# An Efficient Technique for the Alkylation of 4-hydroxycoumarin Using Alcohol in the Presence of Iridium Metal Catalyst

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**Abstract.** The survey deals with a description of synthesis of asymmetrical analogues of dicoumarol using iridium metal complex ($[Cp^*IrCl_2]_2$). The title compounds (1a-g) were synthesized from one step reaction involving 4-hydroxycoumarin and its derivatives (2a) and different aromatic alcohols. The products which were obtained are in good yields and their purity confirmed by their melting point, mass spectrometry, IR, $^{13}C$ and $^{1}H$ NMR spectroscopy.

**Key words:** synthesis, asymmetrical analogues of dicoumarol, borrowing hydrogen methodology.

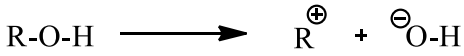
## Introduction

The metal-catalyzed auto-transfer of hydrogen, otherwise famously described as 'borrowing hydrogen methodology', is a powerful tool for functional group interconversion. Following the discovery made by Grigg and co-workers (Grigg et. al. 1981: 4313), who used alcohol as alkylating reagents, borrowing hydrogen methodology has emerged as a useful technique in organic synthesis. The technique has, as to a little extent, replaced traditional couplings and reductive aminations for the formation of C-C and C-N bonds respectively (Fristrup et al., 2012).

Environmental regulation has emphasized the importance of using techniques involving high selectivity, high atom economy, excellent yields and that are environment friendly in organic synthesis (Schreiber, 2000: 1964-1969; Spring, 2003: 3867-3870). Consequently, this has led to intensive investigation into the development of new synthetic approach for the formation of C-C and C-N bonds. One of the most promising strategies is the direct metal-catalysed alkylation of esters, ketones, aldehydes and imines with alcohols.

The indirect functionalization of alcohols using catalytic amount of metal complex and base, which produces only water as a by-product, is eco-friendly in contrast to standard C-C and C-N forming reactions. The reaction can be achieved using different metal catalysts such as ruthenium, rhodium, copper, iron and iridium complexes, where the iridium complex ($[Cp^*IrCl_2]_2$), in particular, has been considered as the most effective (Zhao et al., 2015: 22996-23008; Fujita et al. 2004: 3525-3528).

Alcohols are generally poor electrophiles in dissociative alkylation reactions as their ionization is almost impossible because $R^+$ is a high energy intermediate as depicted in Fig. 1. The activation of the 'OH' into a suitable leaving group is therefore required to enable nucleophilic substitution reactions to occur.




R = alkyl, phenyl, etc

Fig. 1. Ionization of an alcohol producing high energy charged intermediate ($R^+$)

Previously, the activation of alcohol molecules has been accomplished by protonating the alcohol or converting it into a sulfonate ester (one of the most common being a tosylate ester **3a**) or halide (**3b**) as shown in (Fig. 2, Fig. 3) respectively. Sulfonate and halide anions are both good leaving groups. These methods of alcohol activation

have some limitations: apart from poor economy, protonation can deactivate the incoming nucleophile and the alkyl halides and alkylsulfonate that are generated as intermediate can also be mutagenic (Hamid et al., 2007: 1555-1575).

