Direct Synthesis of 5-Arylbarbituric Acids by Rhodium(II)-Catalyzed Reactions of Arenes with Diazo Compounds

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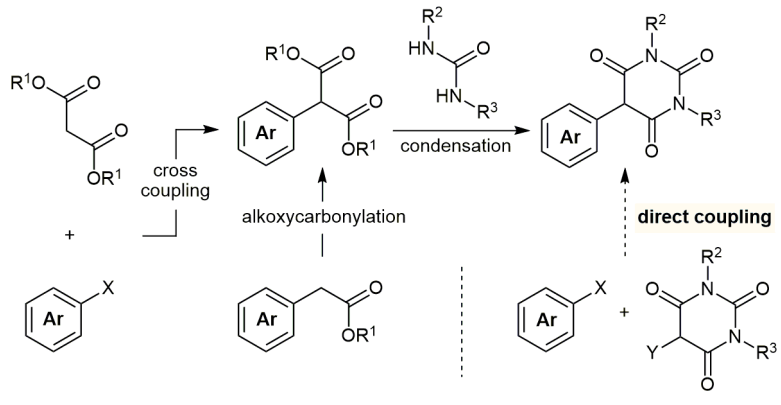
Barbiturates are central nervous system (CNS) depressants having a well-known sedative, hypnotic and anxiolytic effect. First synthesized in 1864 by Adolph von Bayer, barbiturates have been used as sedatives and anticonvulsants since the discovery of the pharmacological properties of barbital by Emil Fischer in 1903. More recently, 5-arylbarbituric acids have found use in cancer treatment and in *in vivo* imaging as matrix metalloproteinase (MMP) inhibitors. The synthesis of barbituric acids essentially relies on the base-promoted condensation of urea with substituted malonate esters, which is highly moisture-sensitive and generally suffers from low yields. Recently, the group of Professor Hon Wai Lam at the University of Nottingham (UK) has developed a conceptually novel approach to the barbiturate ring.

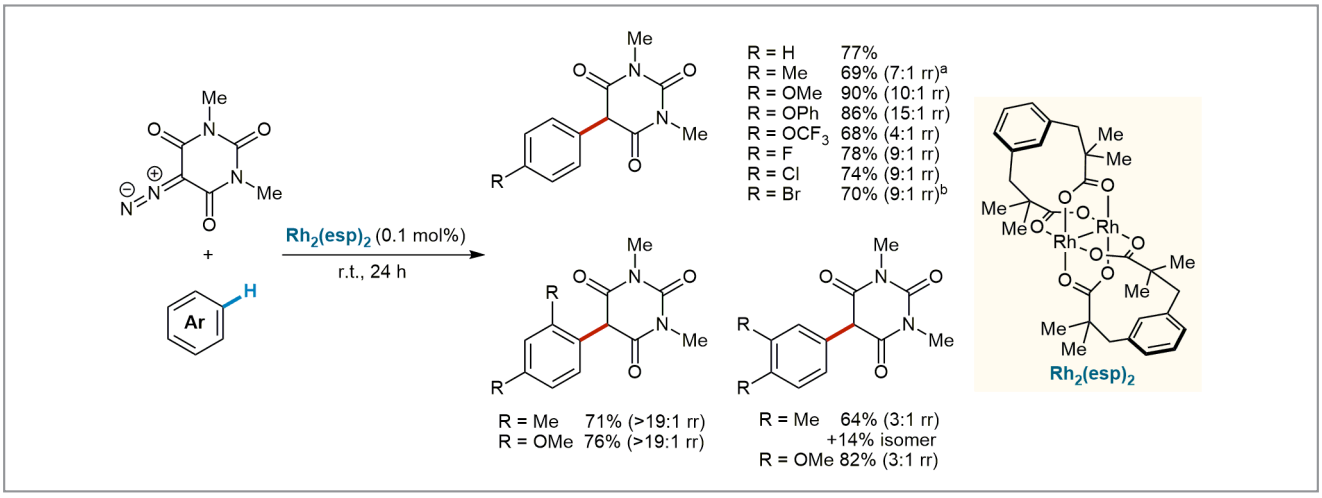
The use of cyclic 1,3-dicarbonyls, including barbituric acids, as directing groups for C(sp^2)–H functionalization reactions has been an ongoing area of interest within Professor Lam's group.[1] Professor Lam's team said: "We recently discovered a new mode of oxidative annulation of certain 1,3-enynes with 5-arylbarbituric acids,[1f] and with a view to investigating the scope of this reaction, a library of variously substituted 5-arylbarbituric acids was required." They continued: "Given their long history, we assumed that the straightforward synthesis of 5-arylbarbituric acid libraries would be a solved problem, but as we dug deeper into the literature, it soon became apparent that this was not the case. 5-Arylbarbituric acids are conventionally prepared by the condensation of ureas with 2-arylmalonates (Scheme 1), and application of this strategy would therefore require the preparation of various 2-arylmalonates."

