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INTRAMOLECULAR RADICAL CYCLIZATION REACTIONS. AN APPROACH TO THE INDOLE ALKALOIDS

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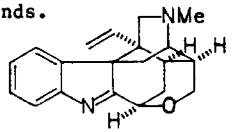
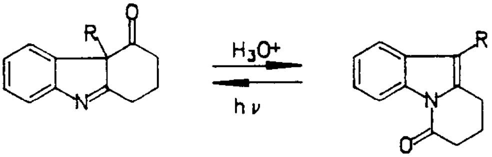
Abstract: The intramolecular radical cyclization reaction of N-allyl substituted derivatives of o-bromoacetanilide provides a short and effective route to a variety of dihydroindole systems.

In connection with our work on the synthesis of the Chinese medicinal alkaloid koumine (1)[1] we required a synthesis of the 4-keto-11-alkyltetrahydrocarbazolenine ring system 2. Previous attempts to prepare this system via acid catalyzed Fischer Indole synthesis were unsuccessful.[2] Under the conditions of the Fischer Indole reaction, the desired product undergoes acid catalyzed ring opening to a carboxylic acid and subsequent lactam formation (2→3). Interestingly, the lactam 3 is convertible back to the desired carbazolenine 2 by photochemical means although in poor yield.[3] Consequently, we have initiated an investigation of the radical mediated arylation reaction (4→5) as a means for preparation of these compounds.



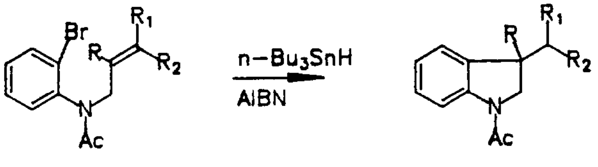
1



2 3

4 5

Radical cyclization reactions have received a significant amount of attention in recent years.[4] The literature is abundant in examples of intramolecular radical induced cyclizations for the preparation of carbocycles[5] and heterocycles[6], often with good stereochemical control. Free radical arylation reactions are less widely published but show considerable promise for the preparation of benzofuran and dihydrobenzofuran systems.[7] Relatively little attention, however, has been given to preparation of the indole and dihydroindole ring systems by this method.[8] We present here a fast and efficient method for the preparation of dihydroindoles 7 from the corresponding allyl amides 6.



6 R = H, Alkyl 7

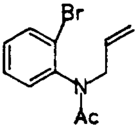
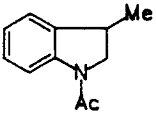
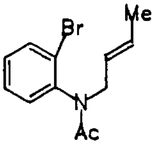
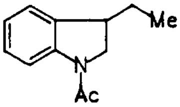
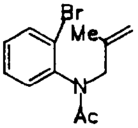
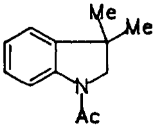
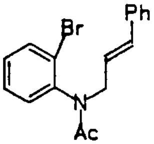
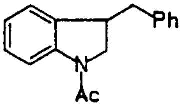
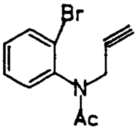
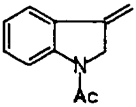
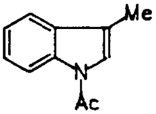
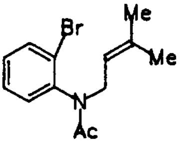
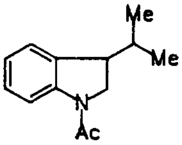
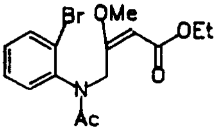
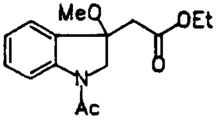
All cyclizations were carried out in refluxing benzene with 1.2 molar equivalents of n-Bu_3SnH and AIBN as catalyst. Workup simply entailed evaporation of the solvent. Facile separation of the tin byproducts was achieved by flash chromatography to afford cyclized products 7 in 81-99% yield [9] (Table 1). The following general procedure is given for the preparation of the allyl amides 6 and dihydroindoles 7. o-Bromoacetanilide was prepared by the usual procedure from o-bromoaniline[10], pyridine and acetic anhydride.

Preparation of Allyl Amides 6. o-Bromoacetanilide (10 mmol) was added to a stirred suspension of KH (30%, 1.33 g) in dry THF (75 ml) under nitrogen at -78 °C. Stirring was continued until a clear solution was obtained. The allyl halide (10 mmol) was then added and stirring was continued at -78 °C for 30 min and at room temperature for 8 h. The reaction mixture was poured into water (250 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford crude 6. The products were chromatographed on silica gel (hexane: ethyl acetate, 2:1) to provide allyl amides 6 in 73-95% yield).

Preparation of Dihydroindoles 7. To a refluxing solution of allyl amide 6 (1 mmol) and AIBN (10 mg) in dry benzene (80 ml) was added a solution of n-Bu_3SnH (1.2 mmol) in dry benzene (20 ml) over 30 min. The resulting mixture was heated at reflux for 1 h and the solvent was removed at reduced pressure. Chromatography on silica gel (hexane: ethyl aetate, 2:1) provided dihydroindoles 7 in 81-99% yield.

Thus far the range of products available by the radical cyclization procedure include 3-monosubstituted and 3,3-disubstituted dihydroindoles (entry 1-4 and 6-7), 3-alkoxy-3-alkyl

TABLE I

ENTRY		YIELD/mp		YIELD/mp
1		92% -		91% 75-76°C
2		-		93% 78-79°C
3		82% -		93% 98-99°C
4		89% 75-76°C		92% 113-114°C
5		95% 45-47°C	 and 	99% mixture
6		84% -		93% 85-86°C
7		73% 86-88°C		81% 95-96°C

dihydroindoles (entry 7) and dihydroindole systems with an exomethylene substituent at the 3 position (entry 5). In conclusion the radical cyclization reaction of N-allyl substituted o-bromoacetanilide derivatives provides a short and effective means for the preparation of a variety of dihydroindole systems.

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9. All products gave spectral data (^{1}H NMR, IR, and MS) which was consistent with the assigned structures. Satisfactory combustion analyses were obtained for all new products.
10. Aldrich Chemical Co.

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