Intramolecular Alkyllithium Additions to Lactams; a Synthesis of 2,3,9,9a-Tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles (Pyrrolo[1,2-*a*]indolenines) Related to Mitomycins

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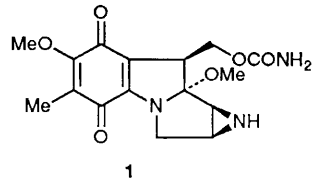
Cyclisation of **5**, **8**, **10a** and **10b** *via* their lithium derivatives followed by *in situ* reduction with lithium aluminium hydride gives pyrroloindolenines **2** and **9** and pyridinoindolenines **11a** and **11b**, respectively.

The mitomycins have attracted a great deal of synthetic interest since their isolation, culminating in Kishi's synthesis of mitomycin A **1**.[1] Much of this attention has been focused on the preparation of the core ring system common to all the mitomycins, namely the pyrrolo[1,2-*a*]indolenine system.[2] An attractive strategy for the synthesis of the pyrrolo[1,2-*a*]-indolenine skeleton **2** is to form the final C-ring from an oxindole utilising a nucleophilic attack on the lactam carbonyl as the key reaction (Scheme 1). Recently, Raphael described an approach to the mitomycins based on the intermolecular attack of an acetylene anion on the oxindole carbonyl group.[3] Unfortunately, this reaction failed. We have been interested for a number of years in the preparation and use of oxindoles in synthesis[4] and we wish to describe a short synthesis of the mitomycin model compounds **2** and **9** utilising the intramolecular addition of an organometallic nucleophile to the oxindole carbonyl.

We have recently demonstrated that cyclisation from the 3-position of an alkyl- or vinyllithium (prepared *in situ*) onto the carbonyl group of an oxindole followed by reduction with $LiAlH_4$ gives hexahydrocarbazoles in good yield.[5] Initially, we believed that the 5-*exo*-trig cyclisation of an *N*-3-lithiopropyl chain onto the oxindole would prove troublesome because the planarity of the amide nitrogen would prevent approach by the organolithium at the stereoelectronically-preferred angle.[6] Debenzylation of 1-benzyl-3,3-dimethyloxindole **3** using sodium in liquid ammonia (Na/NH_3, 8 min) gave 3,3-dimethyloxindole **4** selectively in 85% yield whilst avoiding Birch reduction. Alkylation of **4** with 1,3-dibromopropane [KH, tetrahydrofuran (THF), 60 °C] gave bromooxindole **5**† in 87% yield. Cyclisation and reduction of **5** (2.1 equiv. of Bu^tLi, THF, −78 °C, 1 h warmed to 0 °C and 3 equiv. of $LiAlH_4$ in ether, reflux, 12 h gave pyrrolo[1,2-*a*]indolenine **2**† in 45% yield (Scheme 2). Thus, even though the flexibility in the chain connecting the nucleophile and the electrophile appears to be poor, the cyclisation proceeds in moderate yield. Interestingly, similar treatment of the chloro-analogue of **5** also led to cyclisation to give **2** but in only 19% yield. It has been reported that chlorides and bromides are relatively poor precursors to alkyllithiums by halogen/metal exchange and alkyl iodides are the preferred reactants.[7] It is quite probable that use of the iodo-analogue of **5** would lead to higher yields.



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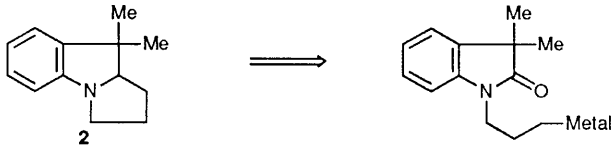

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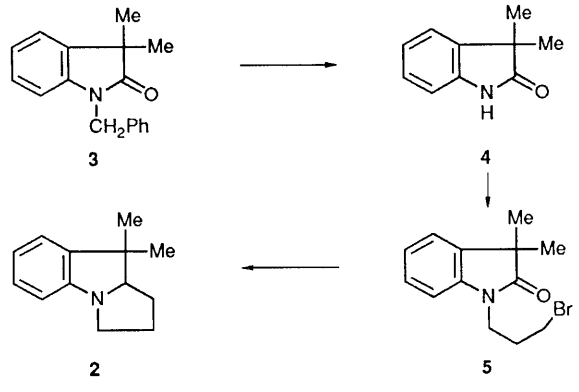
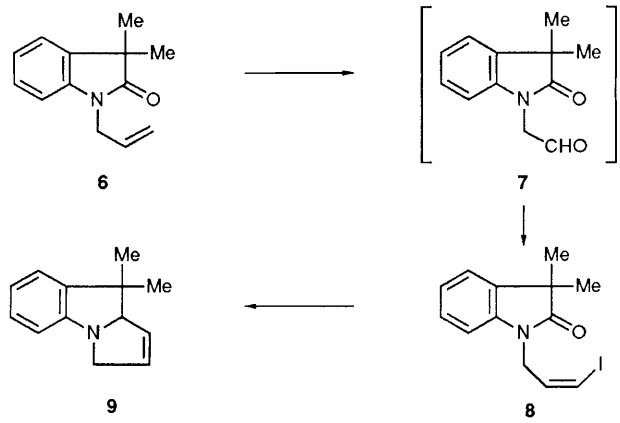
Scheme 1

† All new compounds gave satisfactory spectroscopic and analytical data.

