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The aryl radical route to oxindoles: dependence on temperature and tin hydride concentration

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Abstract

The cyclisation of anilide **3** via an aryl radical gives both oxindole **4** and dihydroquinolone **5**. The ratio of these products is shown to depend not only on the concentration of tributyltin hydride but crucially on the temperature at which the reaction is conducted.

We have previously described the 5-*exo* cyclisation of *N*-alkyl-2′-bromoacryloylanilides **1** via the derived aryl radical to give oxindoles **2** as the sole product in high yields.[1] However, in the case of amides derived from methacryloyl chloride such as **3**, aryl radical cyclisation results in a mixture of oxindole **4** and dihydroquinolone **5** products (Scheme 1). In our original work, we found that the ratio of these two compounds was about 3:1 in favour of the oxindole. Subsequently, we used this type of cyclisation in the synthesis of natural products[2] although in the case of horsfiline where the cyclisation substrate is the 2-bromoanilide of 2,5-dihydropyrrole-3-carboxylic acid we were delighted to find a ratio of oxindole:dihydroquinolone exceeding 10:1.[3] Recently, we have had cause to revisit the cyclisation of methacryloylanilides and we wish to present the results of these further studies.

The dihydroquinolone product can arise in principle by three alternative pathways (Scheme 2). Firstly, there could be a simple 6-*endo* cyclisation pathway via radical **6**. Literature precedent[4] from the synthesis of dihydrobenzofurans and pyrans by this chemistry would indicate that the 5-*exo* pathway is some five times faster than the 6-*endo* pathway. Secondly, the oxindole radical **7** produced by 5-*exo* cyclisation of the aryl radical could add to the aromatic ring to form the cyclopropyl species **8** which would undergo ring opening to the dihydroquinolone radical **6**. The intramolecular addition of alkyl radicals to an aromatic ring followed by this type of ring-opening has been reported by Beckwith[5] although it generally requires a radical stabilising group at the *ortho* position in the aromatic ring to stabilise the intermediate cyclohexadienyl radical (e.g. **8**).[6] Thirdly, the oxindole radical **7** could undergo addition to the carbonyl group leading to radical **9** which on ring opening would give dihydroquinolone radical **10** in a similar

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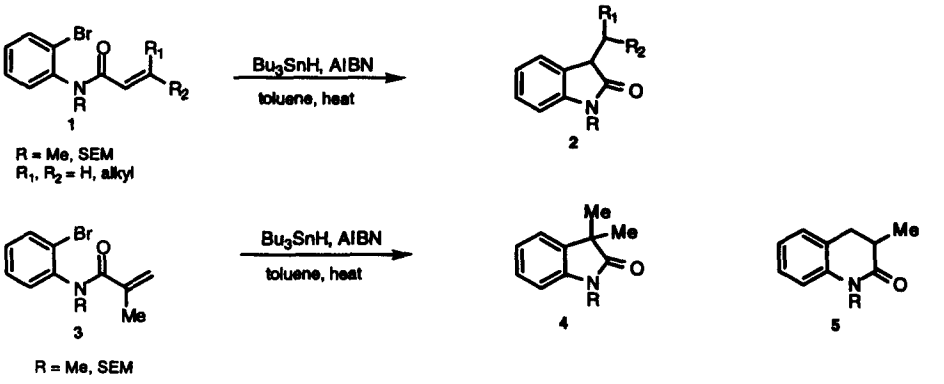
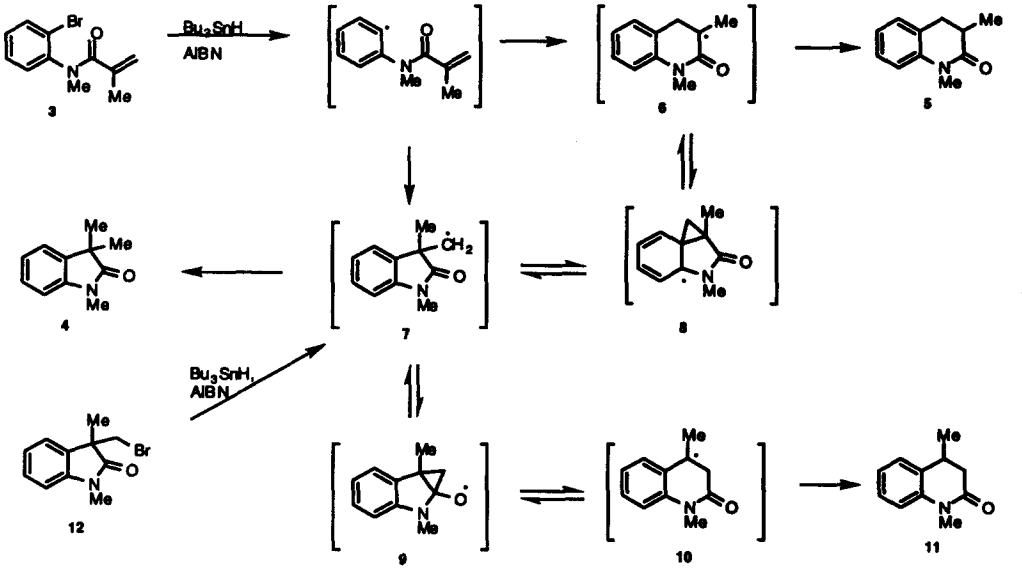


Scheme 1.

manner to that observed by Dowd[7] in cyclic ketones and esters. This latter pathway was immediately ruled out as the 4-methyl compound **11** would be formed and the product was shown (by unambiguous synthesis from dihydroquinolone via enolate formation and methylation) to be the 3-methyl compound **5**.



