Sequential one-pot bimetallic Ir(III)/Pd(0) catalysed mono-/bis-alkylation and spirocyclisation processes of 1,3-dimethylbarbituric acid and allenes†

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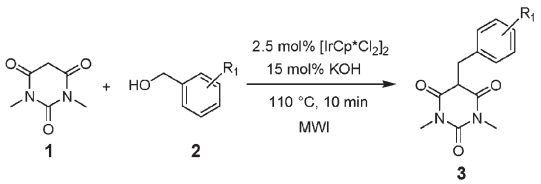
Microwave assisted indirect functionalization of alcohols with 1,3-dimethylbarbituric acid followed by spirocyclisation employing a sequential one-pot Ir(III)/Pd(0) catalysed process, involving the formation of three new C–C bonds, one spirocyclic ring and one di- or tri-substituted exocyclic alkene, is described.

5-Alkylated or benzylated barbituric acids have proven useful both as pharmaceuticals and as important intermediates in the synthesis of new drugs.[1] Barbiturates produce changes in mental activity ranging from mild sedation and sleep, to deep coma and are commonly used in the treatment of anxiety, insomnia, seizure disorders, migraine headaches, and in surgery as general anaesthetics.[2]

More recently, derivatives of barbituric acids have been reported to exhibit anti-cancer, analeptic, immunomodulating and anti-AIDS activity[3] whilst others are reported to be selective matrix metalloproteinase (MMP) inhibitors.[4] It is therefore clear that the barbituric acid skeleton is an intriguing and reemerging member of the privileged structure class.

There was no simple general synthetic procedure for the preparation of 5-monoalkylated barbituric acid derivatives until, quite recently, Jursic *et al.* described an effective reductive alkylation protocol.[5] Direct catalytic alkylation with alcohols is an alternative and attractive green chemistry solution[6,7] which generates only water as a byproduct. In this communication we report microwave assisted redox neutral processes (Scheme 1) for the selective monoalkylation of 1,3-dimethylbarbituric acid by alcohols and their extension to sequential one-pot bimetallic Ir(III)/Pd(0) catalytic processes that afford either spirocyclic barbiturates **6** or unsymmetrical *C*5-bis-benzylated/2′-arylallylated barbiturates **8**. In an initial series of experiments we demonstrated that our solvent-free microwave protocol developed for α-alkylation of arylacetonitriles with alcohols[6f] was equally effective with



Scheme 1

Table 1 Catalytic alkylation of 1,3-dimethylbarbituric acid **1** with various alcohols **2** under solvent-free microwave irradiation (MWI) conditions[a]

Entry	Alcohol	Product	Yield (%)[b]
1	**2a**	**3a**	84
2	**2b**	**3b**	79
3	**2c**	**3c**	83
4	**2d**	**3d**	82
5	**2e**	**3e**	76[c]
6	**2f**	**3f**	74
7	**2g**	**3g**	84[d]
8	**2h**	**3h**	85[d]
9	**2i**	**3i**	91

[a] The reaction was carried out in a microwave reactor with **1** (1 mmol), alcohol (1.5 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%) and KOH (15 mol%) at 110 °C for 10 min. [b] Isolated yield. [c] Alcohol (1.5 mmol) was used in toluene (0.5 mL) for 10 min. [d] Reaction was performed using traditional heating with alcohol (1.0 mL) at 100 °C for 14 h.

