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Iodobenzene catalysed synthesis of spirofurans and benzopyrans by oxidative cyclisation of vinylogous esters†

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Vinylogous esters bearing *para* or *meta* methoxy benzyl groups undergo oxidative cyclisation with 5–20 mol% iodobenzene and *m*-CPBA to give spirofuran or benzopyran containing heterocycles. The reaction allows rapid generation of skeletal complexity in good to excellent yields *via* a novel oxidative cyclisation.

The scope of λ3-iodonium reagents in modern synthesis is remarkable.[1–7] In addition to being stoichiometric oxidants ideally suited to transition metal catalysed C–H aminations,[2] oxygenation,[3] and couplings;[4] they directly mediate a range of cyclisations[5] and rearrangements.[6]

The oxidative cyclisations of electron rich aromatics are an important class of hypervalent iodine mediated reaction.[7–9] While allowing rapid generation of complexity from ubiquitous starting materials, such reactions proceed using environmentally mild conditions.[8] Although a range of carbon and heteroaromatic nucleophiles have been exploited,[7] the use of ketones is yet to be realised. We postulated that by using a sufficiently nucleophilic ketone, such as a vinylogous ester (*i.e.* **1**),[9] it should be possible to access either spirocyclic, or ring-fused, oxygen heterocycles. Beyond synthetic novelty, these heterocyclic products (*i.e.* **2** and **3**) are well represented in bioactive and naturally occurring products,[10] thus the realisation of this methodology would have potentially broad significance (Fig. 1).

Herein, we report our studies on this topic, that have resulted in the discovery of a novel oxidative cyclisation, which provides access to both spirocyclic furans and benzopyrans. Optimal results were obtained using catalytic iodobenzene, making this transformation one of a limited family of hypervalent iodine mediated transformations viable under catalytic conditions.[11]

Exploratory studies commenced with vinylogous ester **1a**, prepared in one step from commercial materials.[12] While this substrate bore the required electron rich ketone an initial concern related to the potential for this functionality to undergo oxidation. Thus, it was satisfying to find that when **1a** was treated with 1.5 equivalents of phenyliodonium *bis*(trifluoroacetate) (PIFA) in 2,2,2-trifluoroethanol (TFE)[13] 52% conversion into the spirocyclic furan **2a** was observed by LCMS (Table 1, entry 1). The reaction was comparable when conduced in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), but poorer using trifluoroacetic acid (TFA) (Table 1, entries 2 and 3). An optimal solvent mixture of 9 : 1 HFIP/TFA increased the conversion to 71% (Table 1, entry 4), while with phenyliodonium diacetate (PIDA) the conversion increased to 83% (Table 1, entry 5). Unfortunately, while the conversion was acceptable, isolation of the product from the unreacted iodonium reagents and aryl iodide was challenging, and decreased the yield (Table 1, entry 5).

To increase the efficiency of the transformation, and improve the isolated yield, the reaction was trialled using 10 mol% iodobenzene and 3.0 equivalent of *m*-CPBA.[14,15] To our great

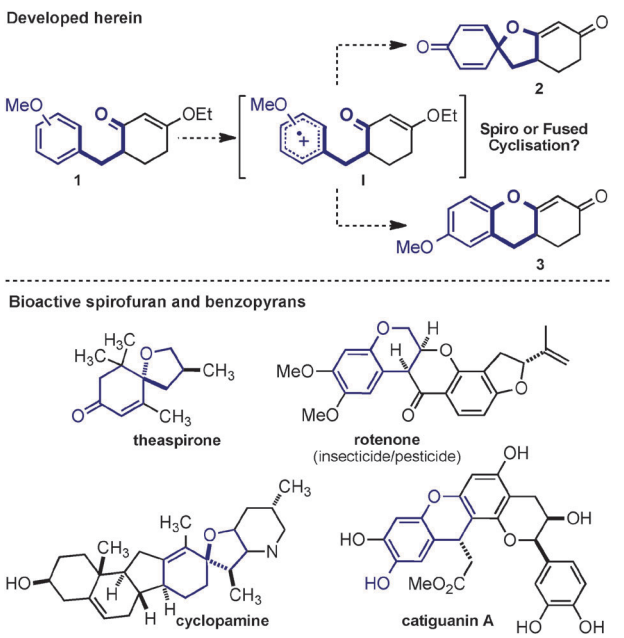

Fig. 1 Proposed studies and spirofuran and benzopyran heterocycles.