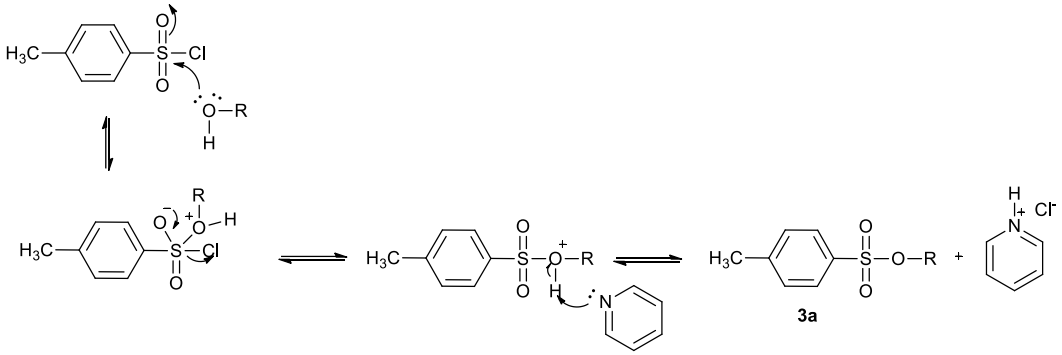



Fig. 2. Mechanism of tosylate ester (3a) formation

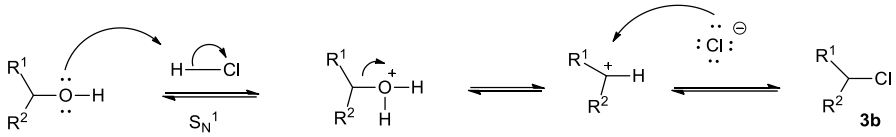



Fig. 3. Mechanism of halide (3b) formation

*Synthesis*

A range of asymmetrical analogues of dicoumarol (**1a-g**) was synthesized using 5 mol% of iridium metal complex $[(Cp^*IrCl_2)_2]$ in a general reaction termed as 'borrowing hydrogen methodology'. The reaction was carried out by reacting 4-hydroxycoumarin and its derivatives (**2a**) with aromatic alcohol using caesium carbonate ($Cs_2CO_3$) and isopropanol *via* one-pot protocol as depicted in Fig. 4. The reaction was left to react over night at temperature of 110 $^oC$. The structural identities of all the synthesized compounds were confirmed using IR, $^1H$ NMR spectroscopy and mass spectrometry.

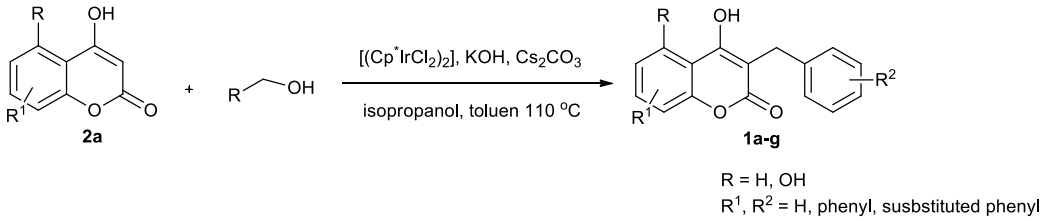



Fig. 4. General procedure for the synthesis of asymmetrical analogues of dicoumarol (1a-g) using iridium metal complex ($[Cp^*IrCl_2]_2$) as a catalyst

**Materials and Methods**

Melting point was measured using a Sanyo Gallenkamp MPD 350 variable heater instrument and are uncorrected. IR spectra were recorded in the solid state using a Bruker Alpha P FT-IR instrument. $^1H$ NMR spectra were recorded using Bruker Avance 400 spectrometers. Chemical shifts are given in ppm to the nearest 0.01 ppm and referenced to the solvent residual peak. The abbreviations used are s-singlest, d-doublet, t-triplet, dd-doublet of doublets, td-triplet of doublets, m-multiplet.

*General method for the synthesis of compounds (1a-g)*

*Method A*

A solution of 4-hydroxycoumarin and its derivatives (1 equivalent), an appriopriate aromatic alcohol (5 equivalents), pentamethyl cyclopentadienyl iridium(111)chloride

dimer ($[Cp^*IrCl_2]_2$) (5 mol%), caesium carbonate (10 mol%), isopropanol (20 mol%) in toluene (1.4 M) was heated under reflux at 110 ºC for 24 hours under nitrogen. The resultant mixture was concentrated in vacuo and purification of the crude product was carried out using flash column chromatography on silica gel (ethyl acetate: petroleum ether) or by washing with cold methanol (Appendino et al., 1991: 1451-1458).

*Synthesis of 3-benzyl-4-hydroxy-2H-chromen-2-one (1a)*

Using method A, reaction of 4-hydroxycoumarin (136 mg, 0.84 mmol) and benzyl alcohol (454 mg, 4.19 mmol) gave the title compound (**1a**) as a white solid (111 mg, 52%): Mp 208–210 ºC [Lit.[262]207-209ºC] (Khoobi, 2011: 580-586); $\nu_{max}/cm^{-1}$ 3031 (br, OH), 1685 (s, C=O), 1605 (s, C=C); $\delta_H$ (400 MHz; $CDCl_3$) 4.05 (2H, s), 7.28-7.34 (2H, m), 7.36-7.38 (5H, m), 7.55 (1H, ddd), 7.75 (1H, dd); *m/z*(-ES), 251 ($[M-H]^-$, 100%).

