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EVIDENCE ON THE NATURE OF COBALT-MEDIATED ARYL RADICAL CYCLISATIONS

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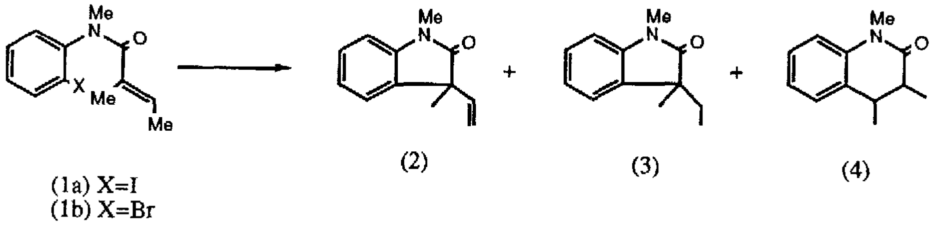
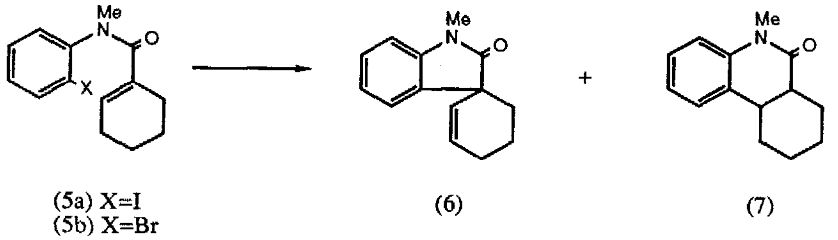
Abstract: Regiochemical and stereochemical evidence is presented which indicates that cobalt-mediated aryl radical cyclisations involve simple free radicals.

Radical cyclisation reactions have achieved considerable importance in synthetic chemistry[1]. However, a major drawback of the tin hydride method of generating free radicals from alkyl, vinyl, and aryl halides is the reductive nature of the carbon/carbon bond formation which leads to the loss of two functional groups in exchange for the new carbon/carbon bond. Owing to this problem, other methods have been explored for the generation of the requisite free radicals which do not involve such loss of functionality[2]. Among the methods available, the use of low valent cobalt complexes to generate organo-cobalt intermediates which undergo radical type cyclisations has been explored as an alternative approach. The initial products of these reactions are alkyl-cobalt complexes which can undergo a range of subsequent reactions. Recently, Geise[3] has published evidence based on kinetics and stereochemistry, showing that **alkyl** cobalt-mediated cyclisations occur with no direct involvement of the cobalt in cyclisation. This prompts us to present our results on the nature of cobalt-mediated **aryl** radical cyclisations.

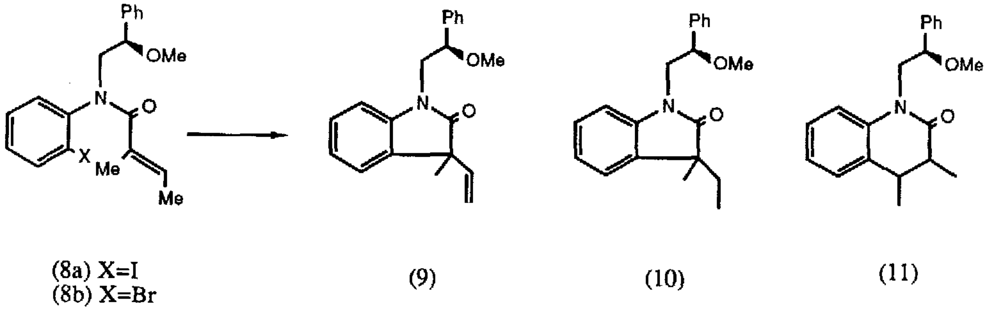
The use of aryl radical cyclisations in synthesis is less widespread than alkyl radical cyclisations. Our interest in preparing oxindoles via such cyclisations[4] and their subsequent use in alkaloid synthesis[5] prompted us to explore the use of cobalt(salen) complexes to mediate the reaction. Pattenden has reported the use of cobalt(salen) complexes in preparing indoles and benzopyrans from the appropriate ortho-iodo aniline or phenol[6]. We have extended this to the cyclisation of various 2'-halo-acryloylanilides leading to oxindoles and 2-dihydroquinolones. The regiochemical



Scheme 1



Scheme 2



Scheme 3

and stereochemical features of these reactions indicate that they involve simple free radicals.

Regiochemical results.

Treatment of the unsaturated anilides(1) in THF with Co^{I}[salen] (generated by Na/Hg reduction of Co^{III}[salen]PPh_3Br) in the light gave rise to three products [Scheme 1 and Table 1].

As expected, aryl iodide(1a) cyclised in higher yield (66%) than aryl bromide(1b) (40%). However, the ratio of (2):(3):(4) was the same in each case namely 72:2:26. The major product (2) is formed by β-elimination from the intermediate alkyl cobalt complex whereas (3) and (4) are formed by abstraction of hydrogen from the solvent by the appropriate radical. In the case of (4) the intermediate alkyl cobalt complex is not formed because of the tertiary nature of the alkyl group and hence the β-elimination pathway is not available[7]. The ratio of 5-:6-membered ring formation is 74:26 which is, within experimental error, the same as the tin hydride induced cyclisation of (1b), (see Table 1).

Similar cyclisation of (5a) gave only 2 compounds, (6) and (7) in 70% overall yield (Scheme 2). As in the case (1), the 6-membered ring product is saturated, and the ratio of (6):(7) is 74:26. This agrees with the ratio of 5-exo : 6-endo cyclisation observed for the Bu_3SnH reaction (Table 1). The fact that the ratio of 5-exo : 6-endo cyclisation is independant of whether tin hydride or cobalt(I) is used suggests that a common free-radical intermediate is involved.

Substrate	Method	Yield	Ratio of 5-exo:6-endo
1a	cobalt	66%	74:26
1b	cobalt	40%	74:26
1b	Bu_3SnH	65%	72:28
5a	cobalt	70%	74:26
5b	Bu_3SnH	91%	74:26[4]

Table 1

Stereochemical results

Cobalt-mediated cyclisation of the mandelate-derived homochiral acryoylanilide(8a) gave three products (9),(10), and (11) as expected. When the reaction was carried out at room temperature (9) was isolated in 40% yield and with a diastereomeric excess(d.e). of 15%. At -78°C the yield was 35% and the d.e. 17%. This should be compared with the tin hydride induced cyclisation of (8b) which gave saturated compound (10) in 79% yield with a 14% d.e.(reaction carried out at 110°C) or a 15% d.e. when the reaction was carried out at room temperature[8] (Table 2). Again this points to a common intermediate in both the tin hydride and cobalt aryl radical cyclisations.

Substrate	Method	T(°C)	d.e. of (9)	d.e. of (10)
8a	cobalt	20	15%	-
8a	cobalt	-78	17%	-
8b	Bu_3SnH	110	-	14%[8]
8b	Bu_3SnH	20	-	15%[8]

Table 2

In summary, our results provide evidence that the cobalt-mediated aryl radical cyclisation involves simple free radicals and that attempts to use a chiral cobalt complex to induce enantioselectivity in such reactions will probably lead to poor results.

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