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Lewis Acid-Catalyzed Double Addition of Indoles to Ketones: Synthesis of Bis(indolyl)methanes with All-Carbon Quaternary Centers

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We report herein a Lewis acid-catalyzed nucleophilic double-addition of indoles to ketones under mild conditions. This process occurs with various ketones ranging from dialkyl ketones to diaryl ketones, thereby providing access to an array of bis(indolyl)methanes bearing all-carbon quaternary centers, including tetra-aryl carbon centers. The products can be transformed into bis(indole)-fused polycyclics and bis(indolyl)alkenes.

Introduction

Indole is a well-known privileged scaffolds due to their wide occurrence in natural products as well as broad applications in medicinal chemistry.¹ Bis(indolyl)methanes, which contain two indole units in a molecule, are recognized to be the core structure of numerous biologically active compounds such as potent anti-cancer agents.² Thus, the development of efficient methods to construct such compounds has been an active area of studies.^{2,3} A majority of reported methods includes the reactions of two equivalents of indoles with various aldehydes, ethers, and alcohols that yield bis(indolyl)methanes containing a tertiary carbon center at the junction of two indole units, in the presence of various promotors including Lewis or Brønsted acid catalysts, metal-based catalysts, enzymes, or under electrochemical conditions.^{3,4}

By comparison, progress to date in the synthesis of bis(indolyl)methanes with an all-carbon quaternary center has been less developed perhaps due to the challenge associated with steric hindrance around such centers.⁵ Markovnikov additions of indoles to terminal aryl alkynes catalyzed by various metal-based catalysts or a main-group Lewis acid (LA), B(C₆F₅)₃, provides access to indole-adducts that bear a quaternary carbon center (Scheme 1a).6 Indium(III)-catalyzed reactions azides indoles between vinyl and also furnish bis(indolyl)methanes of this type (Scheme 1b).7 While highly useful, the products obtained from these processes have a structural restriction that one of the substituent at the quaternary center would always include a methyl group along with two indole moieties. Double-addition reactions of indoles to diverse ketones would have the potential to address this challenge. Condensation reactions between indoles and

ketones have been described through the use of various promotors including N-bromosuccinimide, iodine-based organocatalysts, and Brønsted acids;8 however, the scope of ketones or the functional group tolerance of the process have been rather unexplored. Recently, the photoinduced doubleadditions of N-H indoles to dialkyl or aryl(alkyl) ketones have been reported via the formation of a CF₃ radical from CF₃SO₂Na (Scheme 1c);9 while this process has allowed preparation of various bis(indolyl)methanes with quaternary carbon centers, the reactions with N-protected indoles or diaryl ketones have not been included. Given the prominence importance of bis(indolyl)compounds in medicinal chemistry,² we sought to develop an efficient process that occurs under mild conditions, with a broader range of ketones as well as indoles for the introduction of a diverse set of all-carbon quaternary centers to bis(indolyl)methanes.

| (a) Catalytic Markovnikov | addition of | f indoles to | alkyne |
|---------------------------|-------------|--------------|--------|
|---------------------------|-------------|--------------|--------|



Scheme 1. Strategies for the synthesis of bis(indolyl)methanes with all-carbon quaternary centers.

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Main group LAs such as boron and silicon-based LAs, which can efficiently promote activation of ketones and therefore facilitate nucleophilic additions,¹⁰ have been underexplored for the coupling reactions between indoles and ketones. In this report, we establish that $B(C_6F_5)_3$ and $PhSiCl_3$ can achieve the synthesis of bis(indolyl)methanes by the two-fold addition reactions of indoles to ketones. This process proceeds with a broad range of ketones, including dialkyl ketones, aryl(alkyl) ketones, and diaryl ketones. Bis(indolyl)compounds containing various all-carbon guaternary centers, such as a tetra-aryl carbon center, can be produced under mild conditions, releasing H₂O as the only by-product. Moreover, we present palladium-catalyzed, intramolecular transformations of bis(indolyl)methanes that generate useful bis(indole) derivatives, bis(indole)-fused aromatic polycyclics as well as bis(indolyl)alkenes.

