An Efficient Synthesis of Spiro[cyclohexane-1,3′-indol-2′(3′*H*)-ones] *via* Radical Cyclisation

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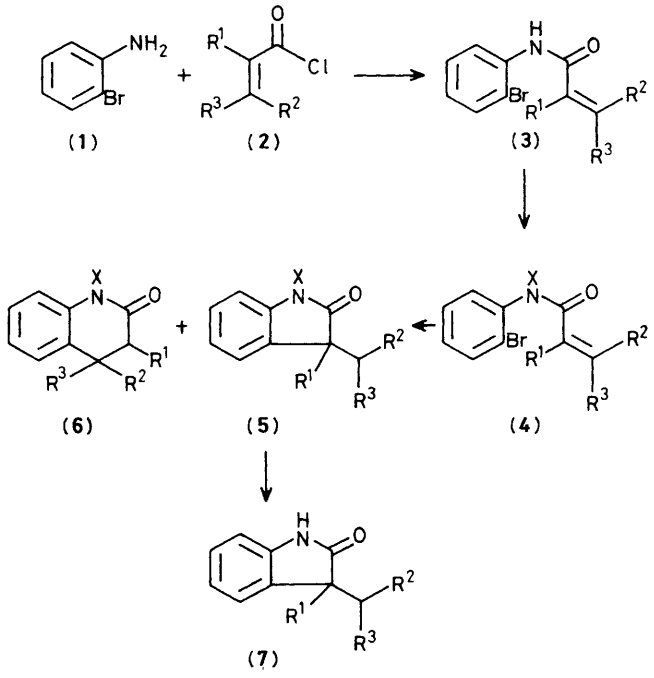
Treatment of the *o*-bromo-*N*-acryloylanilides (**4**) with tri-n-butylstannane leads to the formation of 3-substituted- and 3,3-disubstituted-2-oxindoles (**5**) in high yield.

In connection with our work directed towards the synthesis of the *Gelsemium* alkaloids,[1] we required a mild method for the formation of the 3-spiro-2-oxindole system late in the synthetic route. Although there are several methods available for the synthesis of 2-oxindoles in general[2] and 3-spiro-2-oxindoles in particular,[3] none of these methods seemed compatible with our planned synthetic approach. Recently, radical cyclisation has been shown to be a powerful method for the construction of 5-membered rings under neutral, mild conditions[4] and we report now the application of this approach in a new synthesis of 2-oxindoles.

We envisaged forming the 2-oxindole ring by the cyclisation of the aryl radical generated from the *o*-bromo-*N*-acryloylanilide (**4**) onto the carbon–carbon double bond of the



a; X = Me, $R^1 = R^2 = R^3 = H$
b; X = R^3 = Me, $R^1 = R^2 = H$
c; X = $R^2 = R^3$ = Me, $R^1 = H$
d; X = R^1 = Me, $R^2 = R^3 = H$
e; X = Me, R^1,R^3 = $-[CH_2]_4-$, $R^2 = H$
f; X = SEM, R^1 = Me, $R^2 = R^3 = H$
g; X = SEM, R^1,R^3 = $-[CH_2]_4-$, $R^2 = H$

Scheme 1. SEM = $Me_3SiCH_2CH_2OCH_2$.

α,β-unsaturated amide side chain as shown in Scheme 1. Reaction of *o*-bromoaniline (**1**) with the appropriately substituted acryloyl chloride (**2**) proceeded at 0 °C in ether to give the acryloylanilides (**3**).† Protection of the nitrogen‡ was achieved with either methyl iodide [NaH, tetrahydrofuran (THF), room temp.] or 2-trimethylsilylethoxymethyl (SEM) chloride[5] (NaH, THF, reflux) to give the cyclisation substrates (**4**)† in high overall yields (Table 1).

Treatment of the *N*-substituted *o*-bromoacryloylanilides (**4**)† with tri-n-butylstannane and a catalytic amount of azoisobutyronitrile (AIBN) in toluene under reflux gave the 2-oxindoles (**5**)† in high yields (Table 1). As expected, cyclisation of compounds (**4a—c**) gave the 3-alkyl-2-oxindoles (**5a—c**) as the sole products confirming the high bias for 5-membered ring formation in such radical cyclisations.[6] Cyclisation of (**4d**) and (**4e**) gave an inseparable mixture of (**5d**)–(**6d**) and (**5e**)–(**6e**) respectively in which the 2-oxindole products predominated over the 2-dihydroquinolone products by 4 : 1 and 3 : 1 respectively.

† All new compounds gave satisfactory spectral data. All compounds were elaborated to known oxindoles for comparison.

‡ Treatment of the *N*-unsubstituted acryloylanilides (**3**) with tri-n-butylstannane under the usual conditions gave no cyclisation products.

Table 1. % Yields[a] of compounds (**3**)—(**6**).

	(3)	(4)	(5)	(6)
a	73	87	79	0
b	84	94	72	0
c	89	98	80	0
d	90	80	72[b]	18[b]
e	95	74	69[b]	22[b]
f		81	70[b]	15[b]
g		85	80[b]	9[b]

[a] Yields are for chromatographically homogeneous material. [b] Yields by ^1H n.m.r. integration of inseparable mixture.

In view of the steric hindrance around the cyclisation terminus in (**4d**) and (**4e**), the predominant formation of the 5-membered ring cyclisation product is unusual.[6] This is probably caused by the shorter C–N bond lengths which, coupled with the conformational rigidity of the acryloylanilides (**4**), favour the 5-*exo-trig* cyclisation pathway.[7]

Interestingly, replacement of the *N*-methyl group by the *N*-SEM group [(**4f**) and (**4g**)] followed by radical cyclisation leads to formation of oxindoles and dihydroquinolones in a different ratio. Thus, cyclisation of (**4f**) under the usual conditions gives a 5 : 1 mixture of oxindole (**5f**) and dihydroquinolone (**6f**) in 85% yield. Similar reaction of (**4g**) gives a 8 : 1 mixture of spiro-2-oxindole (**5g**) and dihydroquinolone (**6g**) in 89% yield. It is apparent from the ^1H n.m.r. spectra of the cyclisation substrates (**4f**) and (**4g**) that the SEM group has a considerable effect on the conformation of these molecules and this no doubt contributes to the increased selectivity for 5-*exo-trig* cyclisation. Purification (by recrystallisation) and removal of the SEM group[5] gave the *N*-unsubstituted-2-oxindoles (**7f**) and (**7g**) in 81 and 80% yield respectively. Thus we have achieved the synthesis of the 3-spiro-2-oxindole (**7**) in 51% overall yield from *o*-bromoaniline (**1**).

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