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New Versatile Route to the Synthesis of Tetrahydro-β-carbolines and Tetrahydro-pyrano[3,4-*b*]indoles via an Intramolecular Michael Addition Catalyzed by $InBr_3$

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Abstract: A simple multistep synthetic strategy to 4-substituted 1,2,3,4-tetrahydro-β-carboline and 1,3,4,9-tetrahydro-pyrano[3,4-*b*]indole derivatives starting from commercially available indole 2-carboxylic acid (**5**) is described. The final intramolecular Michael addition promoted by catalytic amount of $InBr_3$ (5−10 mol %) provided the expected polycyclic compounds in excellent yields (up to 97%) both in anhydrous organic and aqueous media.

The β-carboline skeleton is frequently encountered in pharmacology due to its activity in the CNS (central nervous system) at serotonin receptors. In particular, it shows prominent biological properties at the benzodiazepine receptor (BzR).[1] Here, the specific interactions of indolyl compounds containing the β-carboline framework with BzR are strongly influenced by the presence of substituents on the polycyclic central unit. Cook and co-workers[2] reported that the introduction of a methoxymethyl arm at the C-4 position (ZK 93423, **1**, Figure 1) remarkably amplifies the agonist activity of such compounds toward BzR. Common precursors of β-carboline derivatives are the 1,2,3,9-tetrahydro-β-carbolines (THBCs) that can be easily oxidized to the aromatic systems.[2b]

Although the construction of THBCs with substitution in positions 1−3 can be conveniently accomplished by adopting the Pictet−Spengler cyclization,[1] obtaining 4-functionalized tetrahydro-β-carbolines still remains more challenging, and multistep procedures are normally required. In this context, Busacca and co-workers recently described a useful approach for the preparation of 4-aryl, 4-alkyl, and 4-acetyl carboline derivatives via Pd-mediated cross-coupling of arylboronic acids and Grignard reagents to the 4-trifloxy-β-carboline.[3]

Analogously, 1,3,4,9-tetrahydro-4-functionalized-pyrano-[3,4-*b*]indoles are well-known potent analgesic agents and some 1-acetic acid derivatives, such as the pemedolac **2** (Figure 1), were tested as an antiinflammatory agent as

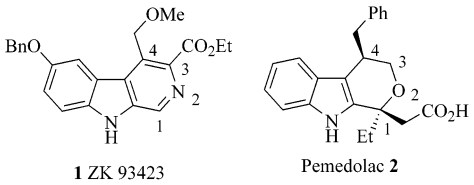
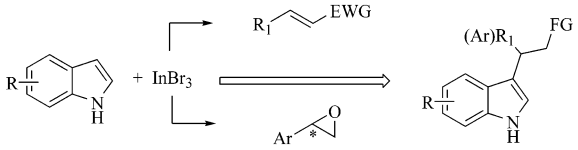


FIGURE 1. Examples of C-4-substituted indolyl-based analgesic agents.

SCHEME 1. Use of $InBr_3$ in Promoting Friedel−Crafts Alkylation of Indoles



well. Also in this case, the presence of substituents in the C-4 position is crucial to guarantee a high level of biological activity.[4,5]

In this contribution, we wish to describe our preliminary findings regarding a new valuable synthetic multistep alternative for the preparation of 4-functionalized tetrahydro-β-carbolines and their tetrahydro-pyranyl analogues by the use of inexpensive and commercially available indole 2-carboxylic acid **5** as the starting material.

We are currently engaged in developing catalytic Friedel−Crafts (FC) alkylation reactions of indoles with electrophilic carbon synthons in the presence of low loading of anhydrous $InBr_3$. In particular, due to the remarkable tolerance of indium salts toward water and strongly coordinating functional groups,[6] remarkable findings have been obtained in the 1−4 addition of indoles to arylcrotyl ketones,[7a] nitro alkenes,[7b] and indolyl enones[7c] and in the stereoselective ring-opening reaction of enantiomerically pure aryl epoxides (Scheme 1).[7d]

In light of these results, we reasoned that a valuable way to construct the carboline skeleton could involve a Lewis acid-catalyzed intramolecular cyclization of the appropriate ϵ-(2′-indolyl)-α,β-unsaturated carbonyl precursor **3** (Scheme 2). To the best of our knowledge, this kind of intramolecular ring-closing approach has never been considered in the synthesis of polycyclic indolyl alkaloids.