*Synthesis of 3-benzyl-4-hydroxy-5-methoxy-2H-chromen-2-one (1b)*

Using method A, reaction of 4-hydroxy-5-methoxy-2H-chromen-2-one (136 mg, 0.71 mmol) and benzyl alcohol (384 mg, 3.55 mmol) gave the title compound (**1b**) as a cream coloured solid (178mg, 89%): Mp 170-172ºC; $\nu_{max}/cm^{-1}$ 3320 (br, w, OH), 1686 (s, C=O), 1643 (s, C=C); $\delta_H$ (400 MHz; $CDCl_3$) 3.91 (2H, s), 4.06 (3H, s), 6.78 (1H, dd), 7.01(1H, dd), 7.16-7.20 (1H, m), 7.25-7.28 (2H, m), 7.40-7.44 (3H, m), 9.73 (1H, s); *m/z* (-ES) 283.1 ($[M-H]^-$, 100%); (+ES) (Found 305.0796; $C_{17}H_{14}O_6Na$ ($[M+Na]^+$), requires 305.0790).

*Synthesis of 4-hydroxy-3-(naphthalene-2-ylmethyl)-2H-chro men-2-one (1c)*

Using method A, reaction of 4-hydroxycoumarin (150.0 mg, 0.93 mmol) and 2-naphthalenemethanol (270.0 mg, 1.71 mmol) gave the title compound (**1c**) as a white solid (168 mg, 60%): Mp 211 ºC [Lit. 202-204] (Gunnarsdottir and Elfarra, 1999: 950-957); $\nu_{max}/cm^{-1}$ 3054 (br, w, OH), 1650 (s, C=O), 1620 (s, C=C); $\delta_H$ (400 MHz; DMSO-$d_6$) 4.06 (2H, s), 7.36-7.45 (5H, m), 7.63 (1H, ddd), 7.69 (1H, s), 7.81-7.83 (3H, m), 8.02 (1H, dd), 11.73 (1H, s); *m/z* (+ES) 325.1 ($[M+Na]^+$, 70%); (Found 325.0853; $C_{20}H_{14}O_3Na$ ($[M+Na]^+$), requires 325.0841).

*Synthesis of 4-hydroxy-5-methoxy-3-(naphthalen-2-ylmethyl)-2H-chromen-2-one (1d)*

Using method A, reaction of 4-hydroxy-5-methoxy-2H-chromen-2-one (150.0 mg, 0.78 mmol) and 2-naphthalenemethanol (249.0 mg, 1.58 mmol) gave the title compound (**1d**) as a white solid (152 mg, 59%): Mp 157 ºC; $\nu_{max}/cm^{-1}$ 3293 (s, OH), 1702 (s, C=O), 1637 (s, C=C); $\delta_H$ (400 MHz, DMSO-$d_6$) 3.99 (2H, s), 4.06 (3H, s), 7.07 (2H, d), 7.47-7.53 (3H, m), 7.63 (1H, t), 7.78 (1H, s), 7.85-7.88 (3H, m); *m/z* (+ES) 355.1 ($[M]+ Na]^+$, 100%); (Found 355.0961; $C_{21}H_{16}O_4$ ($[M+ Na]^+$), requires 355.0946).

*Synthesis of 3-benzyl-4-hydroxy-3,4-dihydro-2H-benzo[h]chromen-2-one (1e)*

Using method A, reaction of 4-hydroxy-2H-benzo[h]chromen-2-one (120.0 mg, 0.57 mmol) and benzyl alcohol (306.0 mg, 2.83 mmol) gave the title compound (**1e**) as off white solid (95 mg, 56%): Mp 260-262 ºC [Lit. 259 ºC] (168 mg, 60%): Mp 211 ºC [Lit. 202-204] (Gunnarsdottir and Elfarra, 1999: 950-957); $\nu_{max}/cm^{-1}$ 3028 (br, w, OH), 1606 (s, C=O), 1557 (s, C=C); $\delta_H$ (400 MHz, DMSO-$d_6$) 3.95 (2H, s), 7.15-7.18 (1H, m), 7.24-7.29 (4H, m), 7.70-7.73 (2H, m), 7.88 (1H, d), 8.01 (1H, d), 8.06 (1H, dd), 8.34-8.37 (1H, m); *m/z* (+ES) 325.1 ($[M+Na]^+$, 100%); (Found 325.0851; $C_{20}H_{14}O_3Na$ ($[M+Na]^+$), requires 325.0841).

