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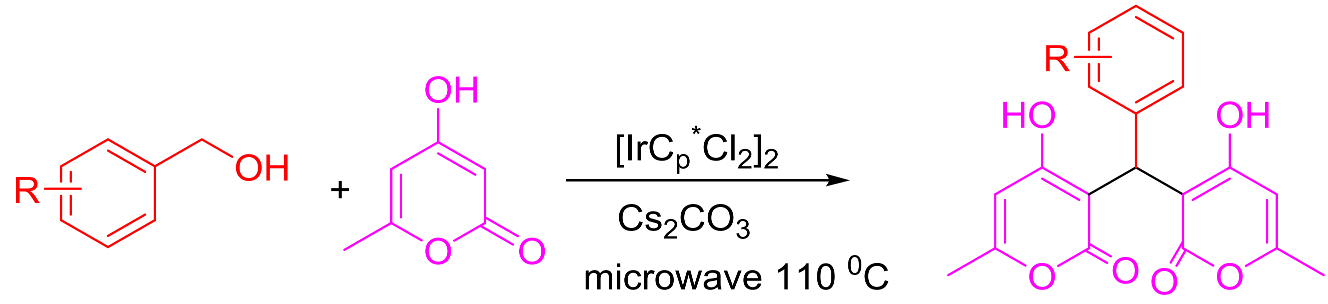
Iridium catalyzed acceptor-less dehydrogenative coupling of alcohols and 4-hydroxy-6-methyl-2-pyrone under microwave conditions.

Mitchell Proud and Visuvanathar Sridharan*



R = Electron donating, neutral and withdrawing group

10 examples

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School of Chemistry, University of Leeds, LS2 9JT , UK

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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 / alkyl methylene)bis(4-hydroxy -2H-pyran-2-ones are important structural skeletons having a wide range of medical properties including anti-inflammatory,[1] and anti coagulant[2] (Fig. 1).

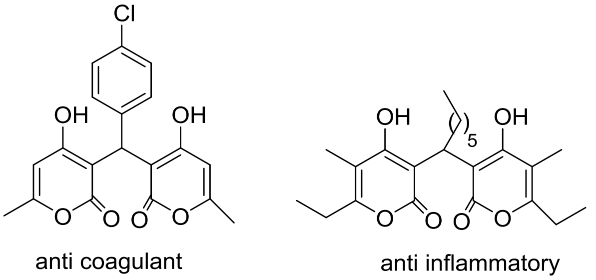
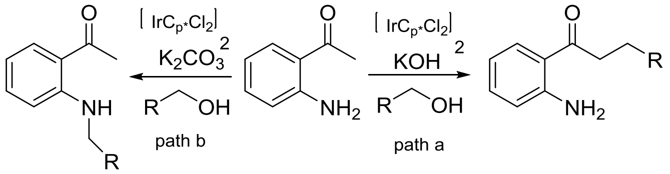


Figure 1

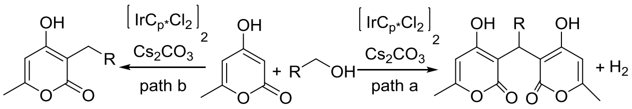
To increase the molecular complexity of a simple organic substrate using efficient (high atom economy), selective, high - yielding, and environmentally benign methods is a significant contemporary challenge for synthetic organic chemists. C-C and C-N bond formations are pivotal methods for achieving this goal. 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 others have been involved in 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 by the use of a ruthenium pincer complex catalyst.[8] Beller, [9] and Saito[10] have also reported example of unsymmetrically substituted N-heterocyclic compounds via a ruthenium catalyzed acceptor-less dehydrogenative coupling process. Recently we have reported an iridium catalyzed chemo selective alkylation of 2' aminoacetophenone with alcohols to form either new C-C or C-N bonds under microwave irradiation (Scheme 1).[11]



Scheme 1

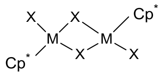
In this communication we report an iridium catalyzed acceptor-less dehydrogenative coupling of alcohols and 4-hydroxy-6-methyl-2-pyrone to generate 3.3'-(aryl methylene)bis(4-hydroxy-2H-pyran-2-ones) (Scheme 2, path a) under microwave conditions.