This strategy was explored briefly, but a number of problems were encountered. "During the attempted condensation of ureas with 2-arylmalonates bearing electron-withdrawing groups on the arene, undesired decarboxylation occurred," the team explained, continuing: "Furthermore, modern cross-coupling methods for 2-arylmalonate preparation were somewhat unreliable in our hands." A classical approach to these compounds is α-alkoxycarbonylation of 2-arylacetates, but very few 2-arylacetates are commercially available. Finally, the length and early-stage divergence of these sequences were unappealing. A more convenient strategy involving the late-stage formation of the arene – barbituric acid linkage was therefore sought.

Professor Lam's team said: "Unable to extend existing Pd- or Cu-catalyzed haloarene-malonate coupling methods to barbituric acids, we turned to α-diazodicarbonyl chemistry. The direct coupling between α-diazodicarbonyls and arenes is not so common, and the chemistry of 5-diazobarbituric acids has scarcely been explored." While the precedented Friedel–Crafts-type reactivity of α-diazocarbonyl-derived Rh(II)-car-



Scheme 1 Existing approaches to 5-arylbarbituric acids and preferable direct coupling

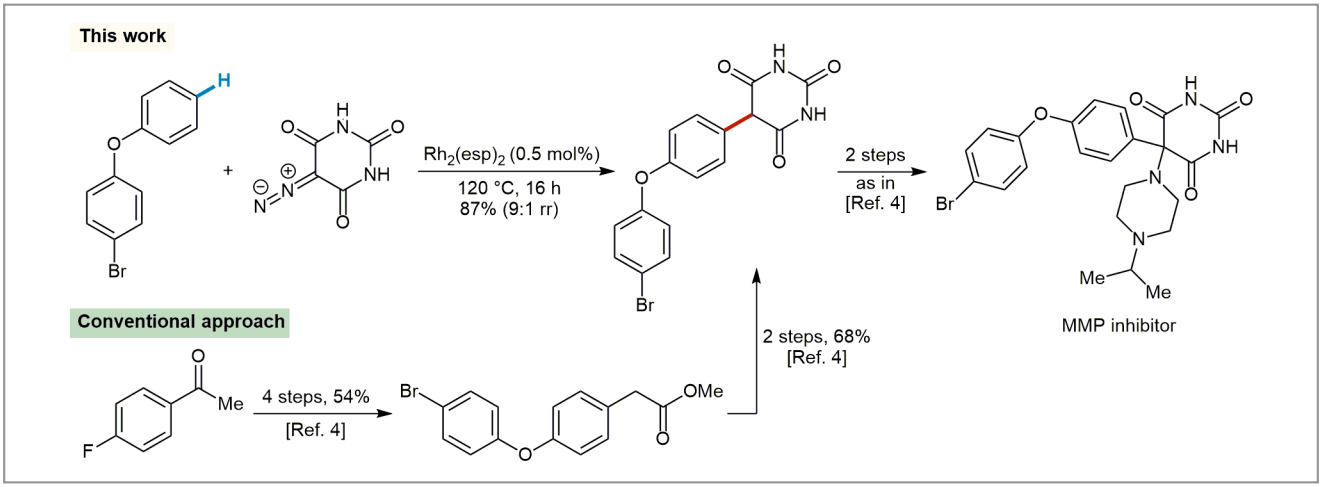


Scheme 2 Reactions of arenes with 5-diazo-1,3-dimethylbarbituric acid; rr = regioisomeric ratio of the crude reaction mixture, and products were isolated as a mixture in the same ratio after chromatography. [a] Isolated as a single regioisomer. [b] Isolated as a 10:1 mixture of regioisomers.

benoids towards arenes was encouraging for Professor Lam and his co-workers,[2] at the outset of their studies the only reported reactions of 5-diazobarbituric acids in this context were cyclopropanations of styrenes conducted in fluorobenzene, *with no indication of reaction with the solvent*.[3]

"Fortunately, we discovered that commercially available $Rh_2(esp)_2$ efficiently catalyzed the direct arylation of 5-diazobarbituric acids with a variety of arenes, and, in the case of 5-diazo-1,3-dimethylbarbituric acid, did so at low catalyst loading (0.1 mol%) at room temperature (Scheme 2)," remarked Professor Lam's team. "The scope of the reaction is fairly broad; this type of transformation is usually limited to electron-rich (hetero)arenes, but in our case, moderately deactivating *o*/*p*-directors (Cl, Br, OCF_3) on the arene were also tolerated."

