Total Synthesis of Indoles from *Tricholoma* Species via Bartoli/Heteroaryl Radical Methodologies

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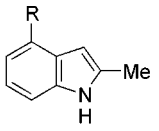
Introduction

The Bartoli indole synthesis is the treatment of an ortho-substituted nitro-aromatic compound with 3 equiv of vinylmagnesium bromide to give the 7-substituted indole,[1,2] and this method has rapidly become the shortest and most flexible synthesis for indoles of this substitution pattern.[1−5] We have recently reported an extension to this methodology, suggesting that it may not be limited exclusively to the synthesis of 7-substituted indoles but that modest yields of other substitution patterns may also be obtained via this methodology.[6] However, there is no doubt that the best yields are obtained when the nitro-aromatic compound possesses an ortho substituent, enforcing selectivity in the 3,3-sigmatropic rearrangement and subsequent cyclization step. This ortho substituent is, of course, undesirable in the synthesis of many indoles when a Bartoli approach may be advantageous.

We have also been interested in the generation and use of heteroaryl free radicals for some time now and have reported the radical reactions and cyclizations of indoles bearing halogen substituents at both the 2- and 7-positions.[3,7,8]

We envisaged a combination of these two methodologies, whereby a range of *o*-bromonitrobenzenes are treated under Bartoli conditions with various vinyl Grignard reagents (using the *o*-bromine atom to direct the cyclization) and then subsequently reduced using the heteroaryl radical methodology to replace the halogen and give a 7-unsubstituted indole, i.e., effectively using the bromine as a labile protecting group (Scheme 1). This method could give a significant reduction in the number of steps required for the synthesis of many complex indoles and also offers the advantage that many functionalities are tolerant to radical-generating conditions without the need for protection.

To test the power of this methodology, we imagined using this approach in a short and efficient synthesis of 2,4-dimethylindole **1**, 4-(hydroxymethyl)-2-methylindole **2**, and 4-(methoxymethyl)-2-methylindole **3**, three alkaloids that have recently been isolated from two species of European Basidomycetes (*Tricholoma virgatum* and *Tricholoma sciodes*).[9]



1 R = Me
2 CH_2OH
3 CH_2OMe

Results and Discussion

A number of model reactions were first performed to examine the scope of the proposed reaction sequence. The Bartoli reaction of *o*-bromonitrobenzene with three simple vinyl Grignard reagents proceeded well and in yields comparable and consistent with previously reported values (Table 1, entries A−C).[1,2,6] The introduction of and variation in the substituent on the vinyl Grignard reagent seemed to have little effect on the indole synthesis. This is of particular interest when employing a cyclic vinyl Grignard reagent 1-cyclohexenylmagnesium bromide (Table 1, entry D) where the immediate product formed is a carbazole derivative, 8-bromo-2,3,4,9-tetrahydro-1*H*-carbazole (and this is probably the shortest synthesis to date of this class of compound). Even more heavily substituted nitroarenes (Table 1, entries E and F) still gave pleasing yields under the Bartoli reaction conditions. Thus, the Bartoli reaction represents a rapid route to a range of complex 7-bromo-substituted indoles.

The second stage in the proposed sequence was the radical reduction of the newly synthesized 7-bromoindoles to give the 7-unsubstituted indoles. This reaction was investigated using all the 7-bromoindoles prepared. First was the reduction of 7-bromoindole with tributyltin hydride under standard conditions (1.2 equiv of tributyltin hydride (compared to 7-bromoindole) and AIBN as initiator in toluene at 110 °C) to give the parent compound, indole. It was pleasing to find that the reaction proceeded in near-quantitative yields (Table 1, entry A). Therefore, these conditions were employed for all subsequent reductions. No evidence of intermolecular radical combination or addition between indoles was observed, irrespective of dilution or concentration of the reactants, suggesting that these reductions are proceeding very rapidly (and in a manner consistent with our previously reported results[3]). Almost identical results were obtained with all the substrates, including a double reduction of 7-bromo-4-bromomethylindole (Table 1, entry F).

Therefore, the combination of these two methods—a Bartoli reaction using *o*-bromonitrobenzenes followed by radical reduction—represents a rapid and very easy route to a range of indoles of varying substitution pattern.

