

OBO Protected Pyruvates as Reagents for the Synthesis of Functionalized Heteroaromatic Compounds

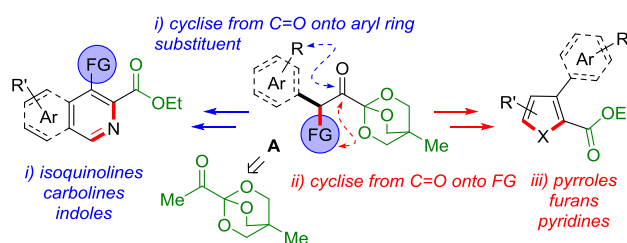
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Supporting Information Placeholder

ABSTRACT: Pd-Catalysed α -arylation of methyl-OBO-ketone (OBO = 4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl) gives rise to arylated OBO-protected pyruvates. By appropriate pre-functionalization of the aryl ring or by subsequent functionalization at the α -carbonyl position of the arylated OBO-ketones, useful diketo OBO-protected carboxylates can be generated. Cyclisation, aromatisation and OBO deprotection of these intermediates, using two distinct routes, gives access to valuable α -acyl heteroaromatic compounds.



α -Acyl substituted aromatic heterocycles are an important sub-class of aromatic heterocycles; they are useful not only for the utility of the carbonyl group as a synthetic handle, but also for their widespread presence both in natural and synthetic biologically-active compounds such as metatacarboline D¹ and lavendamycin² (natural products with anticancer activity) and delavirdine, a marketed drug (Rescriptor®) for the treatment of viral diseases.³

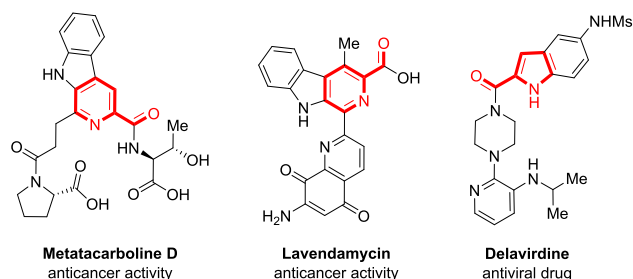


Figure 1. Examples of natural and synthetic biologically active α -acyl aromatic heterocycles

Given their importance, a rich variety of methods have been developed for the synthesis of heteroarenes substituted with an α -acyl group (*i.e.* α - to the heteroatom). These routes consist of traditional methods, such as the Paal-Knorr synthesis of pyrrole carboxylates from the appropriate α,δ -ketoester precursors⁴ or more modern approaches employing metal catalyzed annulation,⁵ cycloaddition,^{6,7} cyclocondensation⁸ or insertion.^{9,10,11} While many of these routes produce good results, the traditional syntheses are limited by the availability of the starting materials (*e.g.* α,δ -ketoesters)¹² and more recent methods are sometimes hampered by the formation of regioisomers,¹³ and/or by limitations in scope. Our experience in the *de novo* synthesis of heteroaromatic compounds using new catalytic methods,¹⁴ together with the general utility of α -acyl arene compounds led us to design a new and

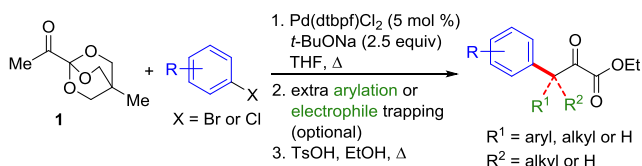
extremely versatile route that would rely on catalytic enolate arylation methodology.

Recently, we reported the synthesis of a variety of mono and multiply α -functionalized pyruvates *via* Pd-catalyzed α -arylation of the pyruvate equivalent OBO-ketone **1** (OBO = 4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)¹⁵ (Scheme 1A).¹⁶ This molecule works as an effective coupling partner in the arylation reaction and subsequent enolate functionalization, which may be run in one-pot after arylation, greatly expanding the types of compounds that can be prepared. The OBO group is readily deprotected under acidic conditions, and so this methodology overcame the incompatibility of pyruvates with the strongly basic conditions that are required for most enolate arylation procedures.¹⁷

Scheme 1. Synthesis of arylated OBO-protected pyruvates and α -acyl heteroaromatic compounds

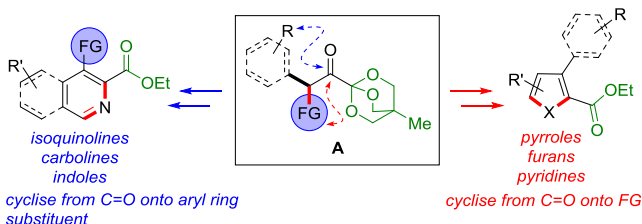
A. Previous work:

