ChemComm

COMMUNICATION

View Article Online
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Cite this: *Chem. Commun.*, 2023, 59, 10797

Received 6th July 2023,
Accepted 11th August 2023

DOI: 10.1039/d3cc03271j

rsc.li/chemcomm

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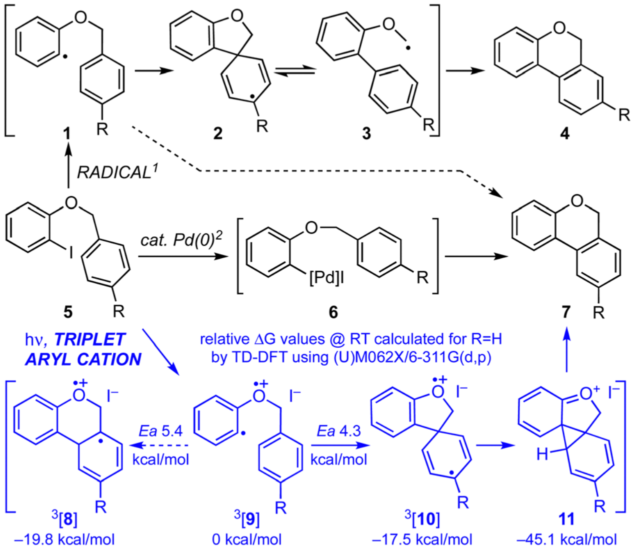
Cyclisations of benzyl *ortho*-iodoaryl ethers to benzo[c]chromenes can be effected without reagents or catalysts by irradiation with UVC under flow. Reactions proceed *via* triplet aryl cation generation, 5-*exo* and 3-*exo*-cyclisations, and rearomatisation. They have wide scope, are easy to effect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

Cyclisations of benzyl *ortho*-iodoaryl ethers to benzo[*c*]chromenes, *e.g.* **5** → **4** or **7** (Scheme 1) are typically achieved by radical cyclisation,[1] 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*-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



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**].

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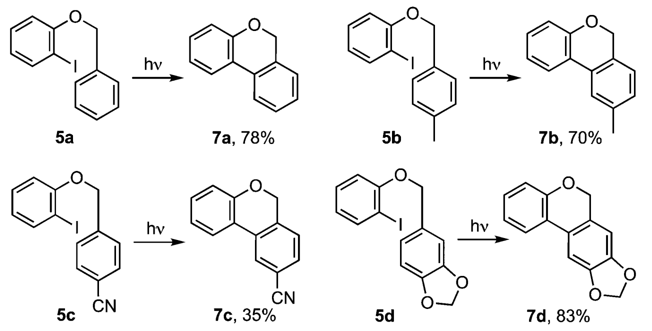
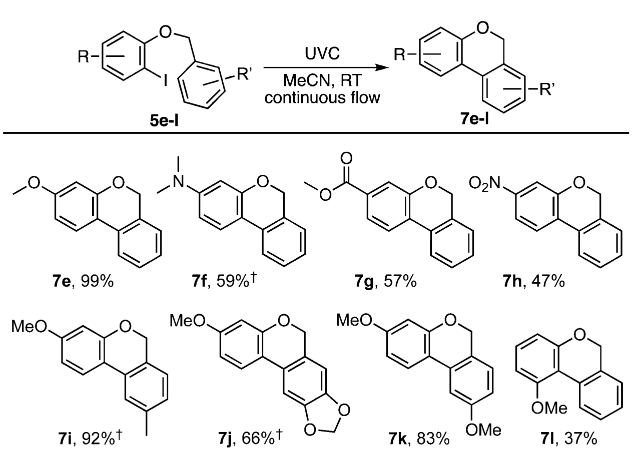
‡ Electronic supplementary information (ESI) available: Experimental accounts with spectral details and copies of NMR spectra are available as supplementary information. See DOI: https://doi.org/10.1039/d3cc03271j

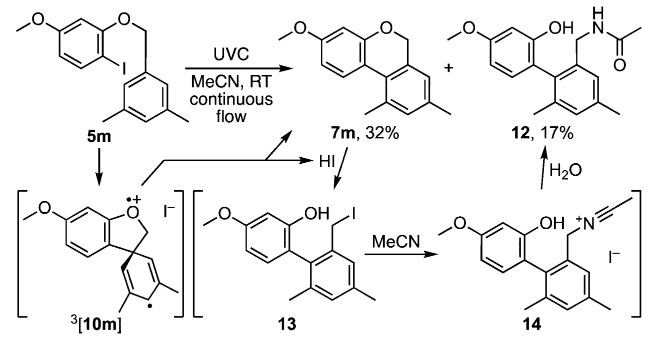


Scheme 2 Regiochemistry observed for cyclisations to substituted benzyl ethers.

