

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

Christian Löffberg,^a Ronald Grigg,^{*a} Ann Keep,^b Andrew Derrick,^c Visuvanathar Sridharan^a and Colin Kilner^a

Received (in Cambridge, UK) 28th September 2006, Accepted 27th October 2006

First published as an Advance Article on the web 15th November 2006

DOI: 10.1039/b614098j

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.

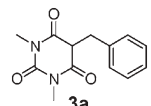
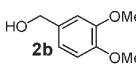
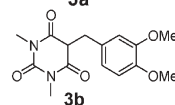
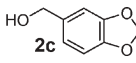
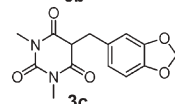
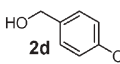
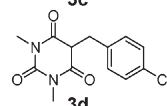
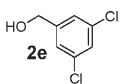
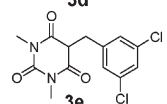
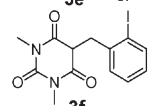
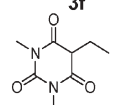
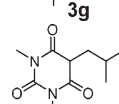
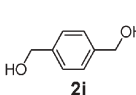
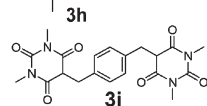
5-Alkylated or benzylated barbituric acids have proven useful both as pharmaceuticals and as important intermediates in the synthesis of new drugs.¹ Barbiturates produce changes in mental activity ranging from mild sedation and sleep, to deep coma and are commonly used in the treatment of anxiety, insomnia, 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 activity³ 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.

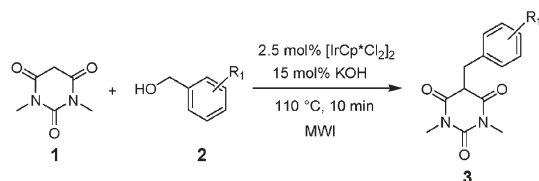
There was no simple general synthetic procedure for the preparation of 5-monoalkylated barbituric acid derivatives until, quite recently, Jursic *et al.* described an effective reductive alkylation protocol.⁵ Direct catalytic alkylation with alcohols is an alternative and attractive green chemistry solution^{6,7} 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 C5-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

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			84
2			79
3			83
4			82
5			76 ^c
6			74
7			84 ^d
8			85 ^d
9			91

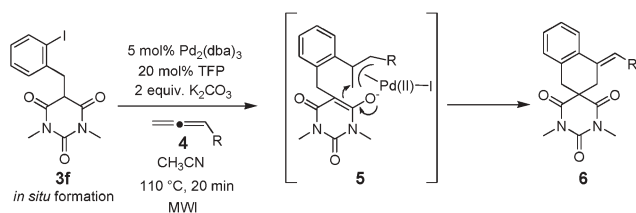
^a The reaction was carried out in a microwave reactor with **1** (1 mmol), alcohol (1.5 mmol), [Cp*IrCl₂]₂ (2.5 mol%) and KOH (15 mol%) at 110 °C for 10 min. ^b Isolated yield. ^c Alcohol (1.5 mmol) was used in toluene (0.5 mL) for 10 min. ^d Reaction was performed using traditional heating with alcohol (1.0 mL) at 100 °C for 14 h.



Scheme 1

^a Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, University of Leeds, Leeds, UK LS2 9JT. E-mail: r.grigg@leeds.ac.uk; Fax: 0113 343 6530; Tel: 0113 343 6501
^b Johnson Matthey, Orchard Road, Royston, Herts, UK SG8 5HE
^c Pfizer, Ramsgate Road, Sandwich, Kent, UK CT13 9NJ