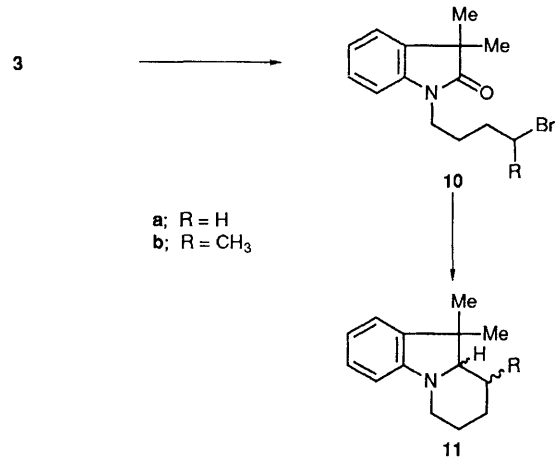
In order to extend this cyclisation towards a synthesis of the mitomycins, we have explored the cyclisation of a vinyllithium to allow incorporation of a double bond suitable for conversion into the aziridine ring found in the mitomycins. Initial attempts involved the alkylation of **3** with commercially available 1,3-dibromopropene. This gave a good yield of *N*-alkylated product as an inseparable mixture of approximately equal amounts of the two geometrical isomers but only a trace of pyrroloindolenine was obtained upon cyclisation of this mixture. The major product isolated appeared to be the alkyne formed by elimination of the vinyl bromide. It is highly unlikely that the *E*-bromoalkene can cyclise, as such halogen/metal exchange is known to occur with retention[8] and the vinyllithium will be configurationally stable under these conditions.[9] Therefore, we decided to prepare the *Z*-vinyl iodide to use as the precursor to the vinyllithium (Scheme 3). Ozonolysis [CH_2Cl_2, −78 °C, then dimethyl sulphide(DMS)] of the *N*-allyloxindole **6**[10]† gave aldehyde **7** which was immediately subjected to Wittig alkenation using the Stork procedure[11] [Ph_3PCH_2I, $NaN(SiMe_3)_2$, THF/hexamethylphosphoramide (HMPA), −78 °C to room temperature] to give the *Z*- and *E*-vinyl iodides in 66% overall yield as a 4 : 1 mixture (*Z* : *E*). Separation of these isomers and cyclisation of *Z*-vinyl iodide **8**† under the usual conditions gave the



Scheme 2



Scheme 3



Scheme 4

unsaturated pyrrolo[1,2-*a*]indolenine **9**† in 53% yield. Thus, in spite of the seemingly demanding stereoelectronic requirements of this cyclisation, the desired reaction proceeds in reasonable yield and reopens the possibility of applying the Raphael strategy, on an intramolecular basis, to a synthesis of the mitomycins.

In order to further explore the scope of this cyclisation, we have synthesised two simple examples of the little-known pyridino[1,2-*a*]indolenine system as shown in Scheme 4. Alkylation of **3** with 1,4-dibromobutane and 1,4-dibromopentane (NaH, THF, room temperature, 12 h) gave *N*-alkylated oxindoles **10a**† and **10b**† in 66 and 57% yield respectively. Cyclisation of **10a** under the usual conditions proved unexceptional and gave pyridino[1,2]indolenine **11a**† in 85% yield. Similarly, cyclisation of **10b** gave pyridinoindolenine **11b**† in 22% yield as a 3:1 mixture of diastereoisomers. The major diastereoisomer was assigned the *cis*-methyl/methine hydrogen stereochemistry on the basis of the coupling constant observed for this hydrogen in the ^{1}H NMR (J 10.3 Hz). The main by-product in this latter cyclisation was the terminal alkene formed by elimination of HBr from **10b**. The slower rate of cyclisation of the secondary alkyllithium derived from **10b** presumably allows elimination to compete. Thus, the cyclisation is successful with primary alkyl- and vinyl-lithiums but less so with secondary alkyllithiums.

Finally, we have explored the possibility of trapping the intermediate carbinolamine formed after organolithium addition to the carbonyl group in order to provide the alkylated carbinolamine functionality present at C-9a of the mitomycins. Unfortunately, thus far, efforts to capture this intermediate by methylation (methyl triflate) and silylation (chlorotrimethylsilane) have proved unsuccessful although there is precedent for such trapping.[12]

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10 The *N*-allyloxindole **6** was prepared by radical cyclisation (Bu_3SnH) of *N*-allyl-*N*-(2′-bromophenyl)methacrylamide (J. M. D. Storey, unpublished results). Further details of the surprising selectivity observed in this radical cyclisation will be presented elsewhere.
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