Iridium catalyzed acceptor-less dehydrogenative coupling of alcohols and 4-hydroxy-6-methyl-2-pyrone under microwave conditions

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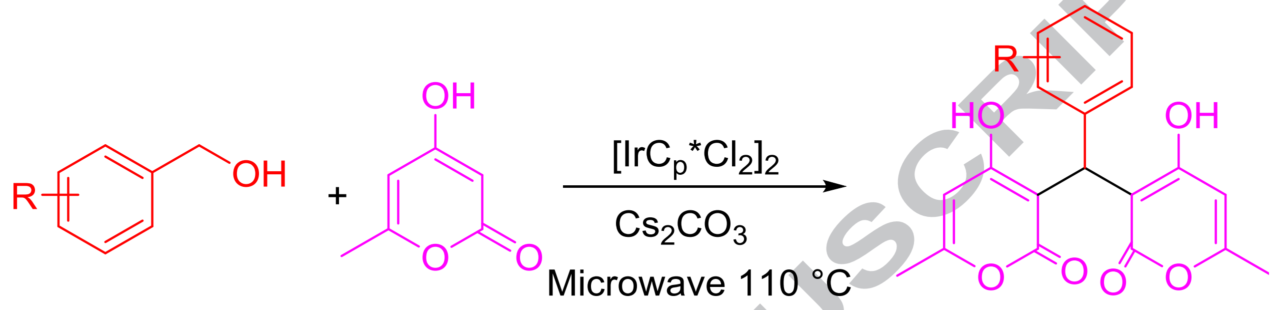

R = Electron donating, neutral and withdrawing groups

10 examples

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ABSTRACT

Iridium catalysed acceptor-less dehydrogenative coupling of benzyl type alcohols and 4-hydroxy-6-methyl-2-pyrone under microwave conditions afforded 3,3'-(arylmethylene)bis(4-hydroxy-6-methyl-2H-pyran-2-ones) in good yields

3,3'-(Aryl/alkylmethylene)bis(4-hydroxy-2H-pyran-2-ones are important structural skeletons possessing a wide range of medicinal properties including anti-inflammatory,[1] and anti coagulant[2] activities (Figure. 1).

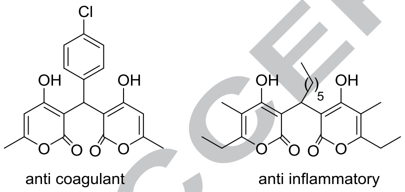
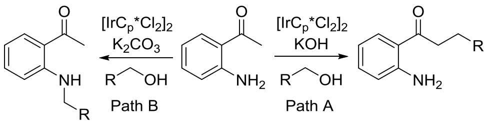


Figure 1. Bioactive bis-pyrone compounds

To increase the molecular complexity of simple organic substrates using efficient (high atom economy), selective, high yielding, and environmentally benign methods is a significant contemporary challenge for synthetic organic chemists. C-C and C-N bond formations are pivotal methods for achieving this goal. The indirect functionalisation of alcohols using catalytic amounts of a metal complex and base which generates only water as a by-product is an attractive green alternative to standard C-C and C-N bond forming reactions. These cascades are termed as Redox – neutral, hydrogen auto transfer or borrowing hydrogen processes.[3]

We and other groups have been involved in the alkylation of amines and active methylene compounds with alcohols catalysed by iridium, rhodium and ruthenium complexes to form new C-N and C-C bonds.[4] Kempe *et al.* have reported new iridium catalysts stabilized by *P*, *N* ligands for the synthesis of quinolines and pyrroles *via* acceptor-less dehydrogenative condensation of primary/secondary alcohols and 1,2- aminoalcohols.[5,6] Benzimidazoles and quinoxalines were also synthesized from aromatic diamines and alcohols *via* an iridium catalyzed acceptor-less dehydrogenative alkylation.[7] Milstein *et al*. have reported the direct conversion of alcohols to amides using a ruthenium pincer complex catalyst.[8] Beller, [9] and Saito[10] have also reported examples for the synthesis of unsymmetrically substituted *N*-heterocyclic compounds *via* a ruthenium catalyzed acceptor-less dehydrogenative coupling process. Recently we have reported an iridium catalyzed chemoselective alkylation of 2'-aminoacetophenone with alcohols to form either new C-C or C-N bonds under microwave irradiation (Scheme 1).[11]



Scheme 1

In this communication we report an iridium catalyzed acceptor-less dehydrogenative coupling of alcohols and 4-hydroxy-6-methyl-2-pyrone to generate 3,3'-(aryl methylene)bis(4-hydroxy-6methyl-2H-pyran-2-ones) under microwave conditions (Scheme 2, Path A).

