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Intramolecular Reactions Using Amide Links: Aryl Radical Cyclisation of Silylated Acryloylanilides

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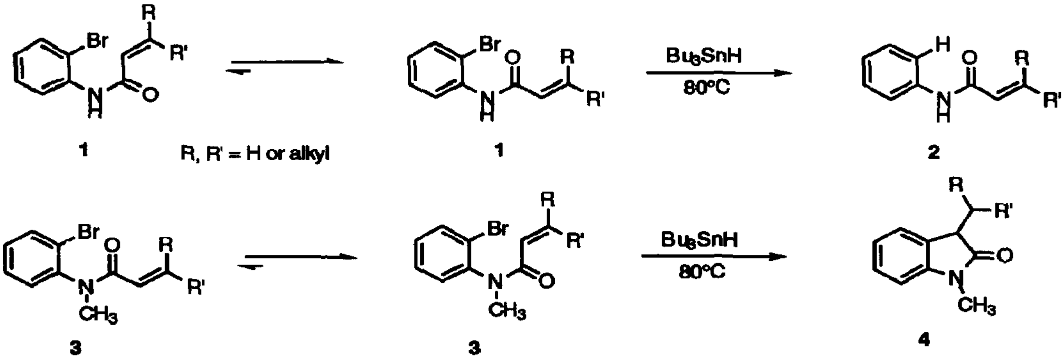
Abstract: Aryl radical cyclisations of *in situ* silylated *o*-bromoacryloylanilides are presented and shown to lead to *N*-unsubstituted oxindoles and dihydroquinolones in very different ratios than those previously observed for the *N*-alkyl *o*-bromoacryloylanilides.

Intramolecular reactions are widely used by synthetic chemists to prepare polycyclic systems in an efficient manner. In recent years two of the most powerful of these reactions have been shown to be intramolecular cycloadditions[1] and radical cyclisation reactions[2]. It has been recognised for some time that the nature of the linking chain can be crucial to the successful outcome of such reactions[3]. When applied to the synthesis of *N*-heterocycles, the linking chain often contains an amide group and the restricted rotation around the carbonyl/ carbon-nitrogen bond coupled with the known propensity for secondary amides to favour the *s*-trans conformation whilst tertiary amides[4] favour the *s*-cis conformation can lead to problems. In the case of intramolecular aryl radical reactions, this effect had been noted some years ago[5] and we discovered another manifestation of this conformational problem when we developed an oxindole synthesis based upon an aryl radical cyclisation[6]. The *N*-unsubstituted *o*-bromoacryloylanilides **1** failed to cyclise but instead gave largely reduction products **2** via the *s*-trans conformation, whilst the *N*-substituted compounds **3** cleanly cyclised to the oxindoles **4** in high yield via the *s*-cis conformation (scheme 1)[6].



SCHEME 1

In order to prepare *N*-unsubstituted oxindoles by this approach, we were forced to introduce removable *N*-substituents (e.g. benzyl or SEM) thereby adding two extra steps to the synthesis. During our work on the synthesis of the *N*-unsubstituted oxindole alkaloid horsfiline[7], we explored an alternative strategy to achieve cyclisation of substrates such as **1**. This strategy was based on the work of Hua *et al.* who reacted *N*-unsubstituted lactams with base and a trialkylsilyl chloride to form *N*-trialkylsilylated lactams which were reacted with organolithiums to generate cyclic ketimines[8]. We felt that treatment of our acryloylanilides **1** with a trialkylsilyl chloride would provide a "temporary" *N*-substitution which would bias the conformation in favour of cyclisation. The *N*-silylated acryloylanilide could be formed *in situ* and the silyl group could be removed easily during the work-up. The questions to be answered were whether the *N*-silyl group would survive the radical cyclisation conditions and whether any residues from the *in situ* silylation would interfere with the radical reaction.