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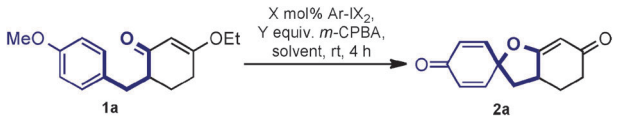
† Electronic supplementary information (ESI) available: experimental details, ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c1cc15015d

Table 1 Selected reaction optimisation



Entry	[equiv.] $PhIX_2$	[equiv.] *m*-CPBA	Solvent	Yield[a]
1[b]	1.5 $PhI(TFA)_2$	—	TFE	(52)[c]
2[b]	1.5 $PhI(TFA)_2$	—	HFIP	(52)[c]
3[b]	1.5 $PhI(TFA)_2$	—	TFA	(16)[c]
4[b]	1.5 $PhI(TFA)_2$	—	9 : 1 TFE/TFA	(71)[c]
5[b]	1.5 $PhI(OAc)_2$	—	9 : 1 HFIP/TFA	(83)[c] 58
6	0.1 PhI	3.0	9 : 1 HFIP/TFA	73
7	**0.1 PhI**	**1.5**	**9 : 1 HFIP/TFA**	**75**
8[d]	0.05 PhI	1.5	9 : 1 HFIP/TFA	71
9	—	1.5	9 : 1 HFIP/TFA	0

[a] Isolated yield following column chromatography except as noted. [b] Reaction conducted at 0 °C. [c] Conversion calculated by LCMS using a calibrated method. [d] Reaction conducted for 14 h.

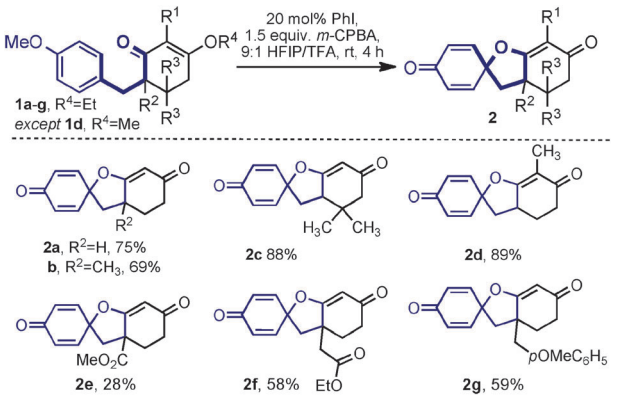
satisfaction these conditions provided spirofuran **2a** in 73% isolated yield (Table 1, entry 6). Decreasing the oxidant loading had little effect on the outcome (Table 1, entry 7), nor did decreasing catalyst loading to 5 mol%, although in the later case the reaction was slower (Table 1, entry 8). The role of the aryl iodide was examined, with no background cyclisation observed in its absence (Table 1, entry 9).

To examine the utility of this transformation *para*-methoxy benzyl substituted vinylogous esters **1a–g** were prepared and oxidized using 20 mol% iodobenzene and 1.5 equivalents of *m*-CPBA, conditions that gave reliable results, in a timely fashion. Of interest was the reactions sensitivity to other potentially nucleophilic functionality and steric congestion. In the event the reaction tolerated substitution at various positions about the cyclohexenone, providing spirofurans **2a–d**, and quaternary carbon containing spirofurans **2b**, **f** and **g**, in good yield. The reaction was equally viable using 3-methoxy cyclohexen-2-one derived substrates (*i.e.* **1d**), as 3-ethoxy substrates. When the β-keto ester derived starting material **1e** was examined **2e** formed in 28% yield. The low yield was presumably due to side reactions involving interception of the radical cation by the ester functionality.

In order to access benzopyran heterocycles the oxidation of substrates bearing *meta*-methoxy benzyl substituents was examined. Fortunately, the reaction conditions developed to access spirofurans (Table 2) translated very well, allowing benzopyrans **3h–n** to be accessed in good yields (Table 3). As with the spirofuran synthesis it was possible to generate diversely functionalised benzopyrans including those bearing quaternary carbon centres.

