Cobalt(II) Chloride–Grignard Reagent: an Alternative to Tin Hydride in Aryl Radical Cyclisations

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Reaction of *N*-methyl, *N*-acryloyl-2-haloanilines with anhydrous cobalt(II) chloride and a Grignard reagent leads to formation of indol-2(3*H*)-ones *via* a reductive aryl radical cyclisation.

Although tributyltin hydride-mediated radical cyclisations have proved to be particularly useful in synthesis,[1] the toxicity of the tin hydride reagent has stimulated the search for alternative methods of carrying out such reactions. In the alkyl radical field, several alternatives have been developed involving a variety of methods.[2] However, the greater instability of the aryl radical precludes many of these methods being applied to aromatic systems. The use of cobalt(I) complexes generated *in situ* has been explored but suffers from the drawback that such complexes are very unstable and considerable practical expertise is required for their successful use.[3] While considering this problem, our attention was attracted to the early work of Kharasch on the use of Grignard reagents to which various transition-metal salts had been added.[4] This work was followed up by Hey[5] who carried out quantitative studies involving the intermolecular trapping of aryl radicals generated from aryl halides by the cobalt(II) chloride–Grignard reagent combination. This work shed considerable light on the reaction pathway and clearly implicated the involvement of aryl radicals (Scheme 1). The use of this reaction in an intramolecular sense to give phenanthrenes from stilbenes has been reported[6] but this involves an overall oxidative radical cyclisation. We decided to explore the potential of this reagent in reductive aryl radical cyclisations.

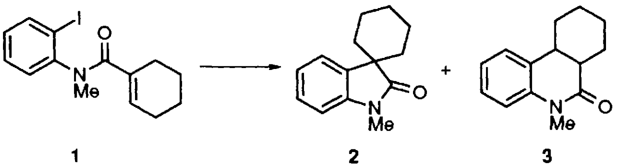
Our first experiment involved addition of *ortho*-iodoacryloylanilide **1** to anhydrous cobalt(II) chloride in THF followed by addition of ethylmagnesium bromide and heating under reflux for 1 h (Scheme 2). We were delighted to find that a mixture of the spiro-oxindole **2** and dihydroquinolone **3** resulted albeit in low yield (35% of the product mixture was isolated along with 31% of recovered starting material). The ratio of oxindole **2** to dihydroquinolone **3** was identical to that obtained under tributyltin hydride-mediated conditions.[7] With a successful result obtained, we decided to further explore these reaction conditions as a route to oxindoles.

Cyclisation of the *ortho*-haloacryloylanilides **4** was explored using the above conditions (Scheme 3). The first variable investigated was the halogen. In each case a higher yield of cyclised material was obtained when the iodo-compound was used as substrate for the reaction rather than the bromo-compound (for example the cyclisation of the bromide corresponding to **4a** led to **5a** in 45% yield). This is in line with results for the cobalt(I) salen [salen = bis(salicylidene)ethylenediamine] approach to aryl radical cyclisations.[3] The second variable investigated was the Grignard reagent. The use of methylmagnesium iodide rather than ethylmagnesium bromide led to higher yields in all cases. On addition of ethylmagnesium bromide to the cobalt(II) chloride solution a green colour reminiscent of cobalt(I) was observed. However, with methylmagnesium iodide as the Grignard reagent, the solution turned black. Clearly, if an alkylcobalt species is involved in the reaction then that derived from the ethylmagnesium bromide can undergo a β-hydride elimination while that derived from the methylmagnesium iodide cannot. The colour of the latter solutions perhaps lends credence to the intermediacy of some form of metallic cobalt.[5] Increasing the reaction time to 4 h gave the products of radical cyclisation (oxindoles **5** and dihydroquinolone **6**) in good yields (Table 1).† The effect of ultrasound on the reaction was briefly investigated. Using 1,4-dioxane as solvent and irradiation in a simple ultrasound bath led to noticeable reaction at room temp. after only 30 min. However, this rate enhancement was not sufficient to warrant changing the standard conditions.

