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$InBr_3$-Mediated One-Pot Synthesis of 2-(Polyhydroxylatedalkyl)-*N*-aryl-/-alkylpyrroles from 1,2-Cyclopropa-3-pyranone and Amines

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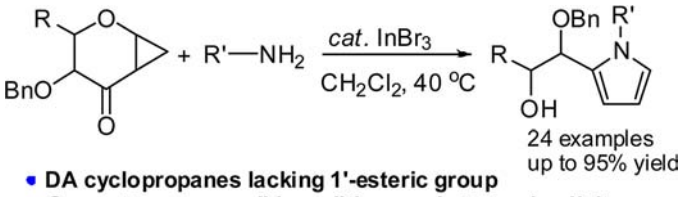
ABSTRACT



- DA cyclopropanes lacking 1'-esteric group
- One-pot process, mild conditions, substrate simplicity
- High yields for both *N*-aryl and *N*-alkyl pyrroles

An efficient one-pot synthesis of polyhydroxyalkyl-substituted pyrroles from 1,2-cyclopropa-3-pyranones with primary amines is reported. With 10% of $InBr_3$ as the catalyst, both aryl- and alkylamines as well as various 1,2-cyclopropa-3-pyranones are well tolerated. This method is highly appealing because of its one-pot process, mild reaction conditions, substrate simplicity, and broad substrate scope.

Pyrroles are a unique class of heterocycles commonly identified in natural products and pharmacological agents.[1] Although construction of the pyrrole ring can be realized by a number of classical synthetic methods, including the Hantzsch reaction[2] and the Paal–Knorr synthesis,[3,4] many new approaches have been recently reported leading to formation of multifunctionalized pyrroles. Among these, cyclopropanes activated by one or two electron-withdrawing substituents have attracted tremendous interest for facile construction of functionalized pyrroles through ring-opening followed by a cycloaddition process.[5−16] For example, Charette and co-workers[8] reported that cyclopropanes

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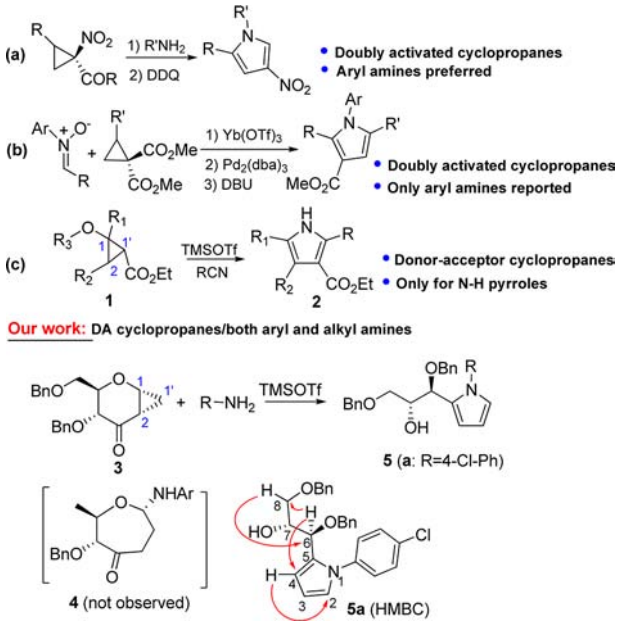
with double activation by nitro and acyl groups can readily react with arylamines to facilitate *N*-arylpyrroles (eq a, Scheme 1). Meanwhile, Kerr's group reported that cyclopropanes doubly activated by two ester groups can react with nitrones affording *N*-arylpyrroles after Pd-catalyzed dehydrocarbonylation and dehydration (eq b, Scheme 1).[9] Alternatively, using donor–acceptor (DA) cyclopropanes[5] (e.g., **1**) as the dipole precursor, Pagenkopf[6] reported a novel [3 + 2] dipolar cycloaddition with various nitriles using catalytic TMSOTf to generate *N*-nonsubstituted pyrroles **2** (eq c, Scheme 1). These new approaches not only showcase the power of advances in organic methodology but also provide pyrroles bearing unique substitution patterns that are useful for high-throughput-screening and for further structural manipulation. In our drug discovery program, we are interested in multisubstituted pyrroles, especially with *N*-aryl and *N*-alkyl substituents, and the above-mentioned methods either suffer from multiple reaction steps or are limited in the synthesis of *N*-aryl- and *N*-H-pyrroles. Therefore, new strategies for versatile synthesis of both *N*-aryl- and *N*-alkylpyrroles, together with simple reaction substrate and a short and facile reaction process, are still highly useful. To this end, we recently found that using glucose-derived cyclopropane ketone **3**,[16] a substrate lacking the 1′-esteric group as that in **1** and without the trouble of diastereomeric selectivity during its preparation, reacts with various amines under the catalysis of a Lewis acid to afford *N*-substituted pyrroles **5**. This strategy represents a versatile method to access both *N*-aryl- and *N*-alkylpyrroles bearing a C2-(polyhydroxylated alkyl) substituent.

