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Synthesis of the 4-arylindole portion of the antitumor agent diazonamide and related studies

Fiona Chan, Philip Magnus * and Edward G. McIver

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

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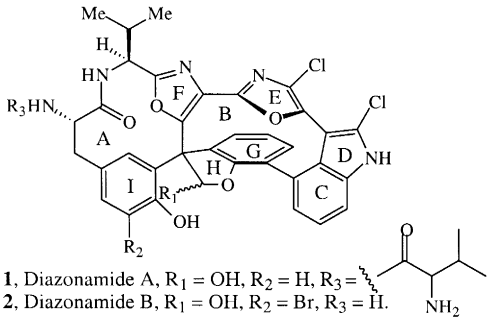
Abstract

The synthesis of **6** comprising the CDG rings of the diazonamides was achieved in an overall yield of 75% from commercially available **3**.

In the preceding letter we have described the synthesis of the CDEF-rings of the diazonamide A, **1** and diazonamide B, **2** (Scheme 1).[1,2] While the synthesis of the 4-arylindole portion comprising the CDG-rings has been reported,[3] the yields for the formation of the 4-aryl bond is frequently low. Consequently, we decided to examine the formation of the 4-arylindole using the Suzuki cross coupling reaction[4] both before and after the construction of the indole portion.



1, Diazonamide A, R_1 = OH, R_2 = H, R_3 =
2, Diazonamide B, R_1 = OH, R_2 = Br, R_3 = H.

Scheme 1.

4-Bromoindole **5**[5] was synthesized from **3** using the Leimgruber–Batcho methodology via the enamine **4** (Scheme 2).[6] Suzuki coupling of **5** with 2-methoxyphenyl boronic acid gave **6** in an optimized 48% yield. Whereas, reversing the sequence and conducting the Suzuki coupling first, gave **7** in 98% yield. Exposure of **7** to the Leimgruber–Batcho reaction conditions gave **6** (76% from **7**).[7]

* Corresponding author.

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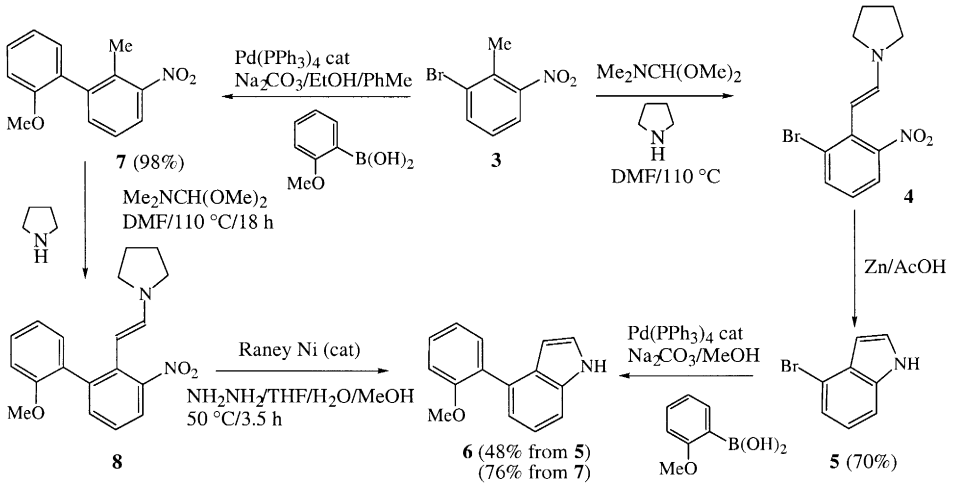
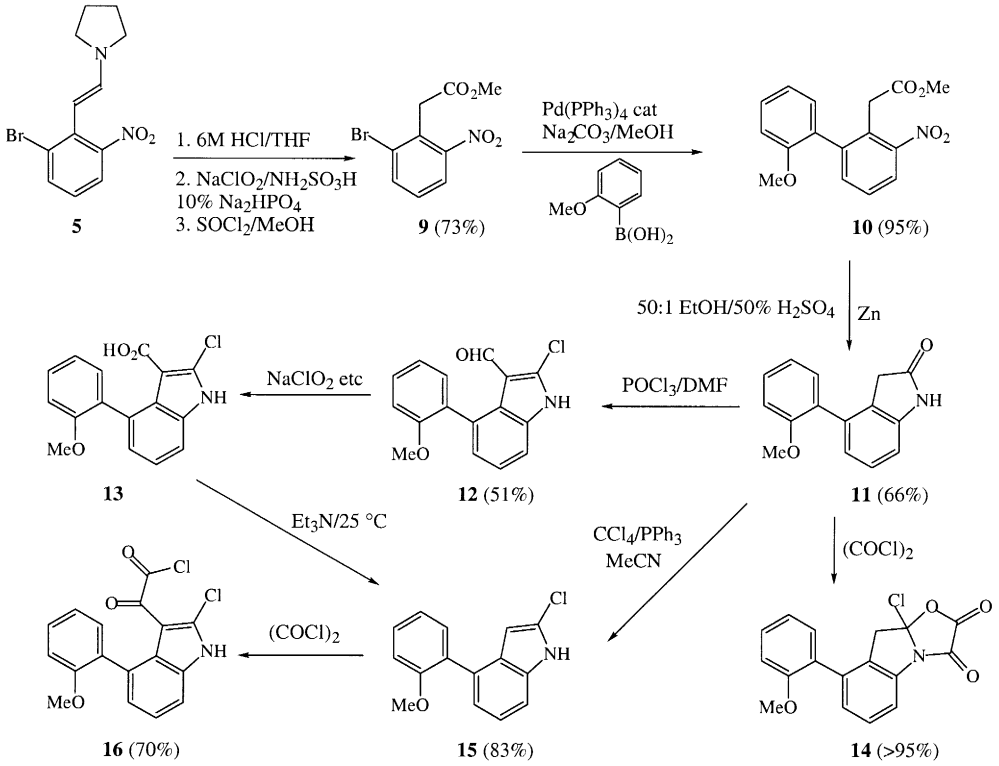