Synthesis of α -arylated and alkylated OBO-protected pyruvates



B. This work:

Functionalised OBO-protected pyruvates **A** used to form α -acyl heteroaromatic compounds (shown after OBO deprotection)

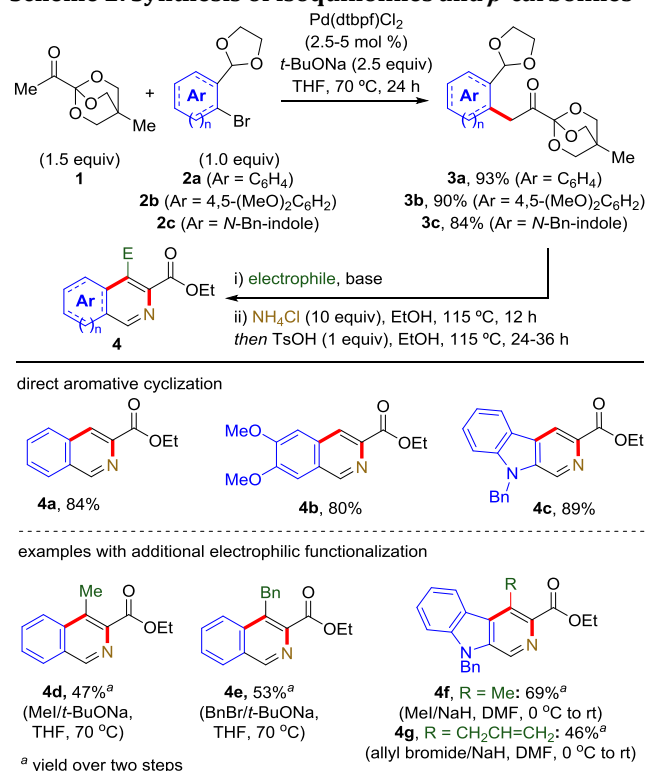


With an efficient method for the synthesis of arylated OBO-protected pyruvates in hand, we envisioned these compounds could serve as a valuable platform for the

synthesis of densely functionalized α -acyl heteroaromatic compounds, Scheme 1B. Two distinct possibilities emerge for the aromative cyclization of compounds such as **A**. On one hand, cyclization between the C=O group and a substituent in the newly installed aryl group would form a range of benzannulated heteroarenes (Scheme 1B, left). Alternatively, cyclization of the C=O onto an appropriate α -functional group (introduced as an electrophile during enolate derivatisation) should lead to a synthesis of monocyclic heterocyclic structures (Scheme 1B, right). Significantly, both routes retain the key α -acyl group in the final product.

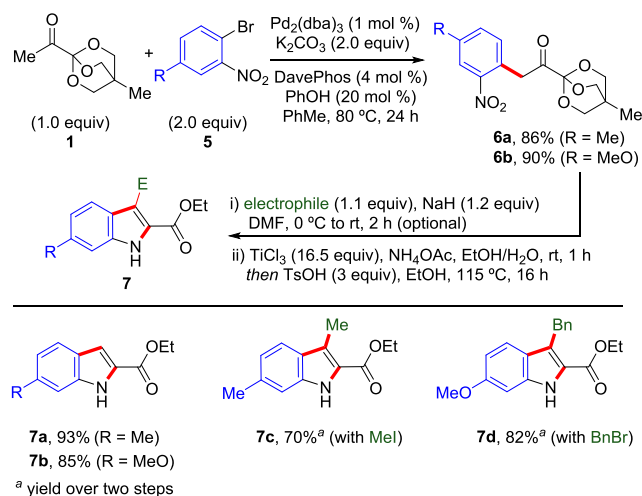
We commenced our study by examining the synthesis of C-3 acyl isoquinolines and carbolines, which would involve cyclization onto an *ortho*-protected aldehyde installed on the aryl halide coupling partner.^{14,18} The synthesis of starting compound **1** was accomplished on a multi-gram scale in 3 steps and 49% overall yield.¹⁶ Coupling of OBO ketone **1** with aromatic acetals **2** allowed the formation of ketoacetals **3a-c** in excellent yields (Scheme 2). If desired, the arylated derivatives thus formed could be readily deprotonated and quenched with electrophiles to introduce additional functionality onto the ketone skeleton. Cyclization of compounds **3** (with or without α -functionalisation) was then effected with NH_4Cl , leading to the formation of isoquinolines and β -carboline-3-carboxylates. Under these mildly acidic conditions, partial OBO-hydrolysis also occurred. However, we found that complete transesterification to the ethyl carboxylates **4** could be achieved by addition of anhydrous TsOH after aromative cyclization. We note that the β -carboline **4f** built in this *de novo* fashion may be useful in future synthesis projects because it contains the heterocyclic core of the natural product lavendamycin (Figure 1).²