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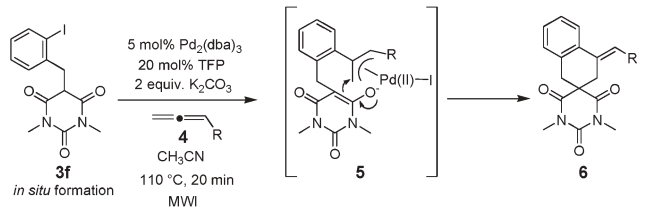
† Electronic supplementary information (ESI) available: Experimental data. See DOI: 10.1039/b614098j

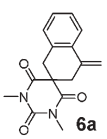
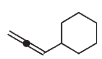
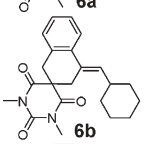
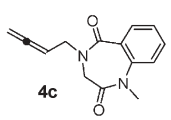
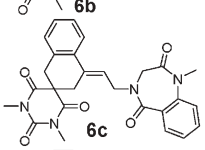
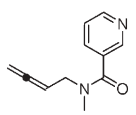
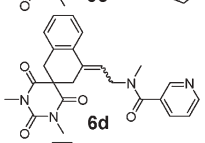
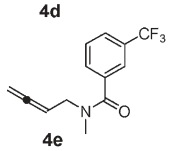
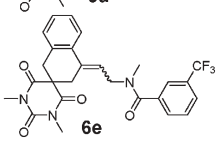


Scheme 2

N,*N*′-dimethylbarbituric acid **1** (Scheme 1, Table 1). A variety of benzylic alcohols were successfully utilised to afford *C*5-mono-alkylated products **3a–f** in high yields (Table 1, entries 1–6). Aliphatic alcohols such as ethanol **2g** and 2-methyl propanol **2h** failed to undergo any reaction using our standard microwave conditions but conventional thermal heating (100 °C, 14 h) resulted in full conversion to products **3g** and **3h** which were isolated in 84 and 85% yield, respectively (Table 1, entries 7 and 8). The bis-alcohol **2i** proved to be an excellent cascade substrate for the microwave protocol, affording **3i** in 91% yield.‡

Formation of **3f** opens up further C–C bond formation with allene/substituted allenes **4a–f** under palladium(0) catalysis to form 6-membered spirocyclic barbiturates **6**. The reaction takes place *via* allene insertion to the arylpalladium(II) iodide species to generate a π-allyl intermediate **5** followed by cyclisation to afford spirocyclic barbituric acid derivatives **6** (Scheme 2).

Table 2 *Inter–intra*-molecular sequential one-pot Ir(III)/Pd(0) catalysed cascades[a]

Entry	Allene	Product	Yield (%)[c]
1[b]	 **4a**	 **6a**	42
2	 **4b**	 **6b**	52
3	 **4c**	 **6c**	53
4	 **4d**	 **6d**	59 *E* : *Z*, 87 : 13
5	 **4e**	 **6e**	50 *E* : *Z*, 95 : 5

[a] The reaction was carried out in a microwave reactor with **1** (1 mol equiv.), alcohol (1.2 mol equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%) and KOH (15 mol%) at 110 °C for 10 min followed by addition of **4** (1.2 mol equiv.), Pd_2dba_3 (5 mol%), TFP (20 mol%), K_2CO_3 (2 mol equiv.), CH_3CN (2 mL) and the reaction was continued under microwave irradiation at 110 °C for 20 min. [b] Allene gas (0.5 bar) was used. [c] Isolated yield.

Investigation of this sequential one-pot Ir(III)/Pd(0) catalysed process clearly demonstrated that iridium and palladium were compatible. A series of microwave activated sequential one-pot Ir(III)/Pd(0) cascades were performed utilising both allene gas and substituted allenes (Table 2). This bimetallic cascade reaction involves a number of fundamental organic transformations: oxidation of an alcohol to the corresponding aldehyde, Knoevenagel condensation of the *in situ* formed aldehyde and the barbituric acid, reduction of the Knoevenagel product, oxidative addition of Pd(0) to the aryl iodide followed by allene insertion generating a π-allyl Pd(II) complex. Finally, this species is captured in a regio- and stereoselective *intra*-molecular nucleophilic attack of the barbiturate *C*5-carbanion at the least hindered sp^2-carbon atom of the π-allyl species affording the *E*-alkene. This highly atom-economic cascade involves the formation of three new C–C bonds, one tetrasubstituted carbon centre, one spirocyclic ring and one di- or tri-substituted exocyclic alkene. Alkene stereochemistry was assigned from n.O.e. data and confirmed, in the case of **6b**, by X-ray crystallography (Fig. 1).§ There are two independent molecules in the asymmetric unit of which only one is shown in Fig. 1.