Scheme 2.

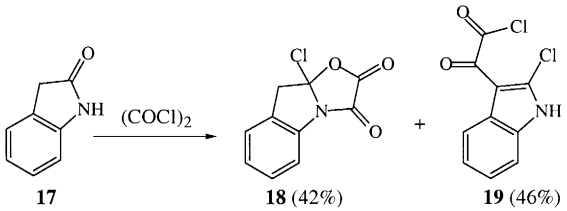
We have also explored the synthesis of the 4-aryl-2-oxindole **11**, which should allow the introduction of the 2-chloro substituent. Acid hydrolysis of **5** followed by sodium chlorite oxidation[8] and esterification gave **9** (Scheme 3). Suzuki coupling of **9**, as for **3**, gave **10** (95%), which was reduced with $Zn/EtOH/H_2SO_4$ to give the 2-oxindole **11**.



Scheme 3.

While it has been reported that 2-oxindole **17** on treatment with oxalyl chloride/CH_2Cl_2/25°C gave **19** (92%) (Eq. (1)),[9] we found that this procedure converted **11** into the oxamide derivative

14 (>95%). Repeating the literature example, we found that treatment of 2-oxindole **17** with oxalyl chloride/CH_2Cl_2/25°C gave a precipitate of **19** (46%) and the filtrate contained **18** (42%). This result is more in keeping with other observations concerning the reactions of oxalyl chloride and amides.[10] Consequently, we examined alternative ways to introduce the 2-chloro and a carbon substituent at C3 into the 2-oxindole **11**.



17 **18** (42%) **19** (46%) (1)

Treatment of **11** with $POCl_3$/DMF (Vilsmeier reagent) gave the aldehyde **12**.[11] Oxidation of **12** using the chlorite procedure gave the acid **13**, which, somewhat surprisingly, underwent decarboxylation at 25°C when treated with Et_3N/CH_2Cl_2 to give **15**. Since the yield of **12** was rather modest (51%), and the acid **13** could not be readily activated without concomitant decarboxylation, it was decided to attempt to convert **11** directly into **15**. While standard methods for converting amides into iminochlorides have been used to transform 2-oxindoles into 2-chloroindoles,[12] the yields are low and dimeric by-products are formed. Indeed, treatment of **11** with $POCl_3/CH_2Cl_2$ gave a complex mixture of products with only traces of **15** present. It was found that treatment of **11** with CCl_4/PPh_3/MeCN under scrupulously anhydrous reaction conditions using freshly purified reagents and solvent gave a pale yellow solution from which **15** (83%) could be isolated. Without these precautions the reaction mixture turned black, and the yield of **15** was very low.

With a practical synthesis of the 2-chloroindole **15** available we now could examine its conversion into **16**, which had eluded us above. Exposure of **15** to $(COCl)_2/CH_2Cl_2$ at 25°C gave **16** in 70% yield, illustrating that the problem in the conversion of **11** into **16** in a single step is the formation of the 2-chloroindole **15**. While we were able to carry out some potentially useful reactions on **16**, the 2-chloro substituent caused a number of problems, and therefore we decided to introduce the chlorine atoms after the formation of the oxazole rings rather than before. The successful outcome of this strategy is described in the accompanying letter.

Acknowledgements

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