Results and discussion

To develop a main group LA-catalyzed method for the double addition reaction of N-methylindole (1a) to ketones, we studied the effect of various LAs as catalysts on the yield of the reaction between 1a and acetophenone (2a) or benzophenone (2b) in toluene at 80 °C (Table 1; see Supporting Information for details). The condensation reactions did not proceed in the absence of a catalyst (entry 1). Boron Lewis acids could promote the double additions of indole 1a to ketones (entries 2-3); in particular, when the reactions were run with 10% $B(C_6F_5)_3$, bis(indolyl)methanes 3aa and 3ab bearing an all-carbon quaternary center were obtained in 96% and 45% yields respectively, after 16 h (entry 2). Whereas employing silanes, zinc-based LAs, and AlCl₃ for the coupling between indole 1a and acetophenone (2a) led to the formation of product 3aa in moderate to excellent yields, the use of such LAs as promoters resulted in low yields of the reaction with 2b to produce the tetra(aryl)methane (3ab) (entries 4-8). In general, the reactivity of 2a toward the addition of indoles (up to 99% yield with

 Table 1. Catalytic Double Additions of N-Methylindole to Ketones: Effect of Catalyst^a

| 1a (2 ec | Me Quiv) 2a, R = Me 2b, R = Ph | 10% LA toluene 80 °C, 16 h | Ph R N Me Baa, R = Me Bab, R = Ph |
|-----------------|--|-----------------------------------|---|
| entry | LA | 3aa yield (%) ^b | 3ab yield (%) ^b |
| 1 | none | <5 | <5 |
| 2 | B(C ₆ F ₅) ₃ | 96 (85) ^c | 45 |
| 3 | BF ₃ •Et ₂ O | 59 | 5 |
| 4 | SiCl ₄ | 44 | <5 |
| 5 | PhSiCl ₃ | 99 (93) ^c | 11 |
| 6 | ZnCl ₂ | 76 | <5 |
| 7 | Zn(OTf) ₂ | 62 | <5 |
| 8 | AICI ₃ | 80 | 15 |

^oReaction conditions: **1a** (2 equiv), **2** (0.05 mmol), and catalyst (0.1 equiv) in toluene (1 M) at 80 °C for 16 h. ^bDetermined by ¹H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. ^c Run for 3 h.



^{*a*}Reaction conditions: **1a** (2 equiv), **2** (0.20 mmol), and catalyst (0.1 equiv) in toluene (1 M) at 80 °C for 16 h; yield of the purified product. ^{*b*}10% B(C₆F₅)₃. ^{*c*}10% PhSiCl₃^{*d*}4 equiv of **1a**. ^{*e*}40°C.

 $B(C_6F_5)_3$ and $PhSiCl_3$ as LA promotors, entries 2 and 5) was higher than that of **2b**. Based on these outcomes, we chose $B(C_6F_5)_3$ and $PhSiCl_3$ as our LAs for the synthesis of a variety of bis(indolyl) compounds **3** by the reactions between indoles **1** and ketones **2**.

Under the LA-catalyzed conditions for the two-fold additions of N-methylindole (1a), an array of aryl(alkyl) ketones **2** reacted to furnish the corresponding bis(indolyl)methanes with an all-carbon quaternary center (Table 2); except for 3aa, 3ad, and 3ah products listed in Table 2 have not been synthesized previously via other methods. Not only acetophenone (2a) but also phenyl-substituted ketones bearing ethyl, trifluoromethyl, and difluoromethyl group as an alkyl substituent underwent the addition reactions, generating the addition products in good yields (3aa-3ae). The reactions of a range of methyl ketones with phenyl rings that bear acetoxy, hydroxy, and fluoro groups at the para-position (3af-3ai) and a chloro group at the ortho-position (3ai), as well as perfluorophenyl and 2-naphthyl groups (3aj and 3ak) proceeded smoothly under the double-addition conditions. The products could contain heteroaryl substituents such as 2-thienyl, 2-furyl, and 2-pyridyl moieties at the quaternary carbon center (3al-3an). Moreover, cyclic ketones reacted with 1a, yielding condensation products 3ao and 3ap.