We initially attempted to replace aryl nitriles with arylamines to react with ester **1**; unfortunately, no reaction was observed. We then employed DA cyclopropane **3** to react with arylamines and speculated that without assistance of the C1′-esteric group as in **1**, ring-opening of cyclopropane **3** at C1–C1′ would be difficult; instead, ring-opening at C1–C2 should be preferred because of the ring strain, thus leading to a Ferrier-rearrangement product **4**.[17,18] To our surprise, following a procedure similar

Scheme 1. Recently Reported and Our Newly Discovered Synthesis of Pyrroles from Cyclopropanes



to that for preparation of **2**, the reaction of glucose-derived cyclopropane **3** (1.0 equiv) with 4-chloroaniline (1.2 equiv) under 30% TMSOTf at −78 °C did not occur. Gradually elevating reaction temperature to rt led to major decomposition of carbohydrate **3**, while pyrrole **5a** was isolated as a minor product in appropriately 10% yield. The structure of **5a** was assigned by all spectroscopic data (^{1}H and ^{13}C NMR, MS, HRMS, HSQC). Meanwhile, HMBC correlations characteristic of structure **5a** were also observed (Scheme 1).

Since there is no report on reactions of carbohydrate-derived 1,2-cyclopropa-3-pyranones (e.g., **3**) with amines, and compounds **5** are new *N*-substituted pyrroles with pharmacological potentials, we decided to optimize the reaction conditions to enable compounds **5** to be produced as the major products.

With the reaction of cyclopropane **3** and 4-chloroaniline as the model reaction, we first screened various Lewis acids (see the Supporting Information). Using $BF_3 \cdot Et_2O$ as the catalyst, the reaction did not occur at rt, and high temperature led to decomposition of cyclopropane **3**. Fortunately, 30 mol % of indium halides[19] were found to efficiently promote the reaction and the yield of the product was dependent on the acidicity of the indium halides.

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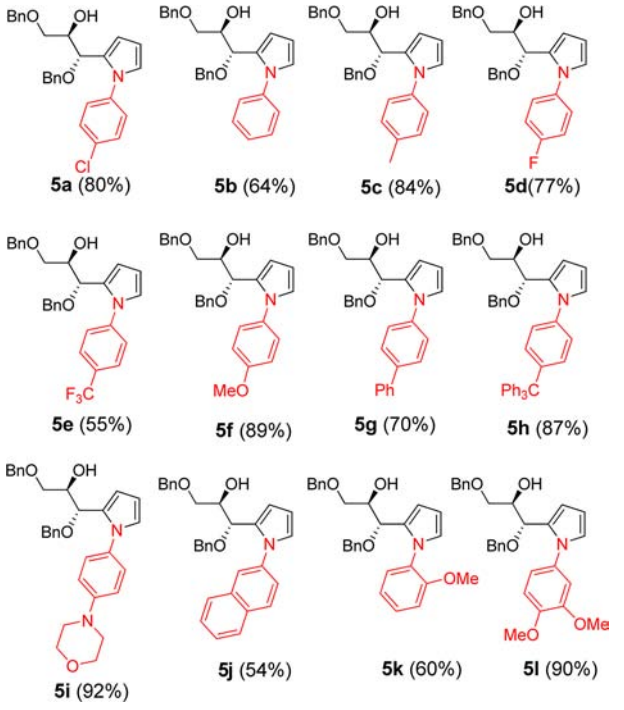


Figure 1. *N*-Aryl-2-(polyhydroxylkyl)pyrroles.