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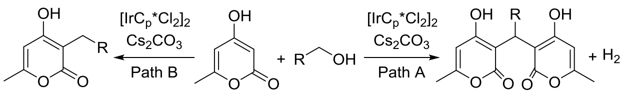


Scheme 2

We initially surveyed a range of catalysts and identified the iridium chloro-bridged compound **1** [X = Cl, M = Ir (III)] (Fig. 2) as an effective catalyst for this transformation (Scheme 2).[11]

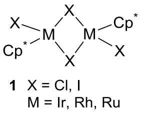
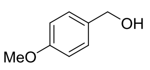
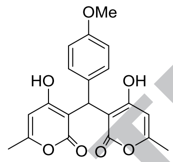
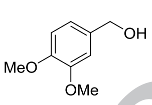
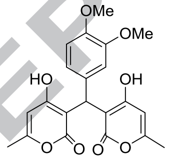
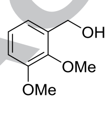
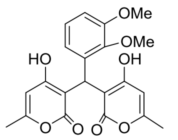
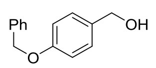
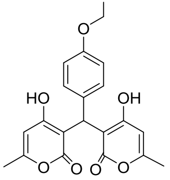
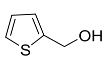
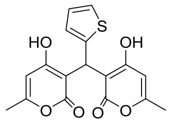
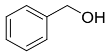
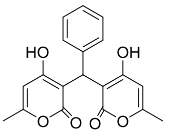
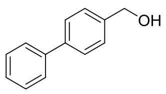
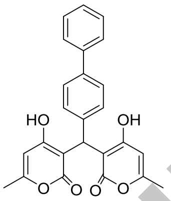
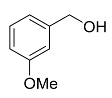
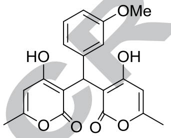
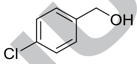
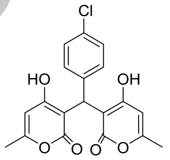
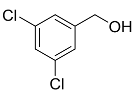
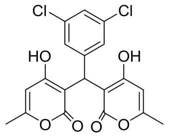


Figure 2

Microwave irradiation has been reported to dramatically accelerate a number of metal catalysed reactions.[12] Further optimisation showed that the reaction could be achieved under microwave conditions (300W, temperature automatically controlled by an IR sensor) and identified cesium carbonate as the base of choice. Initially, we carried out the alkylation reaction of 4-hydroxy-6-methyl-2-pyrone (1 mmol) using *para*-methoxy benzyl alcohol (3 mmol), Cs_2CO_3 (20 mol%) and $[Cp^*IrCl_2]_2$ (2.5 mol%) in toluene (3 mL) at 110 °C for 90 min under microwave irradiation to cleanly afford the bis *C*-alkylated product **1** in 60% yield (Table 1, entry 1).

Table 1. Iridium catalyzed dehydrogenative coupling[a]

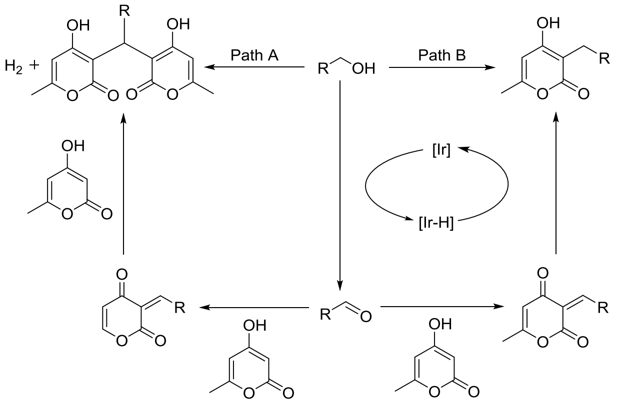
Entry	Alcohol	Product	Yield (%)[b]
1		 1	60
2		 2	70
3		 3	40
4		 4	60
5		 5	65
6		 6	51
7		 7	53
8		 8	70
9		 9	70
10		 10	64

[a] 4-hydroxy-6-methyl-2-pyrone (1 mmol), alcohol (3 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol%), Cs_2CO_3 (20 mol%), 110 °C, 90 min, microwave irradiation. [b] Isolated yield

In the above process, no product was isolated resulting from the redox-neutral pathway (Scheme 2, Path B). No reaction took place in the presence of Cs_2CO_3 alone, under essentially the same microwave conditions as above, indicating that the combination of the iridium complex and base was necessary for the reaction. Lowering the temperature to 80 °C under microwave irradiation (1 hr) afforded only 50% conversion to the product **1**. We elected to keep the temperature at 110 °C for the remainder of the series of reactions.

Benzyl alcohols substituted with electron-withdrawing or donating groups were readily alkylated to afford the corresponding *bis*-pyrone products **2-11** in good yield (40-70%) (Table 1, entries 2-10). The reaction was not significantly affected by either the location or the electronic nature of the substituents on the aryl ring. The heteroaromatic, thiophene-2-methanol was alkylated to give the corresponding *bis*- pyrone product **5** (Table 1 entry 5) in good yield. During all of these reactions the dehydrogenative pathway (Scheme 2, Path A) was observed with none of the mono alkylated derivatives (Scheme 2, Path B) being observed. Traditionally 3,3’-(arylmethylene)bis(4-hydroxy-2H-pyran-2-ones are synthesized from the corresponding aldehydes and 4-hydroxy-6-methyl-2-pyrone.[2, 13]

The proposed mechanism for this transformation involves dehydrogenation of the primary alcohol to generate an aldehyde and metal hydride species. Knoevenagel type condensation followed by a Michael addition process led to the 3,3’-(arylmethylene)bis(4-hydroxy-2H-pyran-2-ones (Scheme 3, Path A). However Knoevnagel type condensation followed by hydrogenation of the double bond by the *in situ* formed metal hydride would give the C-3 alkylated product (Scheme 3, Path B). In this case, the Michael addition competes with the reduction process under the microwave conditions.



Scheme 3

In conclusion we have developed an iridium catalyzed dehydrogenation/ Knoevenagel type condensation/ Michael addition cascade to give 3,3'-bis arylmethenes (Scheme 2, Path A) in good yields.

Acknowledgments

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