Table 1 Photocyclisations of benzyl *ortho*-iodoaryl ethers to benzoisochromenes

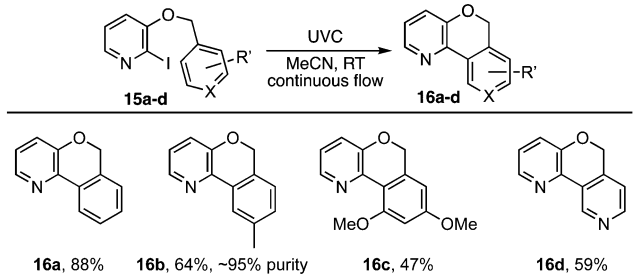


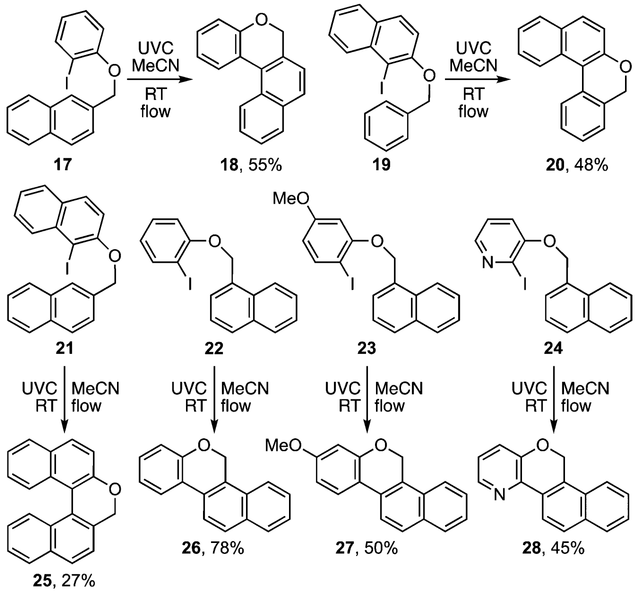
† 1 equiv. pyridine added.



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





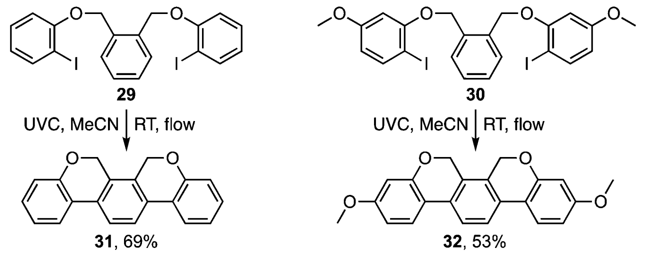
Scheme 4 Photocyclisations leading to polyaromatic ring systems.

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]

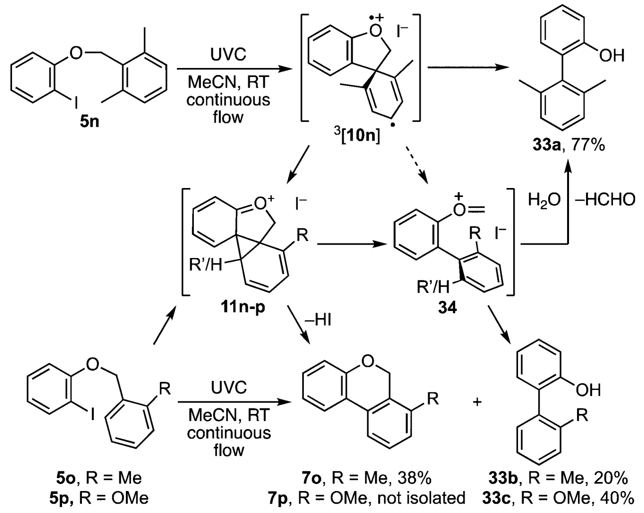
Indeed, while the method was being developed, several starting materials and products proved susceptible to benzyl ether cleavage by HI.[7] For example, photolysis of *p*-nitrobenzyl *o*-iodophenyl ether led to a complex product mixture from which *p*-nitrobenzyl iodide was isolated in low yield. Similarly, 3,5-dimethylbenzyl ether **5m** gave the anticipated product **7m** in 32% isolated yield together with biaryl **12** as a significant by-product (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), 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).