*Synthesis of 1-hydroxy-2-(naphthalene-2-ylmethyl)-3H-benzo[f]chromen-3-one (1f)*

Using method A, reaction of 1-hydroxy-3H-benzo[f]chromen-3-one (150.0 mg, 0.93 mmol) and 2-naphthalenemethanol (270.0 mg, 1.71 mmol) gave the title compound (**1f**) as a cream solid (144 mg, 58%): Mp 270-272 ºC; $\delta_H$ (400 MHz; DMSO-$d_6$) 4.21 (2H, s), 7.40-7.49 (3H, m), 7.54-7.62 (2H, m), 7.68-7.71 (2H, m), 7.81-7.85 (3H, m), 8.05 (1H, d),

8.18 (1H, d), 9.44 (1H, d), 11.99 (1H, br, s); *m/z* (-ES) 351.3 ([M-H]$^-$, 100%); (Found 351.1020; $C_{24}H_{15}O_3$ ([M-H]$^-$), requires 351.1021).

*Synthesis of 4-hydroxy-3-(naphthalene-2-ylmethyl)-2H-benzo[h]chromen-2-one (1g)*

Using method A, reaction of 4-hydroxy-2H-benzo[h]chromen-2-one (150.0 mg, 0.93mmol) and 2-naphthalenemethanol (270.0 mg, 1.71 mmol) gave the title compound (**1g**) as a cream solid (144 mg, 58%): Mp 276-278ºC (Lit. 260-263 ºC) (168 mg, 60%): Mp 211 ºC [Lit. 202-204] (Gunnarsdottir and Elfarra, 1999: 950-957); $\nu_{max}$/cm$^{-1}$ 3160 (br, w, OH), 1650 (s, C=O), 1607 (s, C=C); $\delta_H$ (400 MHz, DMSO-$d_6$) 4.14 (2H, s), 7.41-7.51 (3H, m), 7.70-7.75 (3H, m), 7.82-7.89 (4H, m), 8.05 (2H, dd), 8.38 (1H, dd), 11.92 (1H, br, s); *m/z* (+ES) 375.1 ([M+Na]$^+$, 100%); (Found 375.1002; $C_{24}H_{16}O_3Na$ ([M+Na]$^+$), requires 375.0997).

## Result and Discussion

Borrowing hydrogen methodology was developed as it provides a potential green pathway for the alkylation of alcohols using a metal catalyst. Through this reaction, the dimeric iridium catalyst ([Cp*IrCl$_2$]$_2$) which is an 18 electron complex, undergoes activation by caesium carbonate ($Cs_2CO_3$). This results in the formation of an iridium-carbonate complex, a monomeric 16 electron complex, as depicted in Fig. 5. This occurs in order to allow coordination of the substrate alcohol (Balcells et. al., 2008: 2529-2535).

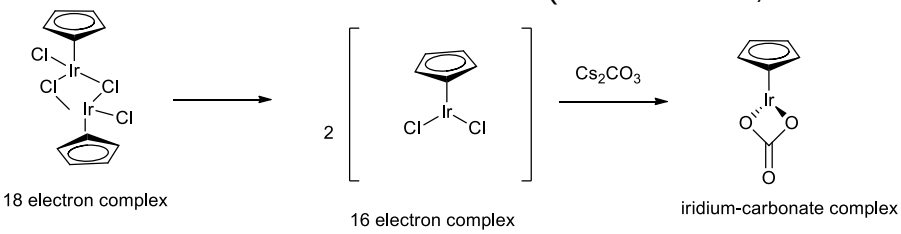



Fig. 5. Dimer-monomer equilibrium

The catalytic cycle occurs *via* three sequential stages: alcohol oxidation, double bond formation and reduction. In the case of C-C bond formation, the metal catalyst alters the reactivity of the alcohol (**4a**) by removing two hydrogen atoms in a formal oxidation reaction as depicted in Fig. 6. This temporarily generates a reactive carbonyl compound (aldehyde or ketone (**4b**), which permits bond formation to occur. The carbonyl undergoes aldol condensation reaction with a suitable substrate to form an *α,β*-unsaturated intermediate (**4c**). In the final step, the *α,β*-unsaturated intermediate is reduced with the return of two hydrogen atoms from the catalyst to the double bond giving an alkylated product (**4d**) without a net change in the overall oxidation state (Hamid et al., 2007: 1555-1575).