Scheme 2.

As part of a project designed to prepare mitomycin analogues, oxindole **4** was required and consequently we have explored in more depth the cyclisation of **3**. These studies have uncovered a significant temperature dependence of the product distribution between oxindole **4** and dihydroquinoline **5** in this cyclisation and shed light on the mechanism by which **5** arises.

As can be seen from Table 1, keeping the concentration of tributyltin hydride (TBTH) low and constant but increasing the temperature leads to a dramatic increase in the relative amount of dihydroquinolone formed. Over a 110°C temperature range the amount of oxindole **4** changes from 85% to only 17% (entries 1 and 5). As the two compounds are difficult to separate by chromatography, judicious use of this temperature effect enables the synthesis of either oxindole or dihydroquinolone. It is interesting to note the significant change that occurs on changing from 80°C to 110°C (entries 2 and 4), two temperatures

Table 1
Cyclisation of **3**

Entry	Temperature (°C)	Concentration of Bu_3SnH (molesdm^{-3})	Ratio of 4:5
1	60	0.02	6:1
2	80	0.02	5:1
3	90	0.02	5:1
4	110	0.02	2:1
5	169	0.02	1:5
6	80	0.2	5:1
7	169	2	6:1

The ratio of oxindole **4** to dihydroquinolone **5** was measured by integration of the peaks for the *N*-methyl groups (δ3.2 for **4** and δ3.36 for **5**) in the ^{1}H nmr of the crude reaction product. The spectra indicated no other *N*-methyl containing species.

widely used for these radical cyclisations. This could explain differing results in similar systems noted above. Significant light is shed on the mechanism of the cyclisation reaction by the comparison of entry 2 with 6 and entry 5 with 7. Increasing the concentration of TBTH should lead to a shorter lifetime for the oxindole radical **7** giving more oxindole **4** and reducing the amount of any rearrangement to **8** and **6** and hence dihydroquinolone **5**. However, at 80°C increasing the concentration of TBTH by a factor of 10 (entries 2 and 6) led to no change in the ratio of 4:5. At 169°C (boiling *t*-butylbenzene), increasing the concentration of TBTH by a factor of 100 (entries 5 and 7) led to a change of ratio from 1:5 to 6:1. This pair of results shows that great care is needed in choosing the temperature for the study of these cyclisation reactions. The table of results taken together also provides good evidence for the following explanation of the reaction pathway. At all temperatures, there is a natural partitioning between 5-*exo* cyclisation and 6-*endo* cyclisation which amounts to a ratio of about 6:1 favouring 5-*exo* cyclisation. As the temperature is increased, the activation energy required for oxindole radical **7** to add to the aromatic ring and form **8** is easier to overcome[8] and the amount of dihydroquinolone increases as the rearrangement favours the relatively stable radical **6** ultimately giving dihydroquinolone **5**. At 80°C, increasing the concentration of TBTH does not affect the ratio of products because there is not enough thermal energy to overcome the barrier to addition to the aromatic ring. At 169°C, increasing the TBTH concentration reverses the ratio of products back to the original ratio that was observed at a lower temperature indicating that at this temperature dihydroquinolone **5** is arising by a mixture of pathways; some background 6-*endo* cyclisation but mainly rearrangement which is suppressed at high TBTH concentrations.

To gain further insight into this reaction, the 3-bromomethyloxindole **12** was prepared by alkylation of the enolate of 1,3-dimethyloxindole. Treatment of this with TBTH generates radical **7** unambiguously. A similar reaction has been explored by Bowman[9] in which the *N*-phenyl derivative of **12** was prepared and subjected to reduction with TBTH under syringe pump conditions at 110°C. They isolated a 2:3 mixture of oxindole:dihydroquinolone but in a total yield of only 52%. At 100°C, reduction of **12** gave a 10:1 mixture of oxindole **4**:dihydroquinolone **5** but at 169°C, the ratio was reversed and a 1:2 mixture of **4**:**5** was isolated. Again this indicates that a high temperature is required to overcome the energy barrier of addition to the benzene ring. These results are reminiscent of the work by Beckwith[10] and Stork[11] on the mechanism of ring expansion in vinyl radical cyclisations. Although in this case the initially-formed radical adds to the vinyl group rather than a benzene ring, Beckwith found that this process had a notably higher activation energy than other steps in the pathway. It would be expected that in the case of addition

to an aromatic ring this effect would be even more pronounced. As a final experiment, we wondered if cyclisation of a simple acryloylanilide **1** (R=Me; R_1, R_2=H) at a high temperature would lead to the formation of some dihydroquinolone. Reaction of **1** at 169°C gave only the oxindole **2** indicating that either the quaternary centre at C-3 of the oxindole radical **7** is crucial for cyclisation to **8** or that the rearranged radical **6** must be tertiary in order to drive the rearrangement.

In summary, we have shown that the cyclisation of 2′-bromomethacryloylanilides **3** can be directed to give mainly the 3,3-disubstituted oxindole product or the 3-substituted dihydroquinolone product by careful choice of TBTH concentration and, most importantly, temperature. Analysis of our results coupled with information for related systems already in the literature, indicates that the 5-*exo* cyclisation of **3** occurs some six times more rapidly than the 6-*endo* cyclisation at 80°C and that rearrangement by cyclopropane formation is insignificant at 80°C but is the major reaction at 169°C.

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