We believe this stereoselectivity arises from steric destabilization of the *syn*-π-allyl palladium complex *syn*-**9** favouring initial formation of *anti*-**9** (Scheme 3) and suppressing π–σ–π isomerization.

Inter–inter-molecular versions of this sequential *inter–intra* one-pot bimetallic Ir(III)/Pd(0) cascade were also performed using

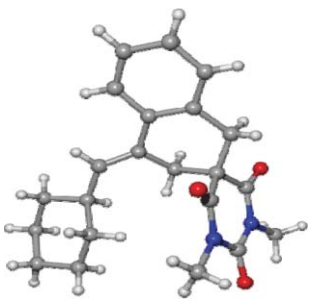
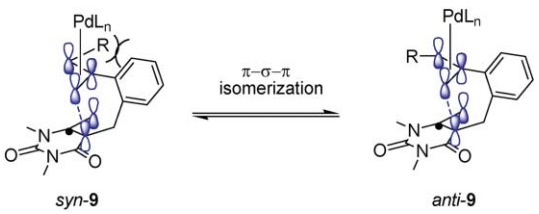
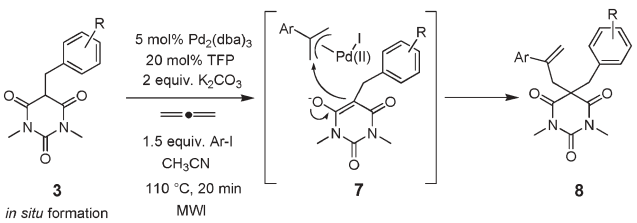


Fig. 1 X-Ray crystal structure of **6b**.

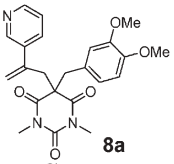
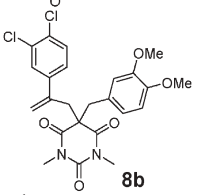
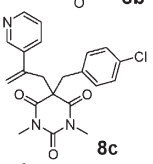
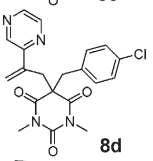
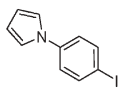
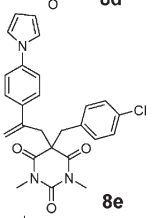
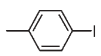
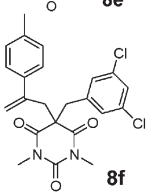


Scheme 3



Scheme 4

Table 3 *Inter–inter*-molecular sequential one-pot Ir(III)/Pd(0) catalysed cascades[a]

Entry	Alcohol	Ar–I	Product	Yield (%)[b]
1	**2b**		 **8a**	45
2	**2b**		 **8b**	51
3	**2d**		 **8c**	65
4	**2d**		 **8d**	48
5	**2d**		 **8e**	53
6	**2e**		 **8f**	56

[a] The reaction was carried out in a microwave reactor with **1** (1 mmol), alcohol (1.5 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%) and KOH (15 mol%) at 110 °C for 10 min followed by addition of Pd_2dba_3 (5 mol%), TFP (20 mol%), aryl iodide (1.5 mmol), K_2CO_3 (2 mmol), CH_3CN (2 mL) and allene (0.5 bar). The reaction was continued under microwave irradiation at 110 °C for 20 min. [b] Isolated yield.

substituted benzyl alcohols together with an aryl iodide and allene gas, as the three carbon component, to afford unsymmetrical *C*5-bis-benzylated/2′-arylallylated products **8a–f** (Scheme 4, Table 3).