The boron Lewis acid-catalyzed double-additions of *N*-methylindole (**1a**) can be applied to the generation of sterically encumbered tetra-arylmethanes (**3ab** and **3aq**) through the

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reactions with diaryl ketones **2b** or **2q** (Scheme 2a). Dialkyl ketones were also suitable substrates in our LA-catalyzed double additions of indoles (Scheme 2b and 2c). Employing acetone as a reaction solvent with $B(C_6F_5)_3$ as a catalyst resulted in affording bis(indole)-adduct **3ar**. Furthermore, ketones containing an ethyl group (**2s** and **2t**) were successfully coupled with **1a** under the silane-catalyzed conditions.

N-H indole and *N*-alkylindoles can be coupled with acetophenone (**2a**) by a Lewis acid catalyst (Scheme 3a). Whereas the reaction of *N*-H indole (**1b**) led to low yields of the corresponding bis(indolyl)compounds (**3ba**), *N*-alkyl-substituted indoles such as ethyl-, benzyl- and allyl-substituted substrates (**1c**-**1e**) reacted to create the corresponding bis(indolyl)methanes (**3ca**, **3da** and **3ea**) in good yields. In addition to the reactions of indoles, *N*-methylpyrrole (**1f**) underwent the catalytic double addition to **2a** in 97% yield of bis(pyrrolyl)methane **3fa** (Scheme 3b).

During the studies of our LA-catalyzed additions, we made observations that provided insights into the reaction mechanism. Alkene side-product **5** was formed along with 18% of bis(indolyl)methane **3ac** by the reaction between indole **1a** and ketone **2c**, likely resulting from the elimination of H₂O from the single-addition product, alcohol **4** (Scheme 4a).^{11,12} The





Scheme 4. Reactivity studies and a proposed catalytic pathway.

reaction of alkene **5** with **1a** produced <10% of bis(indolyl)methane **3ac**, indicating that alkene **5** is not a chemically and kinetically competent intermediate of the double addition process (Scheme 4b). Finally, the generation of compound **3'** by the dehydrative nucleophilic substitution¹³ of tertiary alcohol **4'** with **1a** in the presence of LA suggested the intermediacy of the alcohol in the LA-catalyzed synthesis of bis(indolyl)methanes (Scheme 4c).

Scheme 4d describes the possible catalytic pathway for the LA-catalyzed two-fold additions of indole 1 to ketone 2. A boron or silicon LA coordinates to ketone 2, and the nucleophilic attack of indole 1 to activated ketone A creates the carbon-carbon bond. The resulting zwitterionic species (B) then undergoes aromatization to provide the LA-coordinated alcohol intermediate (C), which can be captured by the second addition of indole 1 presumably by a S_N1 -type mechanism to furnish product 3, H_2O , and the LA catalyst.

The bis(indolyl)compounds with all-carbon quaternary centers that are generated in this condensation process can undergo intramolecular coupling reactions under Pd-catalyzed oxidative conditions, thereby affording bis(indole)-fused polycyclic compounds **6**, a motif found in natural products, pharmaceuticals as well as organic electroluminescent materials (Scheme 5a). ¹⁴ We also observed the generation of unexpected alkene products **7aa** and **7af**, which can potentially serve as valuable synthetic building blocks for the synthesis of bis(indole) derivatives.¹⁵ Alkenes **7** were likely formed by the rearrangement of the initially formed aromatic polycyclics **6**, as observed by ¹H NMR spectroscopy (Scheme 5b).¹⁶

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Scheme 5. Derivatization of the product: palladium-catalyzed, intramolecular oxidative coupling reactions

Conclusions

In conclusion, we have developed a main group, Lewis acidcatalyzed method for the double additions of indoles (and Nmethylpyrrole) to ketones to produce bis(indolyl)methanes containing an all-carbon quaternary center, a family of molecules that are prevalent in a broad range of natural products and biologically active compounds. This process proceeds through the formation of a tertiary alcohol as an intermediate and releases H₂O as the only by-product. The products obtained in this process can be derivatized into other important classes of bis(indole) derivatives, indole-fused aromatic polycyclics and bis(indolyl)alkenes.

Conflicts of interest

There are no conflicts to declare.

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- 16 The mechanism by which **6** forms bis(indolyl)-alkene **7** is not clear.

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