Article:
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Iridium catalyzed alkylation of 2′-hydroxyacetophenone with alcohols under thermal or microwave conditions

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Abstract

2′-Hydroxyacetophenone was alkylated with a range of substituted benzyl and heteroaryl alcohols to afford the corresponding *C*-alkylated products in good yields under microwave irradiation. The *C*-alkylated products were reacted with bromoacetonitrile to afford 2-amino-3-benzyl 1,4-naphthoquinone derivatives in moderate yields.

Keywords: Iridium; Alkylation; Catalysis; Microwave; Amino naphthoquinone

2′-Hydroxyphenyl ketones are important structural motifs which possess a wide range of applications, including as anti-oxidants,[1] flavors and fragrances[2] (Fig. 1).

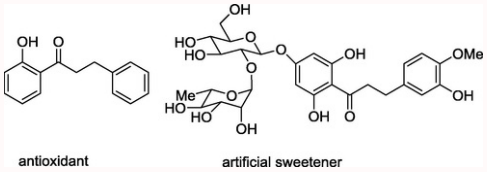


Fig. 1 Selected 2′-hydroxyphenyl ketone motif properties.

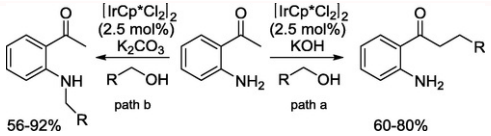
Conventional methods for the alkylation of ketones typically utilise toxic/corrosive alkyl halides; this can be overcome by the use of alcohols as alkylating agents in combination with an appropriate metal catalyst. These latter processes are essentially atom economical with water formed as the only by-product.[3] The α-alkylation of ketones with alcohols has been achieved using hydrogen borrowing methodology under ruthenium,[4] iridium,[5] palladium,[6] and other transition metal catalysts.[7]

These metal ions usually require ligands such as phosphines, *N*-heterocyclic carbenes, and *N*-donors to stabilize the metal ion. Recently Donohoe and co-workers reported an iridium catalyzed redox-neutral reaction to afford α-branched ketones with higher alcohols. However the above reaction was restricted to either *ortho*-disubstituted phenyl or cyclopropyl ketones.[8]

Previously, we reported the iridium catalyzed chemoselective alkylation of 2′-aminoacetophenone with alcohols to form either C

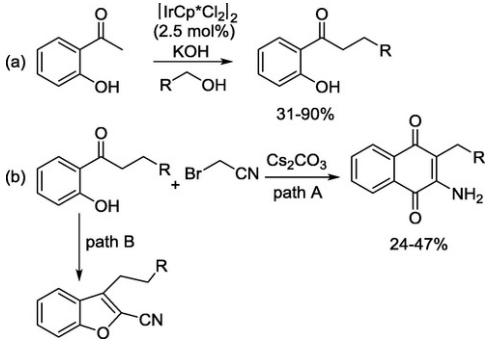
C or C

N bonds under microwave irradiation (Scheme 1).[9]



Scheme 1 Ir Catalysed chemoselective alkylation reactions.

Herein, we report (i) an iridium catalyzed alkylation of 2′-hydroxyacetophenone with alcohols to form a new C—C bond under microwave irradiation (Scheme 2a) and (ii) treatment of the alkylated products with bromoacetonitrile to afford the corresponding 2-amino 3-benzyl 1,4-naphthoquinone derivatives (Scheme 2b) under microwave irradiation.



Scheme 2 Examined Ir catalyzed redox-neutral processes.

Previously, we identified the iridium chloro-bridged compound **1** [X = Cl, M = Ir (III)] as an effective catalyst for the alkylation of ketones with alcohols (Fig. 2).[9]

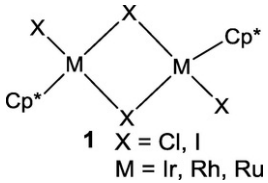
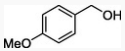
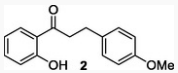
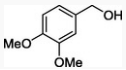


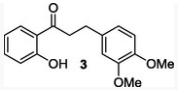
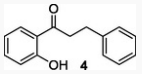
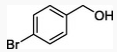
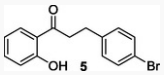
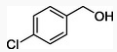
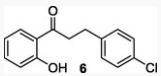
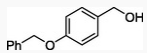
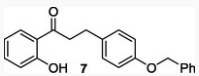
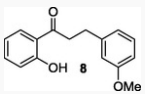
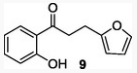
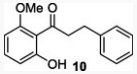
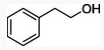
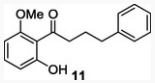
Fig. 2 Examined catalysts.

