Aryl Radical Cyclisations involving an Amide Group in the Linking Chain

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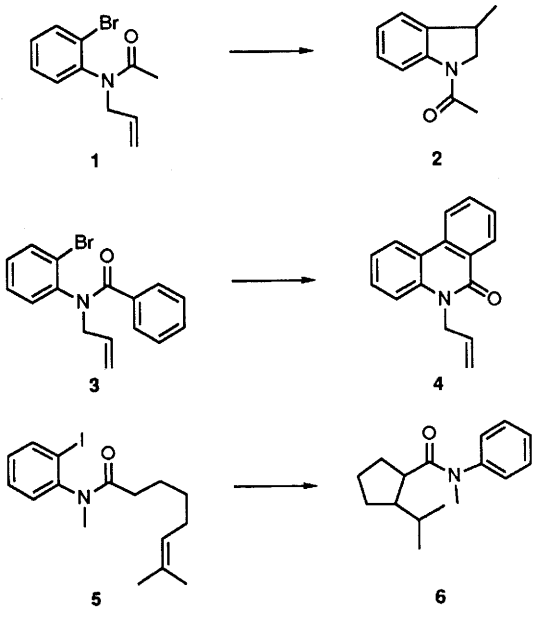
Cyclisation of **7**, **8** and **9** *via* their derived aryl radicals gives products arising from addition of the aryl radical to the acryloyl double bond exclusively.

The cyclisation, *via* the derived aryl radical, of *o*-bromoacryloylanilides appears to be a relatively straightforward reaction provided the amide is *N*-alkylated and hence assumes the s-*cis* form.[1] However, recent results by a number of groups have complicated the picture somewhat and we now wish to present some results which we believe clarify the chemistry of these useful systems.

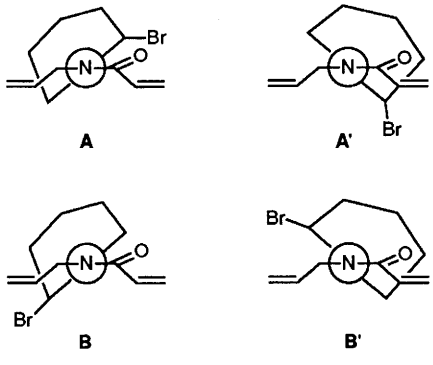
Dittami has shown that **1** cyclises smoothly, in high yield to the dihydroindole **2** on treatment with tributyltin hydride (TBTH).[2] On the other hand, Togo has shown that the *N*-benzoyl derivative **3** cyclises into the aromatic ring on treatment with TBTH to give the *N*-allylated-2-quinolone **4**.[3] Finally, Curran has shown that treatment of **5** under radical generating conditions leads to **6** *via* a rapid initial [1,5]-hydrogen-atom abstraction.[4] Taken together with our previous results,[1] these observations appear somewhat inexplicable, in particular, it is difficult to see why the reaction of Dittami does not simply lead to reduction *via* the type of [1,5]-hydrogen abstraction used elegantly by Curran.

In order to explore the factors operating in these reactions, we have carried out some competitive cyclisation reactions. The three *N*-allylacryloylanilides **7**,† **8**† and **9**† were synthesized by acylation of 2-bromoaniline with the appropriate acid chloride followed by allylation using sodium hydride in tetrahydrofuran (THF) at 0 °C (overall yields 75, 64 and 48%, respectively). Cyclisation of **7** using TBTH in refluxing toluene for 30 min gave the *N*-allylated oxindole **10**† in 77% yield formed by cyclisation onto the electron-deficient double bond of the acryloyl unit. No other cyclisation products were isolated, in particular no dihydroindole formed by cyclisation of the aryl radical onto the allyl double bond was detected. This could be simply the result of the lower energy LUMO of the acryloyl double bond favouring cyclisation to give the oxindole. However, cyclisation of **8** under identical conditions, led to formation of the oxindole **11**† and dihydroquinolone **12**† in a 3:1 ratio in a combined yield of 98%. Again, exclusive cyclisation of the aryl radical onto the acryloyl double bond has occurred with the ratio of **11** to **12** merely reflecting the relative rates of 5-*exo* to 6-*endo* cyclisation as previously observed.[1] No product arising from addition to the allyl double bond was detected. This result is surprising as this cyclisation of the aryl radical derived from **8** onto the acryloyl double bond is expected to be considerably slower than in the case of **7**, outweighing any frontier-orbital effects and leading to competitive cyclisation onto the allyl double bond. Finally, cyclisation of crotonyl derivative **9** gave exclusively the oxindole **13**† in 93% yield after chromatography again with no trace of cyclisation onto the allyl double bond.