The overall reaction involves a reductive radical cyclisation and the source of the hydrogen atom that quenches the alkyl radical formed after cyclisation is not obvious. In all the above cases, we believe this hydrogen atom arises from the solvent (THF) although experiments to confirm this have not been carried out.[8] However, we felt that the yield of the reaction might be improved by addition of a hydrogen atom donor and we have investigated two possibilities. Many obvious hydrogen atom donors are incompatible with the reaction conditions but the use of dicyclohexylphosphine (DCHP) in lithium aluminium hydride reductions has been reported.[9] Addition of DCHP to a representative reaction appeared to lead to a cleaner reaction but only 20% of the product was isolated along with 72% of recovered starting material. Unfortunately, the DCHP seemed to react with the reagent

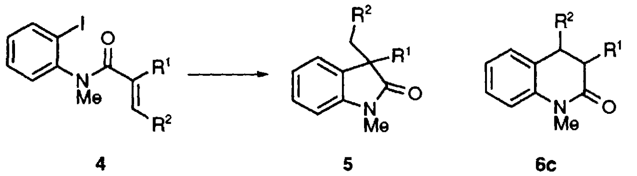
$$
\begin{gathered}
2\,\mathrm{RMgBr} + \mathrm{CoCl_2} \rightarrow \mathrm{R_2} + \mathrm{Co} + 2\,\mathrm{MgBrCl} \\
2\,\mathrm{RMgBr} + \mathrm{Co} \rightarrow \mathrm{R_2Co} + \mathrm{MgBr_2} + \mathrm{Mg} \\
\mathrm{R_2Co} + 2\,\mathrm{ArBr} \rightarrow \mathrm{R_2} + \mathrm{CoBr_2} + 2\mathrm{Ar}^{\bullet}
\end{gathered}
$$

Scheme 1



1 **2** **3**

Scheme 2



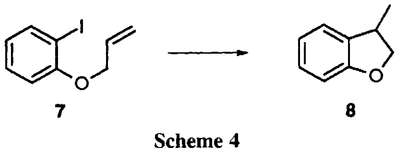
4 **5** **6c**

a; R¹ = R² = H
b; R¹ = H, R² = Me
c; R¹ = Me, R² = H

Scheme 3

Table 1

Substrate	Yield of **5** (%)	Yield of **6** (%)
4a	71	0
4b	67.5	0
4c	52	17



7 **8**

Scheme 4

system and it proved difficult to force the reaction to completion. The use of 1,4-cyclohexadiene was also explored but this reacted with the reagent system and no cyclisation was observed.

A brief study of the use of metals other than cobalt was carried out.[4] Nickel(II) chloride as the metal salt led to cyclisation but in a lower yield than cobalt(II). The use of iron(II) chloride proved to be difficult owing to solubility and stability problems and was abandoned. Finally, the cyclisation of the allylated *ortho*-iodophenol **7** using cobalt(II) chloride under our optimum conditions was undertaken (Scheme 4). Dihydrobenzofuran **8** was isolated in 54% yield indicating that the ether link is stable to this reagent combination.

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Footnote

† Typical conditions for these reactions are as follows: Anhydrous cobalt(II) chloride (0.25 mmol) is dissolved in dry THF (10 ml) under an inert atmosphere. Methylmagnesium iodide (1 mmol) is added and the solution refluxed for several minutes to give a black solution. The aryl iodide (0.5 mmol) is added slowly as a solution in THF (2 ml) and the mixture refluxed for 4 h. The reaction is quenched by careful addition of conc. HCl (1 ml) and the THF is removed *in vacuo*. The residue is partitioned between petroleum ether and sodium bicarbonate solution. After drying the petroleum ether and removal of solvent, the residue is purified by flash chromatography.

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