Metal catalyzed reactions can often be accelerated by microwave irradiation.[10] Optimization showed that the reaction could be carried out under microwave conditions (300 W) with the use of KOH as the base (Scheme 2a). The use of catalytic KOH (20 mol%) failed to give the *C*-alkylated product, due to the presence of the phenolic OH group.[5,9]

Initially, we carried out the alkylation reaction of 2′-hydroxyacetophenone (1 mmol) with *para*-methoxybenzyl alcohol (1.1 mmol), KOH (1.2 mmol), and $[Cp^*IrCl_2]_2$ (2.5 mol%) in *tert*-amyl alcohol (5 mL) at 120 °C for 2 h under microwave irradiation, which cleanly afforded the corresponding *C*-alkylated product **2** in 75% yield (Table 1, entry 1).

Table 1 Iridium catalyzed redox-neutral reactions of 2′-hydroxyacetophenone.[a]

Entry	Alcohol	Product	Yield (%)[b,c]
1			66 (75)
2			60 (91)

			
3			40 (50)
4			82 (96)
5			51
6			41
7			90
8			(75)
9			58
10			31

a Reagents and conditions: 2′-Hydroxyacetophenone (1 mmol), alcohol (1.1 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol%), KOH (1.2 mmol), *tert*-amyl alcohol (5 mL), 120 °C, 120 min, microwave irradiation.

b Isolated yield.

c Yields in brackets refers to isolated yields under thermal conditions. Reagents and conditions: 2′-hydroxyacetophenone (1 mmol), KOH (1.2 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol%), *tert*-amyl alcohol (5 mL), 110 °C, 24 h.

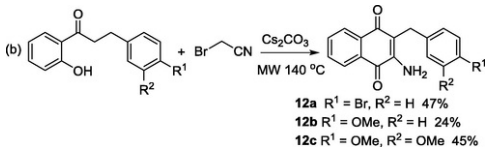
In the above process the dialkylated product was not detected. No reaction took place in the presence of KOH alone, indicating that the combination of the iridium complex and a base was necessary for the reaction. To the best of our knowledge this represents the first reported example of C

C bond formation using 2′-hydroxyacetophenone (a potential chelator for Ir) with an alcohol.

Benzyl alcohols substituted with electron-withdrawing or donating groups were readily alkylated to afford the corresponding *C*-alkylated products **3**–**9** in good yields (40–90%; Entries 2–8). Thermal reactions were also carried out at 110 °C for 24 h, which afforded the *C*-alkylated products in slightly better yields (50–96%; Entries 1–4) (Entries 1-4)).

Next the ketone component was varied. Thus, the reaction of 2′-hydroxy-6′-methoxyacetophenone (1 mmol) with benzylalcohol (1.1 mmol), KOH (1.2 mmol), and $[Cp^*IrCl_2]_2$ (2.5 mol%) in *tert*-amyl alcohol (5 mL) at 110 °C for 24 h, afforded the corresponding *C*-alkylated product in 58% yield (Entry 9). The use of 2-phenyl ethyl alcohol in the above reaction resulted in a low yield (31%; Entry 10).

Next we briefly studied the reaction illustrated in Scheme 2b. The initial reaction was performed using 1-(2-hydroxyphenyl)-3-(4-bromophenyl) propan-1-one **5** (1 mmol), 2-bromoacetonitrile (2 mmol), and Cs_2CO_3 (4 mmol) in 1,4-dioxane (5 mL) in a sealed tube under microwave irradiation at 60 °C for 1 h, then for 2 h at 140 °C to afford naphthoquinone derivative **12a** (path a) in 47% yield as an orange solid (Scheme 3). In the above reaction none of the benzofuran derivative (path B) was observed. The structure of naphthoquinone derivative **12a** was confirmed by single crystal X-ray diffraction (Fig. 3).[11]



Scheme 3 Synthesis of naphthoquinone derivatives. Reagents and conditions: Cs_2CO_3 (4.0 eq.), bromoacetonitrile (2.0 eq.), microwave irradiation, 60 °C, 1 h, then 2 h, 140 °C.

