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Aryl Radical Cyclisation Approach to Highly Substituted Oxindoles Related to Mitomycins

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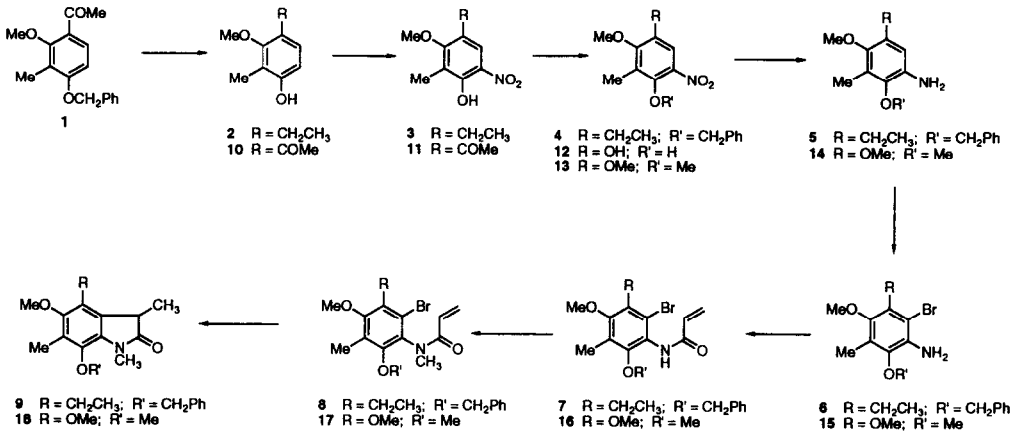
Abstract: *Radical cyclisation of the hexa-substituted aromatic compounds **8** and **17** leads to highly substituted oxindoles **9** and **18** respectively in excellent yields. Oxindole **18** carries the correct substitution pattern for ring-A of mitomycin A.*

The mitomycins represent an important and challenging group of natural products for the synthetic chemist and despite much effort, there have been only a limited number of total syntheses in this area[1]. In 1988, Raphael disclosed an attempted approach to the mitomycins which was designed to proceed via an oxindole followed by nucleophilic attack on the oxindole carbonyl group using an acetylene anion to create ring-C[2]. Although a substituted oxindole was prepared, the nucleophilic addition step failed. Our own interest in the preparation and use of oxindoles in natural product synthesis led us to investigate this latter problem and we have recently described both the intra- and intermolecular addition of alkyl- and vinyllithiums to the oxindole to open up the route to the pyrroloindolenine ring system[3]. We now wish to report the extension of our radical cyclisation approach to oxindoles[4] to prepare fully substituted oxindoles as potential precursors to the A and B rings of mitomycins.

The tetrasubstituted acetophenone derivative **1** is readily available on a large scale from 2-methylresorcinol in 3 steps[2]. Catalytic hydrogenation in ethanol over palladium on charcoal catalyst for 3 days gave a quantitative yield of the phenol **2** (mp. 132°C) which had also undergone benzylic reduction. Nitration of **2** using conc. nitric acid in acetic acid gave nitrophenol **3** (mp. 34°C) in 86% yield. Benzylation of **3** proceeded with no complications using benzyl bromide and potassium carbonate in refluxing acetone to give **4** (mp. 42°C) in 84% yield. The next step involved introduction of a bromine atom at the remaining position on the benzene ring in order to set the scene for an aryl radical cyclisation. In spite of the number of activating groups, electrophilic bromination of **4** proved impossible. Treatment with bromine in dichloromethane gave rise to benzylic bromination at the ethyl group instead. However, reduction of the nitro group in **4** using tin II chloride[5] gave **5** in 99% yield which reacted with bromine in acetic acid to give **6** in 54% yield. This yield was improved to 92% using pyridinium hydrobromide perbromide[6] as the brominating agent. Conversion of **6** to the radical cyclisation precursor was uneventful. Acylation of 6 with acryloyl chloride gave **7** (mp. 163°C) in 96% yield and N-methylation using KH and MeI in THF gave **8** in 90% yield after chromatography. Cyclisation of **8** using Bu_3SnH in refluxing toluene with AIBN as initiator at a concentration of 0.012 M gave



the oxindole **9** as a white crystalline solid (mp. 113°C) in 76% yield. Although we have previously reported aryl radical cyclisations on systems carrying a single methoxy substituent[4b], it was pleasing to find that the presence of a large number of substituents on the aromatic ring does not impede the desired bond formation[7].

Having shown that this approach is suitable for the synthesis of highly substituted oxindoles, we next turned our attention to the preparation of an oxindole carrying the correct substitution pattern in the aromatic ring for mitomycin A but with the quinone functionality protected. Catalytic hydrogenolysis of **1** for 2 hours led to deprotection of the benzyl ether without reduction of the methyl ketone and **10** (mp. 130°C) was isolated in 84% yield. Nitration as before gave nitrobenzene derivative **11** (mp. 70°C) which was submitted to Baeyer-Villiger oxidation with MCPBA to give dihydroquinone **12** (mp. 135°C) in overall 70% yield. Although the bis-MOM ether of **12** was prepared, the MOM ethers gave considerable problems in subsequent steps and so **12** was simply methylated under standard conditions to give **13** in 98% yield. Reduction of **13** to the aniline derivative **14** was achieved by catalytic hydrogenation over Pd in 96% yield. Bromination as before proceeded in 70% yield to give **15** which was acylated and N-methylated as for **6** leading to radical cyclisation substrate **17** in 54% yield. Radical cyclisation occurred uneventfully to give the highly substituted oxindole **18** in 98% yield. Similar aromatic systems have been oxidised to the quinone required for the ring A of mitomycin A[8].

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