In order to overcome the potential problem of residual unreacted alkene, isopropanol is added which acts as a hydrogen donor to replace any loss of hydrogen. Reactions are performed at a higher temperature (110 ºC) in order to achieve complete conversion.

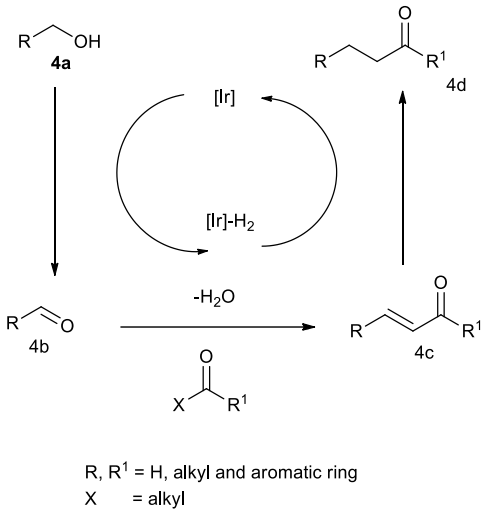



Fig. 6. C-C bond formation using an iridium-catalysed 'borrowing hydrogen methodologhy'. Source: (Hamid et. al., 2007: 1555)

In this research work, C-3 alkylations of 4-hydroxycoumarin and its derivatives (**2a**) were performed using 5 mol% of iridium catalyst ($[Cp^*IrCl_2]_2$) in the presence of caesium carbonate ($Cs_2CO_3$) as a base. A plausible catalytic cycle is depicted in Fig. 7.

