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Aryl-aryl cross-coupling reactions without reagents or catalysts: photocyclization of ortho-iodoaryl ethers and related compounds via triplet aryl cation intermediates:

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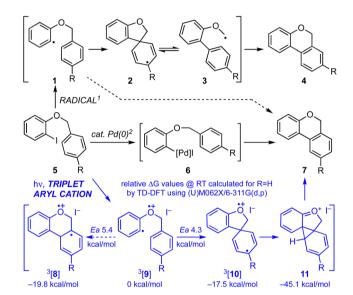


Cyclisations of benzyl ortho-iodoaryl ethers to benzo[c]chromenes can be effected without reagents or catalysts by irradiation with UVC under flow. Reactions proceed via triplet aryl cation generation, 5-exo and 3-exo-cyclisations, and rearomatisation. They have wide scope, are easy to effect and extend to a myriad of related ring systems.

Cyclisations of benzyl ortho-iodoaryl ethers to benzo[c]chromenes, e.g. $5 \rightarrow 4$ or 7 (Scheme 1) are typically achieved by radical cyclisation, or palladium catalysed cross-coupling reactions.2 The products given by the two approaches can differ when cyclisation involves addition to a substituted arene. Thus, while the Pd catalysed cyclisation occurs ortho- to the tethering chain, giving benzoisochromene 7,2 cyclisation via aryl radical intermediate 1 principally gives benzoisochromene 4 through a neophyl rearrangement via ipso-cyclisation to 2 and fragmentation to 3.1,3 Herein we show how it is possible to induced cyclisation without reagents or catalysts through irradiation with UVC.4 Notably, reactions give ortho-addition products 7 rather than those derived by a radical-induced neophyl rearrangement 4, implicating the intermediacy of triplet aryl cations ³[9] and ³[10], ⁵ as supported by TD-DFT calculations. ⁶

Our investigation began with benzyl ortho-iodophenyl ether 5a which, on irradiation with UVC under continuous flow in acetonitrile at ambient temperature, gave benzoisochromene 7a in 78% yield (Scheme 2). To determine if the reaction proceeded via radical intermediate 1, the method was extended to substrates 5b-d with a para-substituent on the benzyl ether residue. In each case cyclisation gave regioisomer 7 rather than 4 indicating that they did not proceed via aryl radical intermediates 1b-d (see ESI‡ for further discussion).1 We next examined the reaction by TD-DFT,6 and found that the 5-exo-

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Scheme 1 Regiochemical outcomes for the common cyclisation reactions of benzyl ortho-iodoaryl ethers [R = H for calculated relative ΔG values via triplet aryl cation 9]

trig cyclisation mode also appeared to be favoured by the corresponding triplet aryl cation ³[9], with 6-exo/endo-trig cyclisation to ³[8] having a higher activation energy. However, relaxation of the thus formed intermediate ³[10] led to spontaneous cyclisation to tetracycle 11, setting up a facile double aromatisation with loss of HI to give the observed product 7. The yields attained in these early experiments indicated that benzyl residues carrying an electron withdrawing substituent (5c) were poorer substrates than those carrying electron donating substituents (5b,d). To probe the impact of substituents further, a series of benzyl o-iodoaryl ethers were prepared with substituents on the iodinated arene, 5e-h, and with substituents on both arenes, 5i-l (Table 1). These experiments showed that yields were enhanced by electron donating substituents on the iodinated arene (7e,f,i-k) and were supressed by electron withdrawing substituents (7g,h). Notably, the reaction was also

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Scheme 2 Regiochemistry observed for cyclisations to substituted benzyl ethers.

Table 1 Photocyclisations of benzyl *ortho*-iodoaryl ethers to benzoiso-chromenes

† 1 equiv. pyridine added.

given in modest yield by benzyl 2-iodo-3-methoxyphenyl ether 5l. In this case we believe a complex product mixture was given due to the sensitivity of the starting material and product 7l towards the HI formed as a by-product of the reaction.⁷

Indeed, while the method was being developed, several starting materials and products proved susceptible to benzyl ether cleavage by HI.⁷ For example, photolysis of *p*-nitrobenzyl *o*-iodophenyl ether led to a complex product mixture from which *p*-nitrobenzyl iodide was isolated in low yield. Similarly, 3,5-dimethylbenzyl ether 5m gave the anticipated product 7m in 32% isolated yield together with biaryl 12 as a significant byproduct (Scheme 3). Its formation implicates benzoisochromene cleavage to benzyl iodide 13 followed by a Ritter reaction with acetonitrile.⁸ Such side reactions were attenuated by an expeditious work-up and/or the addition of an equivalent of pyridine to the reaction mixture (*e.g.* Table 1).