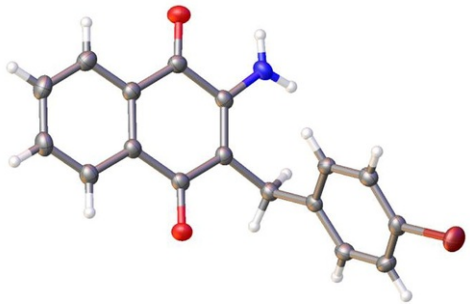


Fig. 3 Molecular structure of compound **12a**.

The reactions of compounds **2** and **3** containing electron donating groups attached to the benzene ring afforded naphthoquinone derivatives **12b** and **12c** in 24% and 45% yield, respectively. The structure of naphthoquinone derivative **12b** was confirmed by single crystal X-ray diffraction (Fig. 4).[11] Examination of the literature suggests that the synthesis of naphthoquinone derivatives **12a–c** *via* this method is novel.[12]

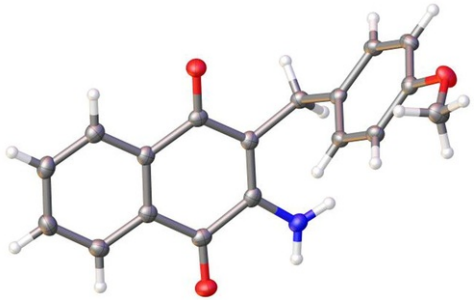
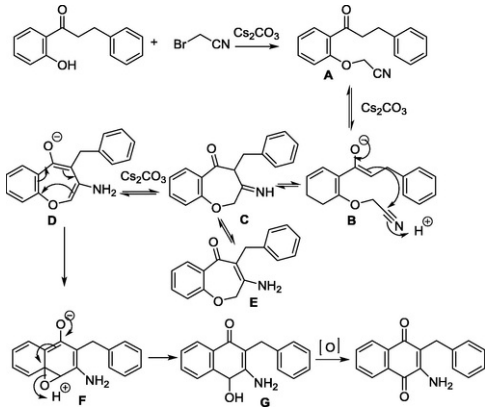


Fig. 4 Molecular structure of compound **12b**.

At this stage it must be emphasized that the proposed mechanism (Scheme 4) for naphthoquinone derivative formation is tentative and the subject of ongoing research. Thus in the presence of cesium carbonate, compound **A** is in equilibrium with enolate **B**, which undergoes nucleophilic addition to give compound **C**. Compound **C** is in equilibrium with enolate **D**, which then undergoes a thermal 6π electron pericyclization reaction to afford intermediate **F**. Finally intermediate **F** undergoes aromatization followed by oxidation in air to give the 2-amino-3-benzyl 1,4-naphthoquinone.



Scheme 4 Proposed mechanism for naphthoquinone formation.

In summary, we have successfully carried out the iridium catalyzed alkylation of 2′-hydroxyacetophenone with a range of substituted benzyl and heteroaryl alcohols under microwave irradiation to afford the corresponding *C*-alkylated products in good yields. The *C*-alkylated products were further reacted with bromoacetonitrile to afford 2-amino-3-benzyl 1,4-naphthoquinone derivatives in moderate yields.

Acknowledgments

We thank Leeds University for support.

A Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.024.

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11. Deposition numbers for compounds **10a** and **10b** CCDC 1542920-1542921 contains the supplementary crystallographic data for these structures. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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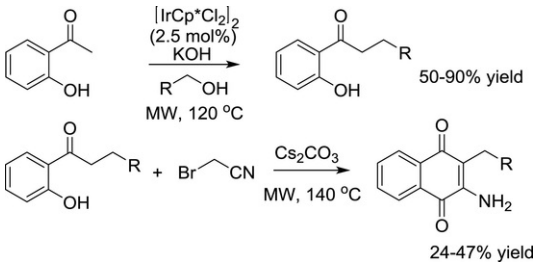
A Supplementary data

Multimedia Component 1

Supplementary data

Graphical abstract



Highlights

- Novel synthesis of 2-amino-3-benzyl 1,4-naphthoquinone derivatives.
- Ir catalysed *C*-alkylation process was carried out under microwave irradiation.
- Atom economical process.

Queries and Answers

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