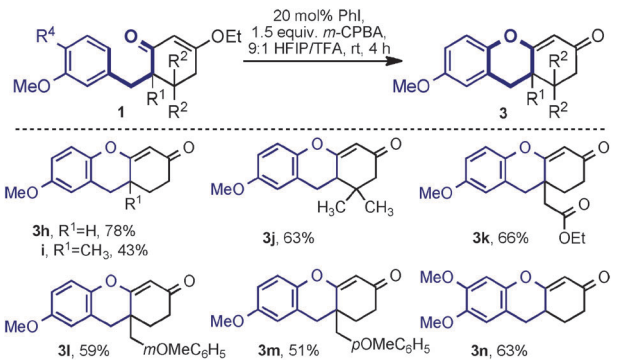
The cyclisation of vinylogous ester **1m** allows the relative rate of spirofuran and benzopyran formation to be compared (Scheme 1). When this substrate was reacted benzopyran **3m** was isolated in 51% yield while spirofuran **2m** was not observed. In the work of Kita it is proposed that oxidation of both *meta* and *para* methoxy aromatic compounds initially generates the corresponding radical cation.[9] The observation of a single product from the reaction of **1m** suggests that either the rate of oxidation of the *meta*-methoxy aryl group is significantly faster than the *para*, or that cyclisation of the

Table 2 Scope of the oxidative synthesis of spirofuran **2**[a]

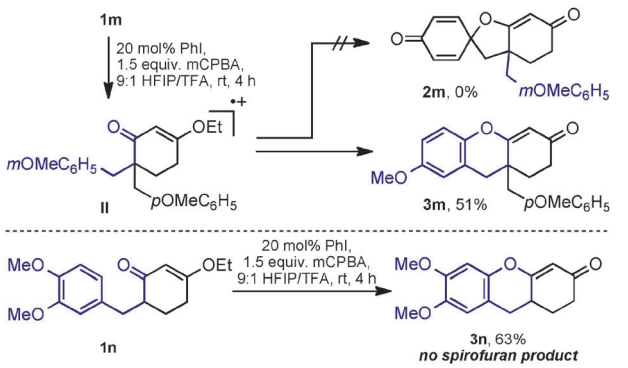


[a] Isolated yield following column chromatography.

Table 3 Scope of the oxidative synthesis of benzopyran **3**[a]



[a] Isolated yield following column chromatography.



Scheme 1 Preferential benzopyran formation.

meta-methoxy radical cation is faster, and that equilibration between the two radical cationic intermediates **II**[16] is possible. To clarify the mechanism of this transformation the cyclisation of vinylogous ester **1n** can be considered. In this case preferential formation of benzopyran products was observed. While these results don't eliminate the former mechanism, it is difficult to rationalise oxidation of the *meta*-methoxy aromatic without any observable oxidation of the *para*-methoxy. Interestingly, this preference for benzopyran formation is in contrast to the preferential spiro cyclisation observed by Kita in related

oxidative lactonisations of electron rich aromatics.[7c] While the origin of this difference in reactivity is not obvious it may relate to the annulation in our substrates disfavouring formation of the spirocyclic products.

Vinylogous esters are valuable synthetic building blocks, with well-defined reactivity, thereby allowing ready access to diversely functionalised materials.[12] The chemistry developed herein expands the utility of these materials, providing facile approaches to spirofuran **2** and benzopyran **3** heterocycles.

Key mechanistic events involve oxidation of the electron rich aromatic ring, by the *in situ* generated hypervalent iodonium reagent, and trapping with the electron rich vinylogous ester. The use of catalytic iodobenzene contributed significant advantages over the stoichiometric variant of this reaction, and illustrates a new catalytic hypervalent iodine mediated reaction. Future studies aim to exploit this novel mode of cyclisation to rapidly access complex polycyclic oxygen heterocycles in the context of total synthesis and medicinal chemistry.

The application of non-traditional nucleophiles in oxidative cyclisation is an emerging theme.[7] The study presented herein demonstrates novel deployment of vinylogous esters as electron-rich aprotic nucleophiles. The development of alternate nucleophiles for oxidative transformations has great potential to deliver useful transformations for rapid skeletal complexity generation, and is a subject of ongoing studies within our laboratories.

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