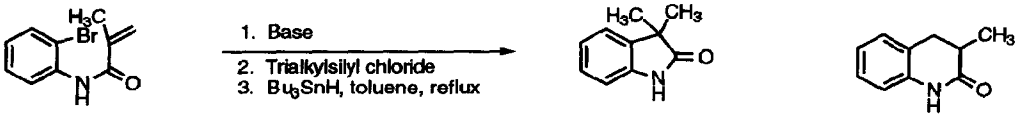
Our first attemps to put this plan into effect involved treatment of *o*-bromoacryloylanilide **5** with triethylamine and t-butyldimethylsilyl chloride (TBDMS-Cl) in toluene followed by dilution of the toluene and addition of Bu_3SnH (TBTH). After 4 hours at reflux, no cyclisation products were isolated only reduction products were obtained. We felt that the anilide anion might be less reactive than a simple lactam anion and so we used more forcing conditions for the silylation ($LiNTMS_2$, THF, room temperature) followed by removal of the solvent and volatile by products and introduction of the radical cyclisation reagents and solvent. After heating under reflux for 2 hours, the reaction was worked up and chromatographed to give a 65% yield of radical cyclisation products (scheme 2). However, much to our surprise, the product was a 3:1 mixture of oxindole **6** and dihydroquinolone **7**. No other *N*-substituent on **5** had ever given any dicernable 6-*endo* product. We then repeated the reaction with trimethylsilyl chloride (TMS-Cl) rather than TBDMS-Cl and again obtained a reasonable yield of cyclisation products (64%) as an 8:1 mixture of **6** and **7** (scheme 2).

5 **6** **7**

Trialkylsilyl chloride			
^{t}BuMe$_2$SiCl	3	1	65%
Me$_3$Si	8	1	64%

SCHEME 2

Intrigued by this apparent attenuation of the 6-*endo* cyclisation pathway, we repeated the reaction on a substrate known to give a mixture of oxindole and dihydroquinolone when *N*-alkyl substituted[6]. Thus reaction of **8** under the standard conditions using TBDMS-Cl gave a 1:2 mixture of oxindole **9**: dihydroquinolone **10** (35% yield) whilst reaction using TMS-Cl gave a 1:3.3 mixture of **9**:**10** (35% yield) (scheme 3). *N*-Methyl **8** gives a 3:1 mixture of *N*-methyl **9**: *N*-methyl **10** and so we are observing the same increase in the 6-*endo* pathway as detected in our first experiment.

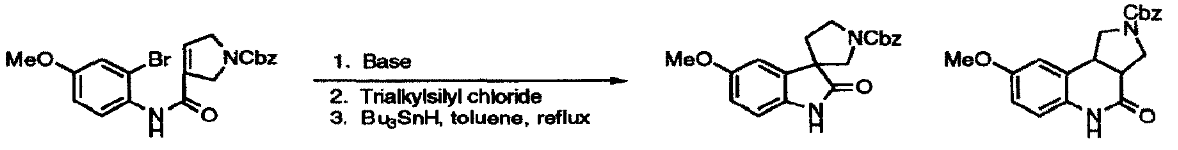


8 **9** **10**

Trialkylsilyl chloride			
^{t}BuMe$_2$SiCl	1	2	35%
Me$_3$SiCl	1	3.3	35%

SCHEME 3

Finally, we utilised this approach to prepare the N-unsubstituted oxindole **12** as part of our approach to horsfiline[7]. Treatment of **11** under the usual conditions using TBDMS-Cl gave a 1:2.1 mixture of oxindole **12**: dihydroquinolone **13** in 55% yield whereas using TMS-Cl gave a 1:1 mixture of **12**:**13** (scheme 4). In the context of a synthesis of the oxindole unit of horsfiline, both reactions give mixtures with an unfortunately high dihydroquinolone content and hence we resorted in that work to using the SEM group as a substituent on nitrogen.