The strongest acid $InBr_3$ afforded compound **5a** in highest yield of 82%. Meanwhile, it was found that in the refluxing CH_2Cl_2 (40 °C), the amount of Lewis acid loading could be reduced from 0.3 to 0.1 equiv (based on cyclopropane **3**) without significant effect on the yield. In addition, some other Lewis acids, e.g., $Dy(OTf)_3$ and $Yb(OTf)_3$, were also investigated, but lower yields were obtained.

On the basis of the results obtained above, 10% of $InBr_3$ was the optimal catalyst (in refluxing CH_2Cl_2), and the expected *N*-arylpyrrole **5a** was successfully obtained as the major product in 80% isolated yield. With this encouraging result, we next evaluated the scope of the reaction by reacting cyclopropane **3** with various arylamines. As shown in Figure 1, all arylamines used herein took part in the reactions smoothly and yielded the expected *N*-aryl-substituted pyrroles **5a**–**l** in 55–92% yield. Arylamines with electron-donating groups generally gave slightly higher yields (**5c**, **5f**, **5h**, **5i** vs **5d**, **5e**). Arylamine with a morpholinyl substituent also gave good yield (**5i**, 92%). A close comparison of the yields between products **5f** (89%) and **5k** (60%) indicated that the steric effect in arylamines played a role and *ortho*-substituted substrates gave lower yields.

To further explore the limitation of the amine substrates and to expand the diversity of the products, we then investigated the reactions of cyclopropane **3** with various alkylamines. It was found that all the reactions using alkylamines proceeded readily, and the expected products were obtained in even higher yields. As shown in Figure 2, reactions of cyclopropane **3** with benzylamine yielded *N*-benzylpyrrole **5m** in 93% yield. (*R*)-2-Methylbenzylamine

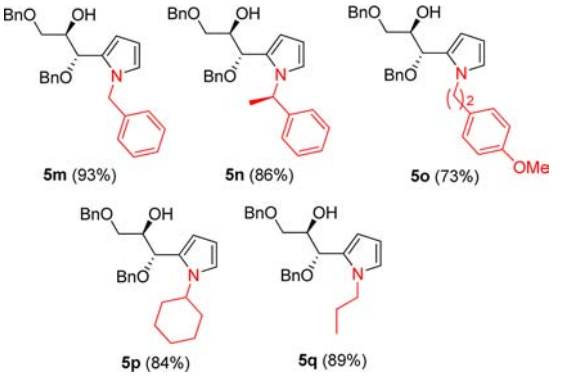
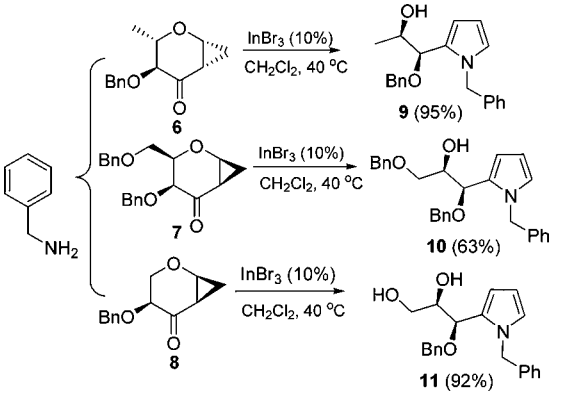


Figure 2. *N*-Alkyl-2-(polyhydroxylkyl)pyrroles.

or phenylethylamine also took part in the reaction very well and afforded corresponding pyrroles **5n** and **5o** in 86% and 73% yield, respectively. Similarly, cyclohexylamine and propylamine were also suitable substrates, and the corresponding *N*-alkylpyrroles **5p** and **5q** were obtained in 84% and 89% yields, respectively.