Encouraged by these results, our attention was turned to employing the method to the synthesis of various

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(1) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129−2132.
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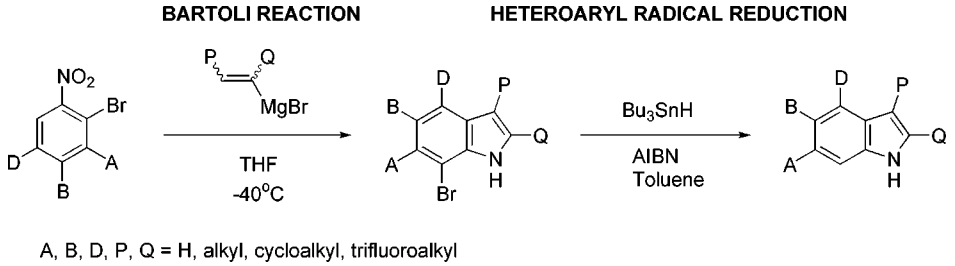
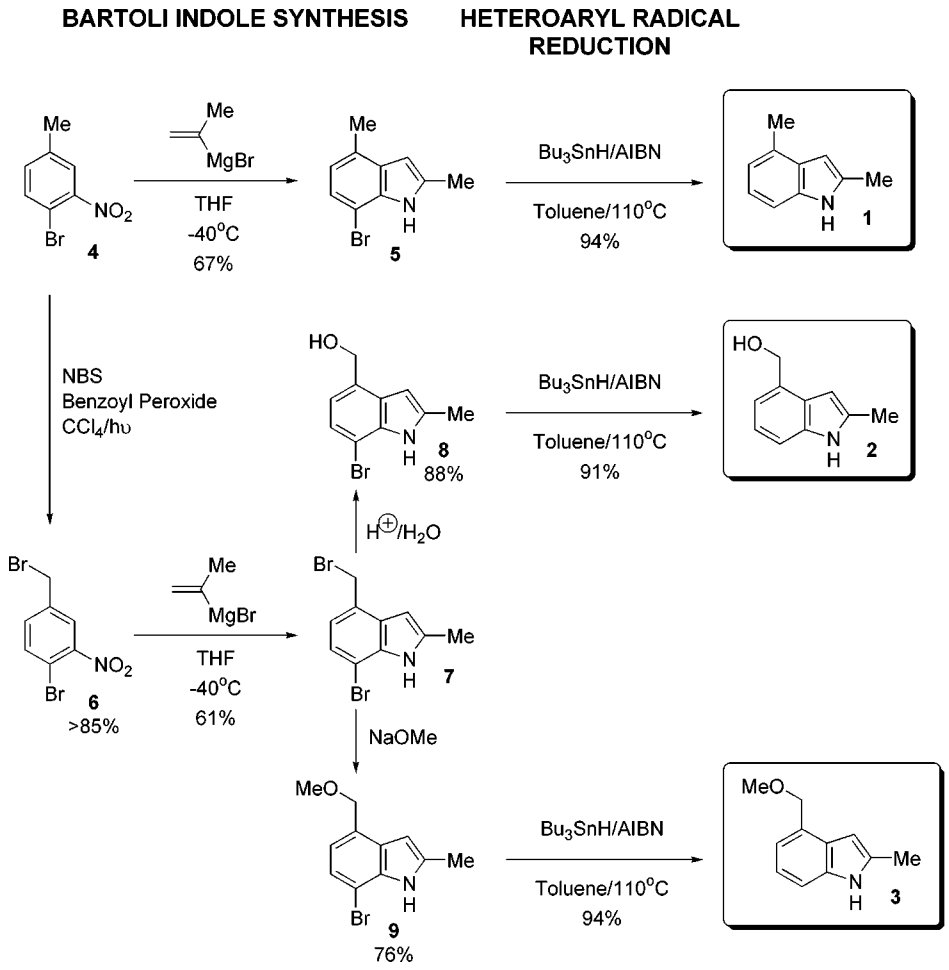
Scheme 1



Scheme 2



indole alkaloids from the *Tricholoma* species. The Bartoli method has recently been used in two total syntheses: by Harrowven in the synthesis of hippadine[10] and Blechert in the synthesis of (±)-*cis*-trikentrin A.[11] To test the power and scope of our methodology, it was envisaged as being used in the total synthesis of 2,4-dimethylindole **1**, 4-(hydroxymethyl)-2-methylindole **2** and 4-(methoxymethyl)-2-methylindole **3**, alkaloids that have recently been isolated[9] from two species of European Basidomycetes (*Tricholoma virgatum* and *Tricholoma sciodes*).[12] The synthesis of **1** also constitutes a total synthesis of the two biindolones peronatin A and B (isolated[13] from damaged fruiting bodies of *Collybia peronata* and *Tricholoma scalpturum*[12,13]) since this has shown to be the key intermediate in a biomimetic synthesis of peronatin A and B.[13]

We chose 4-bromo-3-nitrotoluene **4** as a common starting material for all three alkaloids (Scheme 2). The direct reaction of this with isopropenylmagnesium bromide under the standard Bartoli reaction conditions yielded 2,4-dimethyl-7-bromoindole in a pleasing 67% yield. This is in sharp contrast to a previously reported failed attempt to synthesize these alkaloids employing a Bartoli reaction between isopropenylmagnesium bromide and 4-methyl-2-nitroanisole.[13] As with the test reactions, radical reduction proceeded almost quantitatively (94%) to give the first of the alkaloids, 2,4-dimethylindole **1** in overall 62% yield. Radical benzylic bromination of 4-bromo-3-nitrotoluene gave 4-bromo-3-nitro-1-bromomethylbenzene **6** in excellent yields (consistently >85%). This substrate was then subjected to the Bartoli reaction,