* Cross ponding Author: V.Sridharan@leeds.ac.uk; Tel +44-1133436520



Scheme 2

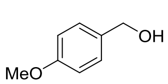
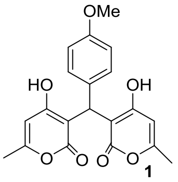
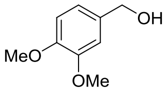
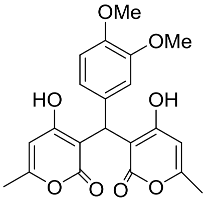
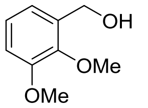
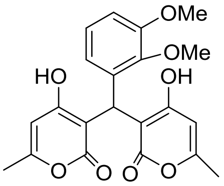
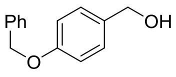
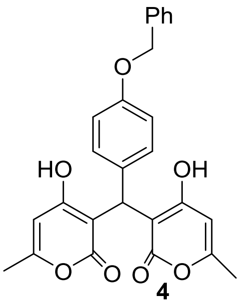
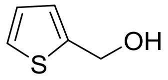
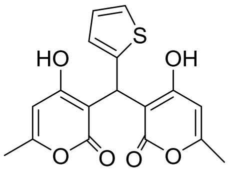
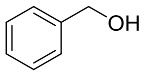
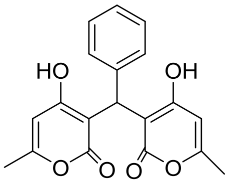
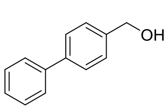
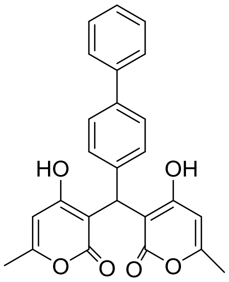
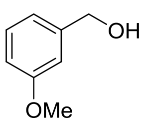
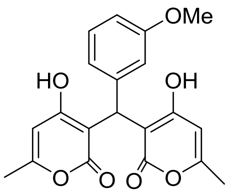
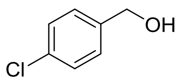
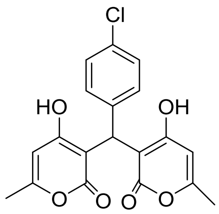
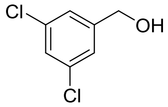
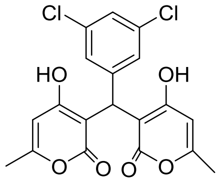
We initially surveyed a range of catalysts and identified the iridium chloro-bridged compound **1** [X = Cl, M = Ir (III)] as an effective catalyst for this transformation (Scheme).



1 X = Cl, I
M = Ir, Rh,Ru

Microwave irradiation is reported to dramatically accelerate a number of metal catalysed reactions.[12] Further optimisation showed that the reaction could be achieved under microwave conditions (300W) and identified cesium carbonate as the base of choice for (Scheme 1 path a). Initially we carried out the alkylation reaction of 4-hydroxy-6-methyl-2-pyrone (1 mmol) with para methoxy benzyl alcohol (2 mmol), Cs_2CO_3(20 mol%) and $[Cp^*IrCl_2]_2$ (2.5 mol%) in toluene (3mL) at 110 °C for 90 min in the microwave which afforded cleanly 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

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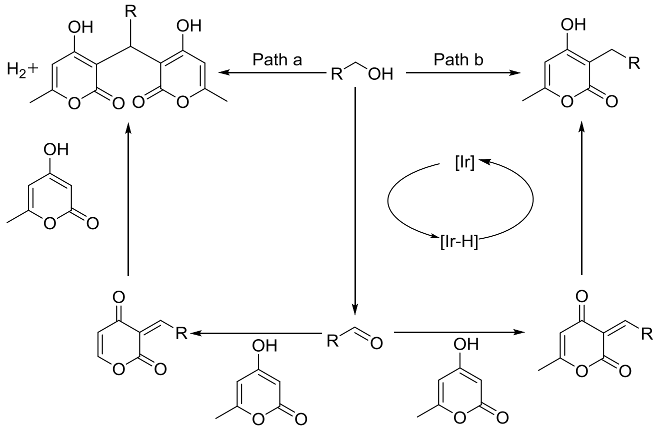
[a] 4-hydroxy-6-methyl-2-pyrone (1 mmol), alcohol (2 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol%), Cs_2CO_3(20 mol%) , 110 °C, 90 min in microwave. [b] Isolated yield

In the above process no product could be isolated from the redox-neutral pathway (Scheme 2, path b). No reaction took place in the presence of Cs_2CO_3 alone, indicating that the combination of the iridium complex and a base is necessary for the reaction. 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 substituent on the aryl ring. The heteroaromatic, thiophene-2-methanol was alkylated to the corresponding bis pyrone product (Table 1 entry 5) in good yield. During all these reactions clean dehydrogenative pathway (Scheme 2, path a) was observed with none of the mono alkylated derivatives (Scheme 2, path b) were observed. Traditionally 3.3’-(arylmethylene)bis(4-hydroxy-2H-pyran-2-ones are synthesized from the crosponding aldehydes and 4-hydroxy-6-methyl-2-pyrone.[1]

The proposed mechanism for this transformation involves dehydrogenation of the primary alcohol to generate an aldehyde and metal hydride species. Knoevenagel type condensation occurs followed by a Michael addition process leading 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 Michael addition is competing with the reduction process under the microwave conditions.



Scheme 3

In conclusion we have developed an iridium catalyzed dehydrogenation/ Knoevenagel type condensation/ Michael addition cascades to 3,3’-bis arylmethenes (Scheme 2, path a) in good yields.

Acknowledgments

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