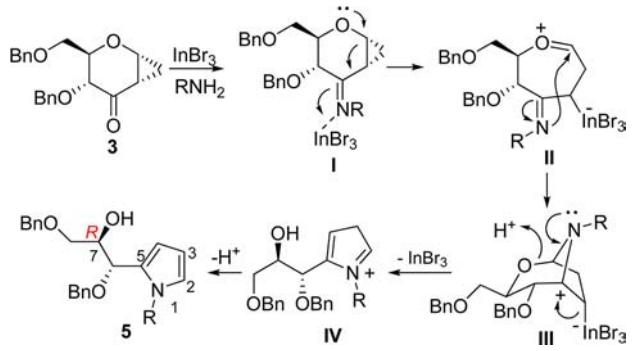
Meanwhile, representative variations in the carbohydrate-derived cyclopropane substrates were also explored. As listed in Scheme 2, cyclopropane ketones **6**–**8** were prepared by cylopropanation of corresponding glycals[16] and subjected to reaction with benzylamine under catalysis of $InBr_3$ (10%) in refluxing CH_2Cl_2. All three reactions proceeded nicely and generated the corresponding *N*-benzylpyrroles **9**–**11** in 63–95% yields. These results further illustrate the generality of this novel strategy.

Scheme 2. Reactions of Benzylamine with Cyclopropanes **6**–**8**



To rationalize the reaction outcomes, we proposed a tentative mechanism. As shown in Scheme 3, treating ketone **3** with an appropriate aryl- or alkylamine would generate imine **I**.[7] Ring expansion of the iminocyclopropane **I** followed by an intramolecular nucleophilic attack of the imino-*N* to the C1 of the oxonium ion[16,18] would yield species **III**. Ring cleavage followed by dehydrogenation would finally deliver pyrroles **5**.

Scheme 3. Proposed Mechanism



According to our proposed mechanism, the 7-hydroxy group in product **5b** was derived directly from the carbohydrate substrate **3**; therefore, the absolute configuration of C7 should be R same as that in **3**. To confirm the diastereomeric purity of **5**, pyrrole **5b** was oxidized to ketone using the Dess–Martin reagent and then subjected to $NaBH_4$ reduction to regenerate the alcohol products as a diastereomeric mixture (see the Supporting Information). With the newly resulting diastereomeric mixture as the comparison, the diastereomeric ratio of compound **5b** was determined to be 99.0%.

The cytotoxicity of representative pyrrole compounds **5b**, **5o**, **5n**, and **11**, as well as clinical anticancer drug etoposide (as positive control),[20,21] was evaluated against several cancer cell lines, including human lung cancer A549 cells, squamous carcinoma KB cells, vincristine-resistant KB/VCR cells, and human lung cancer H460 cells, and the results are summarized in Table 1. Compared to the potency of etoposide, our new synthetic pyrroles showed moderate activity in all the four cancer cells, but slightly higher sensitivity toward vincristine-resistant KB/VCR cell was observed for the pyrroles, opposite from the selectivity profile of etoposide. In addition, compounds

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Table 1. Cytotoxicity of Selected Compounds Against Cancer Cell Lines[20,21]

	IC_{50} (μM)		
compd	KB	KB/VCR	A549
5b	14.71	8.37	20.56
5o	10.99	7.80	12.07
5n	10.05	7.65	13.66
11	77.84	57.99	84.72
etoposide	1.88	54.39	4.61

5b, **5o**, and **5n** were much more potent than pyrrole **11**, with IC_{50} values around 10 μM, indicating that the polyhydroxyalkyl substituents on the pyrroles are important.

In summary, we have reported an efficient one-pot synthesis of polyhydroxylalkyl-substituted *N*-alkyl- and *N*-alkylpyrroles from 1,2-cyclopropa-3-pyranones with both aryl- and alkylamines with 10% of $InBr_3$ as the catalyst. This method is highly appealing due to the substrate simplicity, mild reaction conditions, broad substrate scope, and cheap catalyst. The resulting pyrroles show moderate cytotoxicity against several cancer cell lines and would serve as compound templates worthy of further structural modification.

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Supporting Information Available. Experimental details and full spectroscopic data 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.