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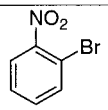
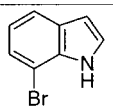
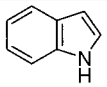
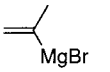
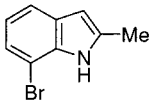
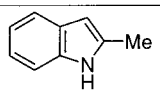
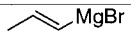
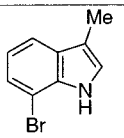
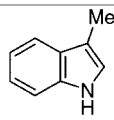
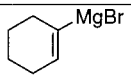
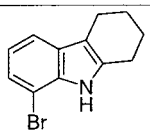
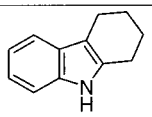
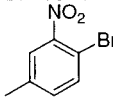
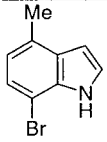
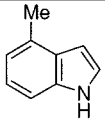
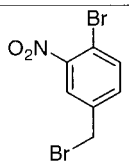
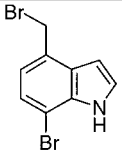
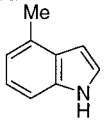
Table 1. Results for the Bartoli Reaction and Subsequent Radical Reduction for a Range of Nitroarenes and Grignard Reagents

	BARTOLI REACTION				HETEROARYL RADICAL REDUCTION		
	Nitroaromatic Compound	Grignard reagent	%Yield of 7-Bromoindole		Radical Reduction Conditions	%Yield Indole	
A				65	Bu_3SnH (1.2 eq) AIBN Toluene		92
B	"			62	"		89
C	"			63	"		86
D	"			43	"		81
E				59	"		89
F				48	"		80

again employing isopropenylmagnesium bromide, to give 7-bromo-4-(bromomethyl)-2-methylindole **7** in good yield (61%). It was at this point that the two syntheses became divergent. Reaction of **7** with water (under acidic conditions) gave 7-bromo-4-(hydroxymethyl)-2-methylindole **8** in high yields (88%) and this was then converted to the alkaloid **2** by radical reduction (91%) without the need for protection or manipulation of the side chain hydroxyl function (overall yield of **2** 41% from **4**). Alternatively from **7**, treatment with sodium methoxide gave 7-bromo-4-(methoxymethyl)-2-methylindole **9** in good yields (76%) and this again was reduced almost quantitatively using tributyltin hydride (94%) to give the final alkaloid **3** in 37% overall yield.

In conclusion, the total synthesis of three indole alkaloids has been achieved employing a Bartoli synthesis/heteroaryl radical approach. Further applications of this synthetic sequence are currently being explored.

Experimental Section

Representative Procedure for Bartoli Reaction. The nitroaromatic compound (5 mmol) was placed in a two-necked round-bottomed flask fitted with a gas inlet (argon) and rubber septum. The flask was purged several times with argon before

adding dry THF (35−40 mL) and cooling to between −40 and −45 °C. The Grignard reagent (3 equiv, 15 mmol) was then added rapidly in one portion to the THF solution and stirring continued for a further 30 min to 1 h (exact length of time had no effect on yield). Saturated ammonium chloride solution was added to the reaction mixture (at ca. −40 °C) before allowing the mixture to warm to room temperature. The mixture was thoroughly extracted with diethyl ether (2 × 200 mL), the ether extracts combined and thoroughly washed with further ammonium chloride (300 mL), water (300 mL), and brine (300 mL) before drying ($MgSO_4$) and concentrating in vacuo to give a dark brown gum, which was purified by flash column chromatography (hexane/ethyl acetate 9:1) to give the *title compound*. Known compounds were in good agreement with literature data; new compounds gave satisfactory spectroscopic and analytical data.

Representative Procedure for Heteroaryl Radical Reduction Reaction.[3] Tributyltin hydride (1.2 equiv, 3.6 mmol) was added to a solution of the 7-bromoindole derivative (3 mmol) in dry deoxygenated toluene (25 mL) under argon, and after the mixture was heated to 110 °C, AIBN (a few crystals, ca. 10 mg) was added and the mixture continued to be heated under reflux for 12 h. After cooling, the toluene was removed under reduced pressure and the residue taken up in diethyl ether (200 mL), which was then washed with 20% aqueous ammonia solution (4 × 200 mL) and water (200 mL) and dried (magnesium sulfate) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (hexane, followed by hexane/ethyl acetate 9:1) to yield the product, either as a white solid or a pale yellow oil, depending on the compound. All compounds were in good agreement with literature data; new compounds gave satisfactory spectroscopic and analytical data. The three natural products **1**, **2**, and **3** were all in good agreement with previously reported data.[9,12,13]

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