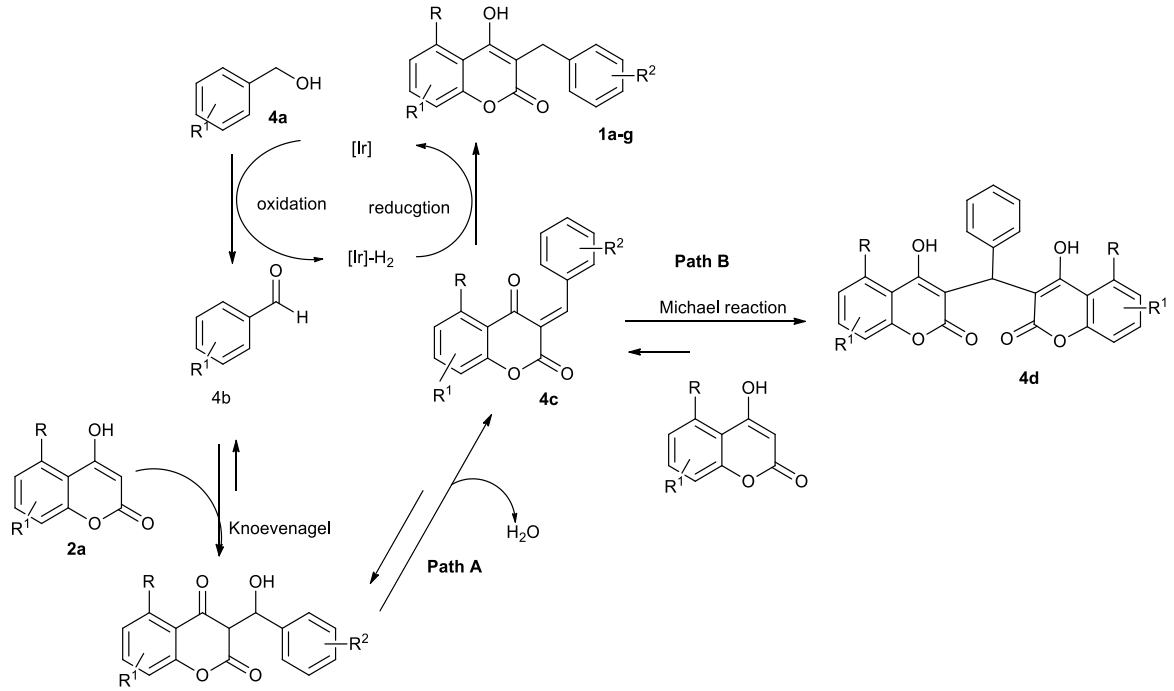



Fig. 7. Proposed mechanism for C-3 alkylation of 4-hydroxycoumarin and its derivatives (**2a**) using an iridium catalyst

During the cycle, activation of the alcohol by catalytic dehydrogenation is followed by a Knoevenagel condensation and catalytic reduction (Path 'A') to form the half-way stage analogues of dicoumarol (**4c**). The reduction of intermediate compound (**4c**) to the desired product is in competition with a Michael addition reaction by the 4-hydroxycoumarin remaining in the reaction mixture through Path 'B' which produces dimer (**4d**) as a by-product. The reaction therefore was left to react for a prolonged period

of time (24 hours) in order to effect complete conversion. The targeted compounds are listed in Fig. 8.

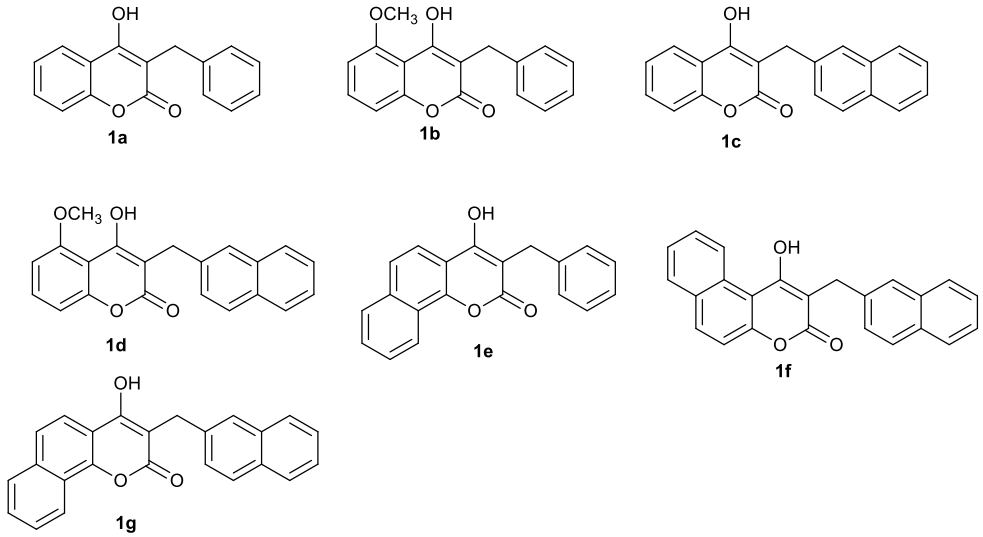



Fig. 8. Targeted compounds (1a-g)

**Limitation**

One of the key challenges of the 'borrowing hydrogen methodology' arises from the use of excess of alcohols both as reagent and solvent, and as a result, a stoichiometric amount of reacting partners (alcohol, 2 equivalents) and (coumarin 1 equivalent) were applied. The result obtained gave lower yields (52-59%), whereas using 5 equivalents of alcohol gave higher yields (60-89%). A second serious limitation of the borrowing hydrogen methodology is the cost of the metal catalyst used. Consequently, effort was focussed on finding a less expensive catalyst with respect to the iridium complex. The ruthenium complex $Ru(PPh)_3Cl_2$\KOH was found to be inexpensive, easily available and has been reported to be effective for borrowing hydrogen methodology.

**Conclusion**

In summary, 'borrowing hydrogen methodology' afforded a higher yield for the asymmetrical analogues of dicoumarol (**1a-g**) and was more atom efficient. Another advantage of this new technique is that the reaction procedure is convenient, involves one-pot reaction sequence and the product isolation is easy. Work up is uncomplicated and the yields are good. Therefore, it is the simple experimental modification compare to the existing method (i.e., traditional couplings and reductive aminations).

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