The X-ray crystal structure§ of **8b** (Fig. 2) suggests there may be some carbonyl π-stacking interaction with the dichloroaryl ring. Thus, the centroid of the dichloroaryl ring is 3.7 Å from the *C*6 and 4.1 Å from the *C*2 carbonyl *C*-atoms.

Further work on these and related Ir(III)/Pd(0) catalysed processes is currently underway.

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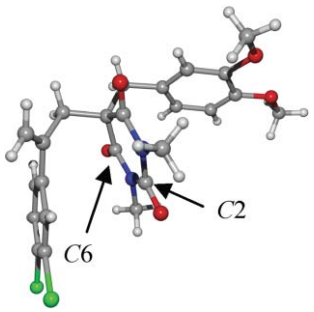

Fig. 2 X-Ray crystal structure of **8b**.

Notes and references

‡ During the purification of the *C*5-monoalkylated barbiturates **3a–i** and when left in chloroform for slow evaporation at ambient temperature an autoxidation at the *C*5-position was observed.

§ Crystallographic data: **6b**; CCDC 622415. **8b**; CCDC 622416. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614098j

1 For instance, see: C. M. Smith and A. M. Reynard, *Essentials of Pharmacology*, W. B. Sanders, Philadelphia, 1995.

2 For general information see: Central Nervous System Drugs, Sedatives and Hypnotics, Barbiturates, ed. B. R. Olin, in *Facts and Comparisons Drug Information*, Facts and Comparisons, St. Louis, MO, p. 1398.

3 (*a*) F. N. M. Naguib, D. L. Levesque, E.-C. Wang, P. P. Panzica and M. H. El Kouni, *Biochem. Pharmacol.*, 1993, **46**, 1273; (*b*) D. L. Levesque, E.-C. Wang, D.-C. Wei, M. H. El Kouni and F. N. M. Naguib, *J. Heterocycl. Chem.*, 1993, **30**, 1399; (*c*) A. Oliva, G. De-Cillis, F. Grams, V. Livi, G. Zimmerman, E. Menta and H. W. Krell, *US Pat.*, 6,335,332, B1, 2002; (*d*) R. I. Ashkinazi, *Int. Pat.*, WO 99/25699, 1999; (*e*) D. M. Neumann, B. S. Jursic and L.-R. Morgan, Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23–27, 2003.

4 (*a*) D. T. Puerta and S. M. Cohen, *Curr. Top. Med. Chem.*, 2004, **4**, 1551; (*b*) J. W. Skiles, N. C. Gonnella and A. Y. Jeng, *Curr. Med. Chem.*, 2004, **11**, 2911.

5 (*a*) B. S. Jursic and D. M. Neumann, *Tetrahedron Lett.*, 2001, **42**, 4103; (*b*) B. S. Jursic and E. D. Stevens, *Tetrahedron Lett.*, 2003, **44**, 2203.

6 (*a*) C. E. Bibby, R. Grigg and R. Price, *J. Chem. Soc., Dalton Trans.*, 1977, 872; (*b*) R. Grigg, T. R. B. Mitchell and S. Sutthivaiyakit, *Tetrahedron Lett.*, 1979, **35**, 1067; (*c*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc., Chem. Commun.*, 1981, 611; (*d*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *Tetrahedron Lett.*, 1981, **22**, 4107; (*e*) R. Grigg, T. R. B. Mitchell and S. Sutthivaiyakit, *Tetrahedron*, 1981, **37**, 4313; (*f*) C. Löfberg, R. Grigg, M. A. Whittaker, A. Keep and A. Derrick, *J. Org. Chem.*, 2006, **71**, 8023.

7 For recent examples of similar transfer hydrogenation processes see: (*a*) P. J. Black, G. Cami-Kobeci, M. G. Edwards, P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Org. Biomol. Chem.*, 2006, **4**, 116; (*b*) R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8982; (*c*) R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8988; (*d*) K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2004, **126**, 5662; (*e*) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72.