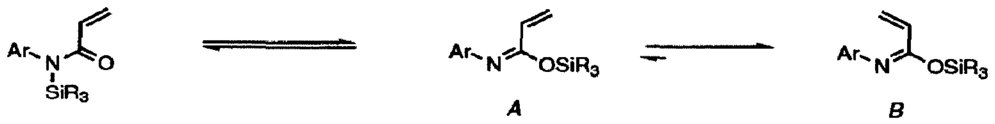
1 1 **1 2** **1 3**

Trialkylsilyl chloride			
^{t}BuMe$_2$SiCl	1	2.1	55%
Me$_3$SiCl	1	1	55%

SCHEME 4

In all the cyclisations involving silylation of the acryloylanilide, the major by-product was the reduced material. This could arise by three routes; incomplete silylation, some loss of the silyl group during the reaction procedure or hydrogen atom abstraction by the aryl radical followed by reduction of the silylmethylradical formed. Unfortunately, it is difficult to gain evidence for this latter route to reduced product since the silyl moiety is lost on work up. However, it is clear that this apparent *N*-silylation causes a dramatic change in the ratio of 5-*exo* to 6-*endo* cyclisation by the straightforward aryl radical cyclisation pathway. We have recently reported on the selectivity for cyclisation of these aryl radicals onto the acryloyl sidechain versus cyclisation onto an *N*-allyl group[9] but here we are observing a different effect.

From all our previous work in this area, we believe that if silylation had occurred simply on the nitrogen of the acryloylanilides, we would obtain very similar ratios of oxindole and dihydroquinolone to those we had obtained for *N*-alkyl substituted acryloylanilides. The dramatic changes in the ratio of 5-*exo*: 6-*endo* cyclisation led us to believe that silylation of our cyclisation substrates did not occur entirely on nitrogen. It is known that *N*-silyl amides exist in equilibrium with the *O*-silyl imidate form[10] and we would suggest that this is the cause of our results. In the *O*-silyl imidate form, it is clear that the unsaturated sidechain would suffer severe steric interactions with the silyl group thus favouring conformation *B* over conformation *A* (scheme 5). Aryl radicals generated in conformation *B* would then cyclise via a 6-*endo* pathway to give dihydroquinolones as the distal end of the double bond is well placed for attack by the aryl radical. Aryl radicals generated in either conformation *A* or from the *N*-silyl amide would be expected to cyclise via the usual pathway (mainly 5-*exo*) depending on the substituents on the double bond.



SCHEME 5

This hypothesis suggests that the larger the silyl group, the greater the preference for conformation *B* and the greater the amount of 6-*endo* cyclisation. This seems to be the case for the examples in schemes 2 and 4 but not so for the example in scheme 3. However it is clear that the ratio of *N*-silyl to *O*-silyl would be affected by the nature of the amide sidechain and acryloylanilide **8** represents probably the most hindered of the amides studied. It is interesting to note that the yield for the cyclisation of **8** is reproducibly lower than the other examples. This could well indicate some particular property of this substrate, for example difficulty of silylation which results in reduction *via* the N-H compound. Finally, we have carried out a brief investigation of the intermediate formed after silylation using ^{29}Si nmr. Treatment of **5** with base and TBDMS-Cl followed by removal of the solvent gave a material with only a single peak in the ^{29}Si nmr at δ 13.38 ppm. The expected ^{29}Si chemical shifts for an *O*-silyl imidate and an *N*-silyl amide are respectively δ19.6 and δ8.7[11]. This suggests a rapid *O*-silyl/*N*-silyl equilibration on the nmr timescale providing some further evidence for the equilibrium shown in Scheme 5. Indeed, as the radical cyclisation conditions involve a higher temperature than the nmr experiment, this silyl group migration would be even faster.

In summary, we have uncovered an unusual effect on the regioselectivity of this aryl radical cyclisation which could have implications for a wide variety of intramolecular reactions involving an amide linking chain. In our example, we are exploring the possibility of controlling the cyclisation product in order to be able to prepare oxindoles or dihydroquinolones as required. The dihydroquinolone products may be of some use in the synthesis of the melodinus alkaloids[12].

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