† 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

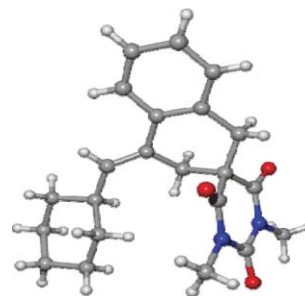
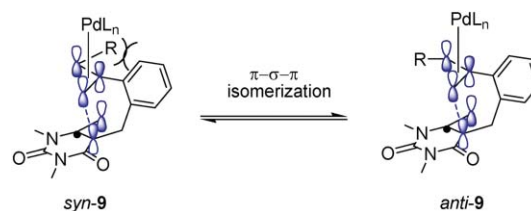
Entry	Allene	Product	Yield (%) ^c
1 ^b			42
2			52
3			53
4			59 <i>E</i> : <i>Z</i> , 87 : 13
5			50 <i>E</i> : <i>Z</i> , 95 : 5

^a The reaction was carried out in a microwave reactor with **1** (1 mol equiv.), alcohol (1.2 mol equiv.), [Cp*IrCl₂]₂ (2.5 mol%) and KOH (15 mol%) at 110 °C for 10 min followed by addition of **4** (1.2 mol equiv.), Pd₂dba₃ (5 mol%), TFP (20 mol%), K₂CO₃ (2 mol equiv.), CH₃CN (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.

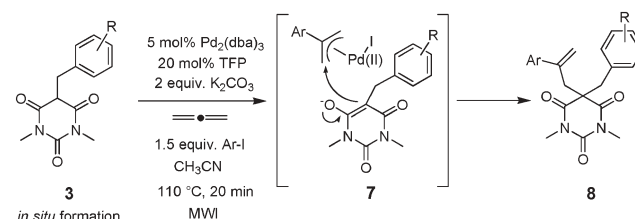
Investigation of this sequential one-pot Ir(III)/Pd(0) catalysed process clearly demonstrated that iridium and palladium were compatible. A series of microwave activated sequential one-pot Ir(III)/Pd(0) cascades were performed utilising both allene gas and substituted allenes (Table 2). This bimetallic 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 sp²-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

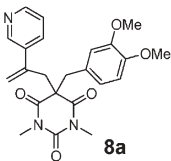
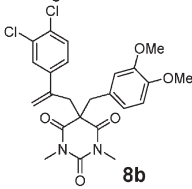
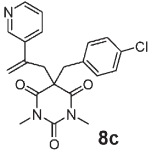
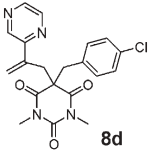
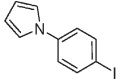
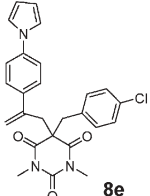
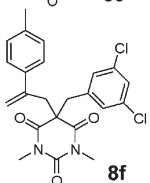
Fig. 1 X-Ray crystal structure of **6b**.

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

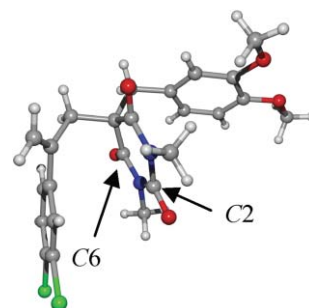
^a The reaction was carried out in a microwave reactor with **1** (1 mmol), alcohol (1.5 mmol), [Cp*IrCl₂]₂ (2.5 mol%) and KOH (15 mol%) at 110 °C for 10 min followed by addition of Pd₂dba₃ (5 mol%), TFP (20 mol%), aryl iodide (1.5 mmol), K₂CO₃ (2 mmol), CH₃CN (2 mL) and allene (0.5 bar). The reaction 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 C5-bis-benzylated/2'-arylallylated products **8a–f** (Scheme 4, Table 3).

The X-ray crystal structure^s 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 C6 and 4.1 Å from the C2 carbonyl C-atoms.

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

This work was a collaboration between the MIDAS Centre, Johnson Matthey and Pfizer (Process R&D). C. L. was financially

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

supported by JM. Colin Kilner is gratefully acknowledged for providing X-ray crystal structures. The Green Chemistry Centre for Industrial Collaboration and Yorkshire Forward are acknowledged for funding the CEM microwave reactor.

Notes and references

‡ During the purification of the C5-monoalkylated barbiturates **3a–i** and when left in chloroform for slow evaporation at ambient temperature an autoxidation at the C5-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

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