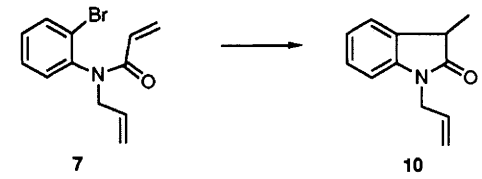


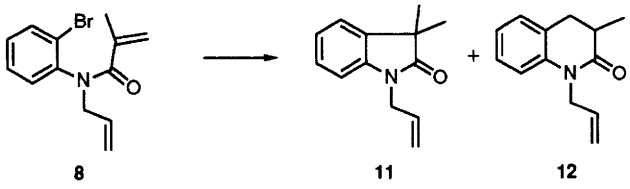
These results, in conjunction with the results in the literature, indicate that another conformational factor besides the restricted rotation around the amide C–N bond is operating. We believe the extra conformational factor which needs to be considered involves restricted rotation around the aryl C–N bond. Examples of atropisomerism arising from just this type of restricted rotation are known.[6] Molecular models backed up by MM2 calculations (carried out using MACROMODEL[7] on a Vax 8650) indicate that the two lowest energy conformations of the *o*-bromoacryloylanilides have the plane of the aromatic ring tilted at some 60° to the plane of the amide carbonyl system with the 2′-bromo substituent pointing either towards the acryloyl unit (conformation **A** and its enantiomeric conformation **A′**) or towards the allyl unit (conformation **B** and its enantiomeric conformation **B′**). In each case MM2 calculations show that conformation **A**/**A′** is favoured for **7**, **8** and **9** by 1.7, 2.4 and 2.5 kcal mol^{-1} (1 cal = 4.184 J) over conformation **B**/**B′**. The energy barrier for interconversion of these two conformations will presumably be larger than this since the system will have to pass through a higher energy conformation. Although these conformations relate to the starting material and not the actual radical intermediate, the short lifetime of the aryl radical (less than 10^{-5} s[5] regardless of which reaction pathway the radical subsequently follows) means that there is no time for rotation around the aryl carbon–nitrogen bond before cyclisation occurs. Thus, these reactions are a very sensitive test of solution conformation under the reaction conditions and the regioselectivity of cyclisation is determined by this conformational equilibrium, which appears to be largely dependant on the size of the acyl group.

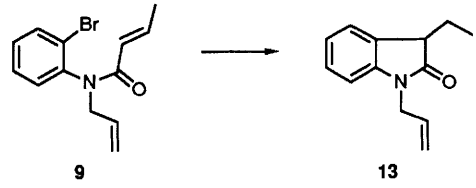
The results of Dittami[2] and Togo[3] are explicable in terms of this model. The small acyl group used by Dittami causes little or no restriction on the aryl C–N bond rotation and leads to



† All new compounds gave satisfactory spectroscopic and analytical data.

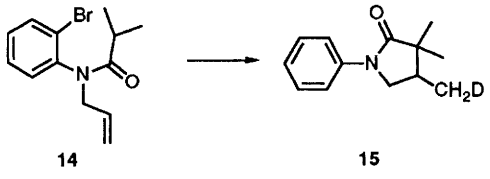






addition to the allyl double bond. The presence of the benzoyl group in the reaction of Togo leads to considerably restricted rotation and a strong preference for the conformation with the radical centre generated close to the phenyl ring, leading to the quinolone.

Furthermore, this model allows us to make a prediction which can be tested experimentally. If the *N*-acyl group is larger than the acetyl group employed by Dittami then no cyclisation onto the allyl double bond should be observed. Instead, the mode of reaction should switch round completely to [1,5]-hydrogen-atom abstraction, which would presumably be followed by a 5-*exo* cyclisation to give a 2-pyrrolidone (Scheme 1). The required substrate **14**† was synthesised in 72% yield by acylation of 2-bromoaniline with isobutyryl chloride followed by allylation as described above. Reaction with 1 equiv. of tributyltin deuteride in refluxing toluene gave



Scheme 1

the pyrrolidinone **15**† in 92% yield after chromatography with >95% deuteration at the site indicated (as determined by ^{1}H and ^{13}C NMR spectroscopy).

In summary, we believe that the apparently contradictory reactions of these systems can be more fully understood if the conformational constraints around the aryl C–N bond are considered. We have supplied evidence to support this view, which incidentally provides a method for the synthesis of the useful *N*-allyloxindoles[8] and has enabled a novel radical translocation reaction leading to *N*-phenyl-2-pyrrolidinones. This phenomenon may have important consequences for other intramolecular reactions that involve amide groups in the linking chain.

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