It is noteworthy that, although intramolecular FC cycloalkylations are well documented,[8] they usually suffer from moderate yields and lack of regioselectivity and

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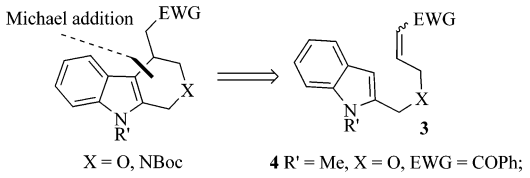
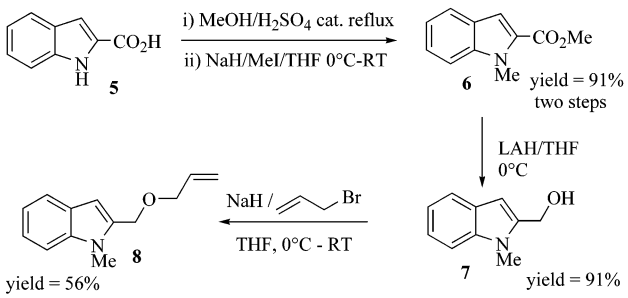
SCHEME 2. Retrosynthetic Approach for the Construction of Polycyclic Indolyl Alkaloids



SCHEME 3

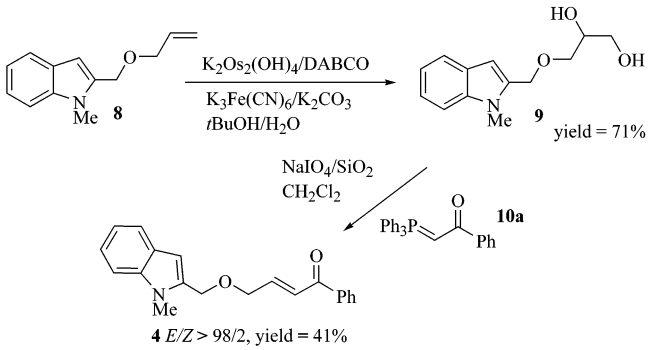


normally great amounts of Lewis acids are needed. On the contrary, $InBr_3$ was able to promote the present intramolecular FC-Michael type reaction in mild experimental conditions (rt, organic and aqueous media) in low catalytic amount (5−10 mol %) with high yield.

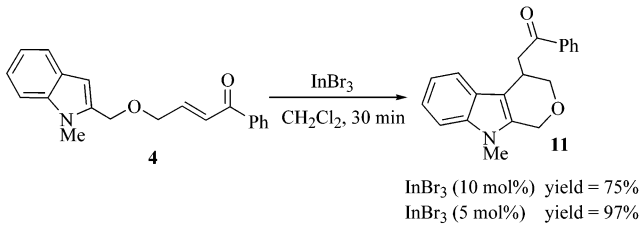
Synthesis of 4-Substituted 1,3,4,9-Tetrahydropyrano[3,4-*b*]indole. At the beginning of our study, we considered the preparation of 4-substituted 1,3,4,9-tetrahydro-pyrano[3,4-*b*]indoles. To this aim, we first took into account the retrosynthetic approach that allowed the synthesis of **4** (Scheme 2). Starting with multigram quantities of indole 2-carboxylic acid (**5**), after esterification of the carboxylic moiety with $MeOH/H_2SO_4$ (cat.) at reflux, the protection of *N*H proton was performed by methylation of the methyl ester (NaH/MeI/THF, 0 °C→rt) to give **6** in 91% overall chemical yield.[9] Finally, reduction of the ester moiety by LAH (THF, 0 °C, 91% yield)[10] and subsequent allylation of **7** (NaH/allyl bromide/THF, 0 °C→rt) led to the isolation of the desired allyl ether **8** in moderate yield 56% (Scheme 3).

Allyl ether **8** was then easily transformed in the racemic diol **9** (71% yield) via the described achiral variant of the AD reaction of Sharpless[11] in the presence of a catalytic amount (5 mol %) of $K_2OsO_2(OH)_4$ and DABCO as the ligand.[12] Finally, the desired indolyl enone **4** was synthesized solely as the (*E*)-isomer, by one-pot oxidative cleavage/Wittig reaction of the glycol **9** (41% yield, $E/Z > 98\%$).[13] For this purpose, **9** was treated with $NaIO_4$ on SiO_2 (20% weight) in CH_2Cl_2 for 20 h in the presence of the preformed ylide **10a** (Scheme 4).[14] The

SCHEME 4



SCHEME 5. Intramolecular Cyclization Catalyzed by $InBr_3$ for the Synthesis of Tetrahydro-pyranyl 11



one-pot two-step procedure avoided the manipulation of the corresponding indolyl-aldehyde that was difficult to handle due to its high sensitivity toward oxidation and thermal instability.

