomatizing alkylation of indoles with not only activated alkyl groups but also nonactivated primary and secondary alkyl halides. These reactions proceed under mild conditions with a broad range of substrates to give C3-quaternary indolenines, pyrroloindolines, furoindoline, and hexahydropyridoindoline in high yields. N1- or C2-alkylation products were not formed. The utility of these reagents was demonstrated in the synthesis of pyrroloindoline-4-cholestene hybrids and in the total synthesis of debromoflustramine B.

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Supporting Information Available. Experimental procedures and characterization data, including ^1H, ^{13}C NMR, and HRMS for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.