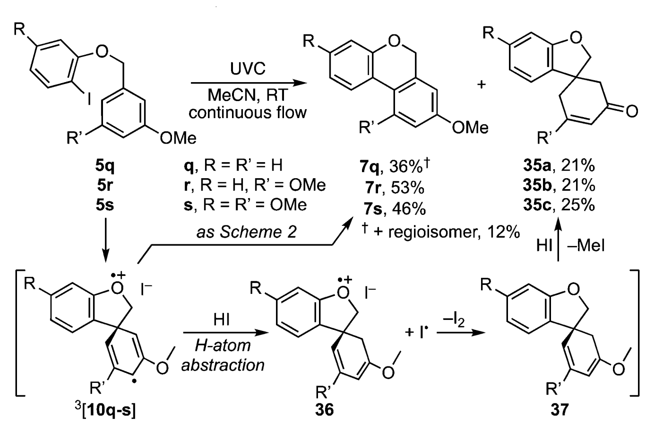
The presence of *ortho*-substituents on the benzyl ether was investigated next and revealed a further subtlety (Scheme 6). When both *ortho* sites carried methyl substituents, **5n**, cyclisation



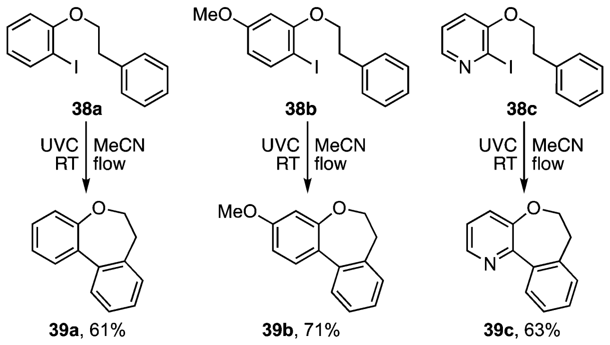
Scheme 5 Tandem photocyclisations leading to terphenyl containing ring systems.



Scheme 6 Substrates giving biaryls by sequential cyclisation and fragmentation.



Scheme 7 Substrates giving benzoisochromenes and spirocyclic enones.



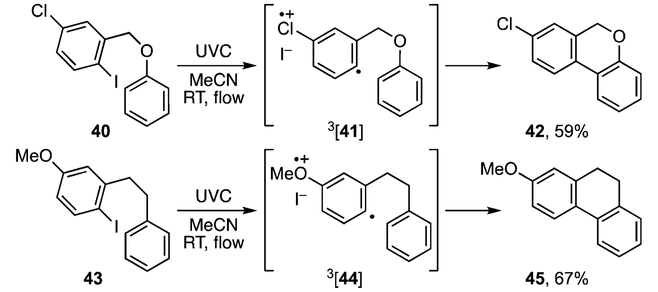
Scheme 8 Extensions to dibenzo[*b*,*d*]oxepines and a benzo[4,5]oxepino[3,2-*b*]pyridine.

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 **5o** favouring benzoisochromene **7o** 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 (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 *para*-methoxy-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 *ortho*- to the iodide.



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

Wei Sun and Luke Wilding-Steele performed the synthetic chemistry under the supervision of Richard Brown and the corresponding author David Harrowven. Wei Sun performed the TD-DFT analyses. We gratefully acknowledge financial support from EPSRC [EP/P013341/1 and EP/K039466/1] and the European Regional Development Fund [ERDF Interreg Va programme (Project 121)], Dr James Pearce for the gift of compound **15a** and Dr Michael I. T. Nunn for some characterisation data presented in the ESI.‡

Conflicts of interest

There are no conflicts of interest to declare.

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