Scheme 2. Synthesis of isoquinolines and β -carbolines



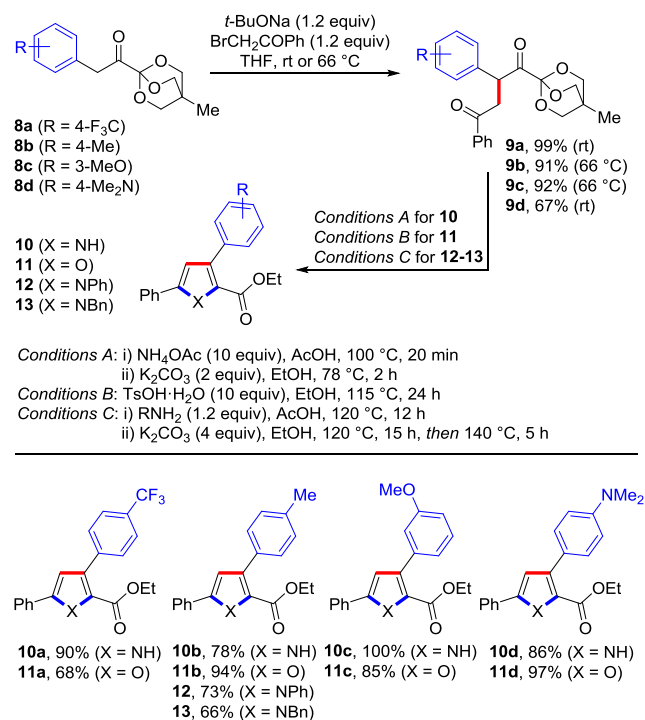
With an efficient method for the synthesis of benzannulated heterocycles in hand, we turned our attention to aromative formation of indole-2-carboxylates. To this end, the coupling of OBO-ketone **1** and 1-bromo-2-nitroarenes **5** was investigated under conditions reported by Buchwald and co-workers (Scheme 3).¹⁹ Initially, poor yields were obtained in this cross-coupling process. However, a screen of different conditions showed that an excess of bromoarene and an increase in temperature from 50 °C to 80 °C allowed clean arylation to occur, affording **6a** and **6b** in excellent yields (Table S1, Supporting Information (SI)). We were pleased to find that subsequent deprotonation (NaH , DMF) followed by electrophilic functionalization proceeded smoothly. Finally, reductive cyclization using TiCl_3 at room temperature, followed by *in situ* transesterification of the OBO ester gave the desired ethyl indole-2-carboxylates **7a-d** in good yields.