Initial attempts for the intramolecular cyclization were performed with 10 mol % $InBr_3$, and **11** was isolated in 75% yield (Scheme 5). Surprisingly, by carrying out the same reaction with a lower catalytic loading (5 mol %), the reaction was complete in a comparable reaction time, but the chemical isolated yield was significantly higher (97%). This result can be partially ascribed both to the concomitant intermolecular Michael addition and to undesired degrading processes of the α,β-unsaturated indolyl ketone observed with 10 mol % catalyst loading.

Synthesis of 4-Substituted Tetrahydro-β-carbolines. With the aim to optimize an analogous strategy for the synthesis of tetrahydro-β-carbolines, also starting from indole 2-carboxylic acid (**5**), we first prepared the corresponding indole 2-carboxy aldehyde **12** in two steps and in high isolated yield (91%).[15] Then, the *N*,*N*-diBoc-indolyl derivative **14b** was easily obtained in three steps without intermediate purification (Scheme 6). The optimized protocol involved the formation of the imine **13** by condensation of **12** with allylamine in toluene at reflux in the presence of $MgSO_4$, and then the reduction of **13** to the corresponding allylamine **14a** was accomplished with an excess of $NaBH_4$ in MeOH. Finally, the necessary protection of the nitrogen atoms was performed in dry CH_2Cl_2 with $(Boc)_2O$ and Et_3N. The overall yield of the last three steps was 65%.

Trying to adopt the same experimental conditions utilized for the pyranyl substrates, we discovered that the one-pot oxidative cleavage/Wittig reaction of **15** did not afford the desired indolyl enones **17** but the intermediate aldehyde **16**, which was isolable in pure form

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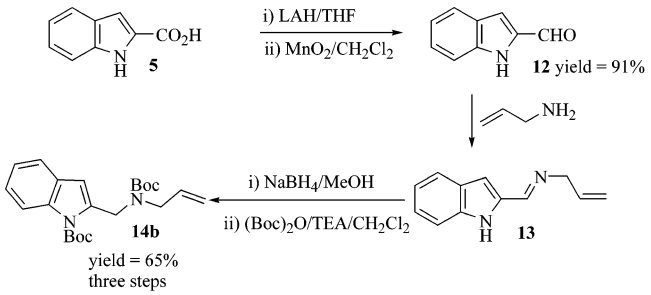
SCHEME 6



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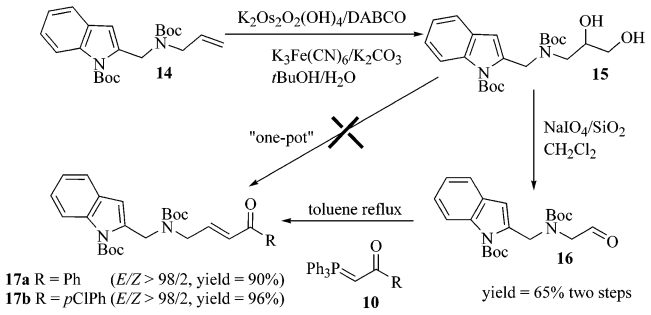
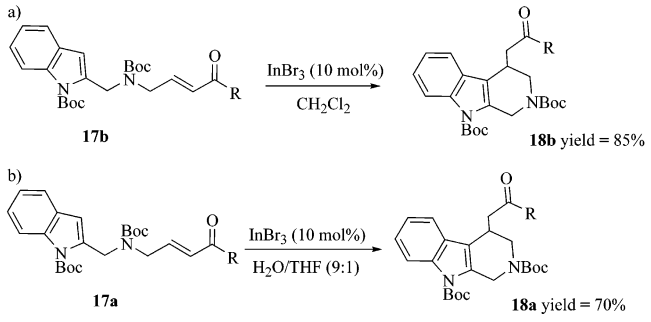


SCHEME 8. Intramolecular Cyclization Catalyzed by $InBr_3$ for the Synthesis of Tetrahydro-β-carbolines 18a,b



after flash chromatography (overall yield of two steps was 65% on the basis on **14b**). The Wittig reaction was then performed in dry toluene at reflux with ylides **10a**,**b**, affording the desired products **17a**,**b** in 90 and 96% yields, respectively (Scheme 7).