The photocyclisation was next extended to analogous pyridyl ethers **15a-d** (Table 2) leading respectively to heterocycles **16a-d**. It also proved effective for the synthesis of an array of polyaromatic ring systems through related photocyclisation (Scheme 4) and tandem photocyclisation reactions (Scheme 5). It is notable that lower yields were generally associated with products bearing substituents in the 'fjord' region (Scheme 4),

Scheme 3 A side reaction promoted by HI involving benzoisochromene cleavage by HI and a Ritter reaction.

Table 2 Photocyclisations of benzyl and pyridyl 2-iodopyrid-3-yl ethers

Scheme 4 Photocyclisations leading to polyaromatic ring systems.

indicating their increased sensitivity towards ethereal cleavage by HI due to steric strain. Nonetheless, the method was able to produce a myriad of polyaromatic ring systems, including oxahelicene 25 and terphenyls 31 and 32 (Schemes 4 and 5).

The presence of *ortho*-substituents on the benzyl ether was investigated next and revealed a further subtlety (Scheme 6). When both *ortho* sites carried methyl substituents, **5n**, cyclisation

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Scheme 5 Tandem photocyclisations leading to terphenyl containing ring systems.

Substrates giving biaryls by sequential cyclisation and frag mentation

of the spirocyclic intermediate ³[10n] to 11n is presumably followed by fragmentation to oxocarbenium ion 34, as the main product given was biaryl 33a.9 The rearrangement pathway to 7 and fragmentation pathway to 33 compete when the benzyl residue carries a single ortho-substituent, with the o-methyl analogue 50 favouring benzoisochromene 70 while the o-methoxy analogue 5p favoured biaryl 33c. The extent to which the spirocyclic triplet aryl cation intermediate ³[10] follows each of these pathways is presumably determined by a combination of steric and electronic factors.

A further curiosity arose when the benzyl residue carried a meta-methoxy substituent, e.g. 5q-s (Scheme 7). Photolysis under the aforementioned conditions principally followed the pathway leading to benzoisochromenes 7q-s respectively. However, these products were each accompanied by a spirocyclic enone, 35a-c, which we presume arises through H-atom abstraction from HI by ³[10q-s] to radical cation 36, then single electron transfer to dienyl ether 37, and demethylation.

A more useful observation came through extension of the methodology to homobenzyl ortho-iodophenyl ethers 38a-c. Photocyclisation of these substrates proceeded smoothly and in good yield to give the corresponding 7-ring ethers 39a-c (Scheme 8). Additionally, we have established that p-chloro- and p-methoxy- substituents on the iodoarene, 40 and 43, can also facilitate triplet aryl cation formation to ³[41] and ³[44] respectively

Substrates giving benzoisochromenes and spirocyclic enones.

Scheme 8 Extensions to dibenzo[b,d]oxepines and a benzo[4,5]oxepino[3,2-b]pyridine.

(Scheme 9). These extensions to regioisomeric benzoisochromenes (e.g. 42) and dihydrophenanthrenes (e.g. 45) demonstrate ways of extending the method to systems that do not carry an ethereal linkage to the iodoarene residue.

In conclusion, we have shown that intramolecular aryl-aryl coupling reactions of benzyl ortho-iodoaryl ethers and related substrates can be effected without reagents or catalysts by irradiation with UVC under flow. Reaction proceeds via triplet aryl cation intermediates such as ³[9] and ³[10] rather than by radical cyclisation. The method can be applied to systems bearing all manner of substituents including extended aromatic ring systems. The reaction works best when the arenes carry electron donating groups, yet also gives good to excellent yields with analogous pyridyl systems. The sensitivity of both starting materials and products towards benzyl ether cleavage by HI can be resolved, in part, by employing an expeditious work-up and/or a scavenger. ortho-Substituents are tolerated on either ring but do lead to diminished yields. When the benzyl residue carries two ortho-substituents, a biaryl is given. Notably, extensions to tandem cyclisation reactions gave terphenyl containing products and extensions to homobenzyl ethers gave 7-ring ethers. Importantly, para-chloro- and paramethoxy-substituents on the iodoarene have also been shown to facilitate triplet aryl cation formation, extending these photocyclisation reactions to systems devoid of an ethereal bond orthoto the iodide.

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Scheme 9 Extension to regioisomeric benzoisochromene**s** and dihydrophenanthrenes.

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Conflicts of interest

There are no conflicts of interest to declare.

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