Scheme 3. Synthesis of ethyl indole-2-carboxylates



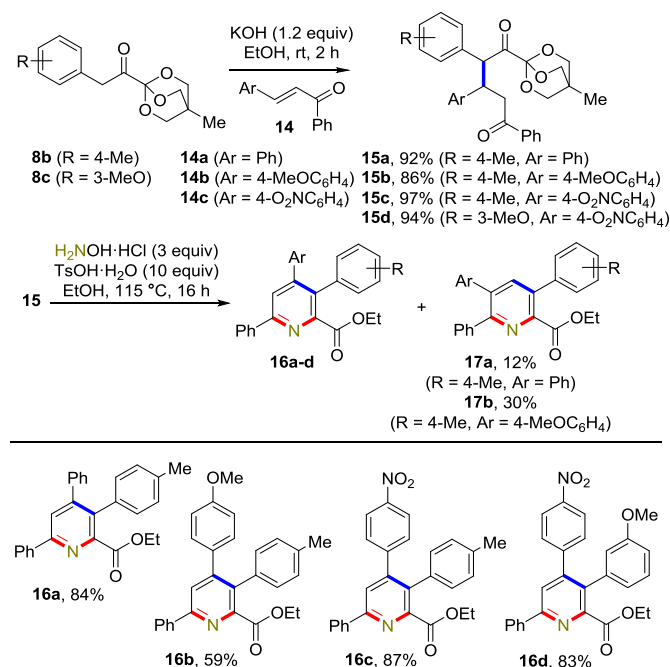
Up to this point, the functionality required to form the heteroaromatic ring was introduced within the aryl halide coupling partner, leading directly to benzo- or indo-annulated α -acyl heterocycles. Next, we considered a complementary mode of cyclization (Scheme 1B, right). In this case, the key functional group required for cyclization (here a carbonyl group) would be incorporated in the electrophile used to functionalize the α -arylated intermediates. This approach would give access to *monocyclic* heteroaromatic-2-carboxylates, substituted with an aryl ring at the C-3 position. We initially investigated alkylation of α -aryl OBO ketones **8** with base and bromoacetophenone as an electrophile (Scheme 4).¹⁶ Pleasingly, both electron-donating (**8b** and **8d**) and electron-withdrawing substituents (**8a** and **8c**) were well tolerated on the aromatic coupling partner, and the desired 1,4-dicarbonyl products **9a-d** were formed in good to excellent yields (67–99%). Notably, the α -arylation/functionalization sequence could also be carried out in one-pot: Pd-catalyzed coupling of OBO-ketone **1** with the appropriate aryl bromide, followed by direct addition of the electrophile gave access to the desired 1,4-dicarbonyl scaffolds **9**. In this way, compounds **9b**, **9c** and **9d** were formed from **1** in yields of 56, 58 and 63%, respectively. Treatment of these intermediates with NH_4OAc in AcOH at 100°C led to the formation of the desired pyrrole ring along with concomitant partial hydrolysis of the OBO group. Base mediated transesterification with ethanol allowed formation of the pyrrole ethyl carboxylates **10** in good to excellent yields (78–100%). Pleasingly, amines such as aniline and benzylamine also reacted with **9b** in AcOH , followed by base promoted transesterification to give the *N*-substituted pyrroles **12** (73%) and **13** (66%). Finally, the versatile nature of the 1,4-dicarbonyl intermediates was demonstrated by treatment of **9** with $\text{TsOH}\cdot\text{H}_2\text{O}$ in EtOH at 115°C which resulted in the formation of ethyl furan-2-carboxylates **11a-d** in good to excellent yields (68–97%). The structures of pyrrole (**10c**) and furan (**11b**) were confirmed unambiguously by single crystal X-ray analysis (SI).²⁰

Scheme 4. Synthesis of pyrrole- and furan-2-carboxylates



Finally, we investigated the reaction of α -aryl OBO-ketones **8** with base and α,β -unsaturated ketones **14**. A base and solvent screen showed that KOH in EtOH promoted the desired conjugate addition reaction and afforded 1,5-diketones **15** in good to excellent yields (86–97%) (Scheme 5). We were delighted to find that these intermediates reacted successfully with $\text{NH}_2\text{OH}\cdot\text{HCl}$ under acidic conditions to furnish the substituted pyridines **16** (along with concomitant transesterification of the OBO-ester). The optimal conditions for the aromatic cyclization were found to be $\text{H}_2\text{NOH}\cdot\text{HCl}$ (3 equiv) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (10 equiv) in EtOH at 115°C (sealed tube). The addition of $\text{TsOH}\cdot\text{H}_2\text{O}$ was necessary to achieve complete transesterification of the OBO-moiety. Interestingly, in some cases the formation of regioisomers (**17a** and **17b**) was observed during the cyclization reaction. Similar results have previously been reported and are thought to proceed via a mechanism involving a 1,2-shift of the 4-aryl group in a cyclic intermediate formed prior to dehydration.²¹ Significant amounts of 5-aryl pyridine **17** were observed in the cyclization of **15b**, while no regioisomers were observed with intermediates **15c** or **15d**. This result suggests that increasing electron density on the migrating aryl ring favours the formation of these isomeric pyridines. Note that the structures of the pyridines **16a** and **17b** were determined by X-ray crystallography (SI).²⁰

Scheme 5. Synthesis of pyridine-2-carboxylates



In summary, the synthesis of a variety of α -acyl heteroaromatic compounds was accomplished *via* the functionalization of arylated OBO-protected pyruvates. The core structures for several of the compounds presented here are found in natural and/or synthetic biologically-active compounds,^{5,22} which shows the potential of the described methodology for future applications in natural product and compound library syntheses.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and spectroscopic data for all new compounds, copies of spectral data (PDF) and crystallographic data (CIF).

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Notes

The authors declare no competing financial interest.

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