Mindful of the fact that very few 1,3-dialkylated barbiturates exhibit potent biological activity, Professor Lam's group next examined the use of 5-diazobarbituric acids bearing free N–H groups. Fortunately, elevated temperatures and increased catalyst loadings did indeed permit access to medicinally important 5-arylbarbituric acids, without complications of N–H insertion. They said: "For example, 5-[4-(4-bromophenoxy)]



Scheme 3 Direct arylation of 5-diazobarbituric acid in the synthesis of an MMP inhibitor, compared with the conventional approach

phenylbarbituric acid, previously prepared in 37% yield over six steps (Scheme 3, bottom),[4] was easily prepared using our methodology (Scheme 3, top). The synthesis of a potent MMP inhibitor in only four steps from barbituric acid (vs eight steps from 4-fluoroacetophenone)[4] exemplifies the advantages of our strategy."

In summary, what began as a seemingly straightforward exercise in substrate synthesis ended up revealing a long-standing, unsolved problem in medicinal chemistry. "In response, we developed a more direct approach to 5-arylbarbituric acids that is much more convenient for library synthesis than traditional strategies," said Professor Lam's team. "The 5-diazobarbituric acids used are all bench-stable solids, all of the arylation reactions were performed under air atmosphere, and all reagents were used as received from commercial suppliers. This method has enabled us to explore a new mode of 1,3-enyne annulation via C(sp^2)–H functionalization,[1f] and we hope that it will find other applications (e.g., in medicinal chemistry) as well," they concluded.

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About the authors

Dr. D. Best

Daniel Best received an M.Chem. degree from the University of Oxford (UK) in 2007, undertaking his final-year research in the laboratory of Professor George W. J. Fleet. Daniel remained in the Fleet group to conduct a D.Phil. degree, which he received in 2011. In January 2011, he moved to the University of Edinburgh (UK) to undertake postdoctoral research in enantioselective catalysis and C–H functionalization in the Lam group, and moved to the University of Nottingham (UK) with the same group in October 2013. Daniel took up a postdoctoral position at the Université de Rennes 1 (France) in January 2015 where is he currently investigating the design and synthesis of highly cytotoxic, natural-product-inspired enediyne warheads for antibody–drug conjugates.

Dr. D. Burns

David Burns was born in Newtownards (Northern Ireland, UK) in 1986. He studied for a Master's degree at the University of Edinburgh (UK) and following the completion of his studies (2009), he moved to the University of York (UK) for his doctoral studies. David's Ph.D. thesis was on the total synthesis of samaderine C and related quassinoidal analogues, and was completed jointly within the groups of Professors Richard Taylor and Peter O'Brien. After obtaining his doctorate in 2013, David began working in the Lam group as a postdoctoral fellow, focusing on the catalytic C–H functionalization of small molecules. His most recent work has been concerned with the development of novel processes involving catalytic 1,4-Rh(III) migration.

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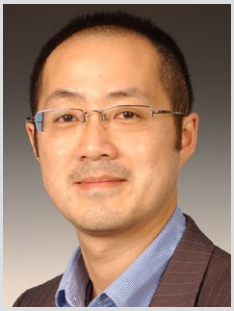

Prof. H. W. Lam

Hon Wai Lam received an M.Chem. degree in chemistry from the University of Oxford (UK) in 1998. He then moved to the University of Nottingham (UK) to carry out his Ph.D. under the direction of Professor Gerald Pattenden. In January 2002, he moved to Harvard University (USA) as a GSK Postdoctoral Fellow to work with Professor David A. Evans. In October 2003, he joined the School of Chemistry at the University of Edinburgh (UK) where he became a Reader in Organic Chemistry. In October 2013, Hon took up the GSK Chair of Sustainable Chemistry at the University of Nottingham (UK). His group's research interests are based around the development of new synthetic methodology, including enantioselective catalysis and C–H functionalization chemistry.