Furthermore, we screened several reaction conditions for the indium-catalyzed intramolecular cyclization of **18a**,**b**. We found that in the presence of 10 mol % indium tribromide, the enone **17b** ($InBr_3$, 10 mol %) underwent cyclization, affording the protected 1,2,3,4-tetrahydro-β-carboline **18b** in high yield (85%, Scheme 8a). The lower yield recorded with **18b** in comparison to **11** (97%, 5 mol % $InBr_3$) could be ascribed to the different type of substituents present on the indolyl nitrogens of the two precursors **4** and **17b**. In fact, while the electron-donating methyl group increases the nucleophilicity of the indole ring, the electron-withdrawing *t*Bu-carbonate function present in **17b** reduces the reactivity of the indolyl system toward the intramolecular FC transformation.

Organic reactions that involve Lewis acid catalysis must be usually carried out under strictly anhydrous conditions to prevent the deactivation/degradation of the catalyst. In this context, Lewis acid-promoted FC reactions are normally identified as moisture-sensitive processes. On the other hand, due to the large number of potential advantages of replacing organic solvents with water (safety, costs, environmental factors), growing interest has continuously been devoted toward the development of water tolerant organic transformations.[16] In(III) salts that are indicated as "Borderline" Lewis acids in aqueous conditions and have been frequently utilized to promote organic transformations in the presence of water.[17] On the basis of these considerations, we tested the effectiveness of $InBr_3$ (10 mol %) in promoting the intra-FC reaction of **17b** in aqueous/cosolvent system (H_2O/THF 9:1, 0.017 M). Under these conditions, the reaction effectively occurred at room temperature, affording **18a** in 70% in 12 h reaction time (Scheme 8b).

In summary, this paper describes a new and efficient protocol for the synthesis of a variety of 1,3,4,9-tetrahydro-pyrano[3,4-*b*]indoles and 1,2,3,4-tetrahydro-β-carbolines. This strategy, starting from commercially available and inexpensive indole-2-carboxylic acid, uses as the key final step an intramolecular cyclization by Michael addition utilizing low catalytic loadings of $InBr_3$. This approach furnished good ring-closing results also by carrying out final cyclization in aqueous media. Studies addressed toward the optimization of a stereoselective version of the present synthetic strategy are under investigation in our laboratories.

Experimental Section

General. Chemical shifts of the ^{1}H NMR spectra are given in δ parts per million with respect to TMS, and coupling constants J are measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = douplet, t = triplet, q = quartet, br = broad, m = multiplet). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ = 77.0 ppm). Flash column chromatographies were run over 270−400 mesh silica gel. Elemental analyses were carried out by using a CHNOS analyzer. IR analyses were performed with a FT-IR spectrophotometer. IR spectra of neat compounds are expressed by wavenumber (cm^{-1}). The melting points were uncorrected. All the commercials were utilized as received.

Typical Experimental Procedure for the Catalytic Intramolecular Michael Reaction of 4 Mediated by $InBr_3$. A flamed two-necked flask was charged, under a nitrogen atmosphere, with 6 mL of anhydrous CH_2Cl_2, $InBr_3$ (1.8 mg, 0.005 mmol), and 31 mg (0.1 mmol) of indolyl enone **4**. The color of the mixture immediately turned from pale yellow to deep red. After 30 min of stirring at room temperature, the initial enone completely disappeared (checked by TLC). The reaction was then quenched with a saturated solution of $NaHCO_3$ (3 mL) and extracted with Et_2O (3 × 3 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure, and the crude mixture was purified by flash chromatography.

2-(9-Methyl-1,3,4,9-tetrahydro-pyrano[3,4-*b*]indol-4-yl)-1-phenyl-ethanone (11). Yellow oil. Yield: 97%. MW = 305.37. R_f: 0.3 (cyclohexane/Et_2O 60:40). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.0 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 2 H); 7.42−7.62 (m, 4 H); 7.08−7.4 (m, 3 H); 4.90−4.97 (m, 1 H); 4.80 (dd, J_1 = 1.4 Hz, J_2 = 14.6 Hz, 1 H); 4.12 (dd, J_1 = 1.8 Hz, J_2 = 11.4 Hz, 1 H); 3.93 (dd, J_1 = 3.0 Hz, J_2 = 8.8 Hz, 1 H); 3.70−3.80 (m, 1 H); 3.63 (s,

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3 H); 3.47−3.52 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4; 137.2; 133.3; 133.1; 128.5; 128.1; 121.3; 119.3; 118.1; 109.6; 108.9; 69.6; 63.2; 41.8; 30.9; 29.7; 29.5; 28.7. IR (neat): 3045; 2926; 2846; 1739; 1666; 1600; 1461; 1374; 1242; 1082; 1036; 738 cm^{-1}. Anal. Calcd for ($C_{20}H_{19}NO_2$): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.62; H, 6.22; N, 4.58.

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Supporting Information Available: Experimental procedures and analytical and spectral characterization data for all the indole compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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