Domino Direct Arylation and Cross-Aldol for Rapid Construction of Extended Polycyclic π-Scaffolds

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Supporting Information Placeholder

ABSTRACT: Five-membered aromatic heterocycles are a ubiquitous skeleton of π-conjugated organic compounds, and their incorporation often requires complex synthetic protocols that are not industrially sustainable or scalable. Improved methodologies for their insertion into π-scaffolds are therefore necessary. We report an efficient and scalable protocol involving a one-pot cross-Aldol direct arylation reaction protocol for the rapid construction of thiophene- and furan-based π-extended organic materials.

Conjugated π-extended organic compounds based on five-membered aromatic heterocycles enjoy an increasing importance in several major chemical sectors, including organic materials,[1] pharmaceuticals,[2] agrochemicals.[3] In the materials arena, their attractive properties have demonstrated useful in light-emitting diodes, organic photovoltaic cells, and field-effect transistors. Complex molecular π-extended compounds incorporating five-membered aromatic heterocycles have proved to be effective at creating high performance materials, however this has often been at the expense of the industrial scalability because of lengthy synthetic sequences. [4]

The successes of organic electronic materials have created a demand for the development of efficient methodologies for the rapid construction of π-extended organic compounds and polymers. In this context, the teachings from "classical" total synthesis wherein atom economical domino/cascade and/or multicomponent reaction approaches are core principles,[5] provide a powerful strategy for materials production.

Pd-catalyzed (Stille or Suzuki) coupling reactions, in sequence with traditional C–C or C–N bond formation methodologies, such as Aldol condensation[6] or Michael reactions,[7] have been recently reported. However, Stille and Suzuki reactions require preactivation of the building blocks through the formation of organometallic Direct heteroarylation reactions (DHA) are becoming increasingly popular as Pd-catalyzed carbon-carbon forming methodologies in organic and macromolecular syntheses, since no such preactivation is required.[8] This peculiarity of DHAs combined with its complementary of reaction conditions with aldol condensation, which both conducted in aprotic polar organic solvents with relatively weak bases, have attracted our attention on the possibility to develop a domino process with both these reactions. [9]

Annulation strategies in the case of thiophene derivatives have been reported before, under rather harsh conditions, involving the use of elemental sulfur.[10] In this communication we report a regioselective and efficient domino cross-Aldol-DHA strategy for construction of fully π-conjugated compounds wherein thiophene or furan rings are fused to arene or heteroarene moieties.

Two alternative synthetic strategies (Figure 1) described herein differ in the relative position of the aldehyde and the acidic protons involved in the Aldol condensation. The position of the halide and the reactive C-H bond of the *α*-thiophene or furan in the DHA are kept unchanged, as this was found to be the best combination in order to ensure high regioselectivity in related systems.[11]

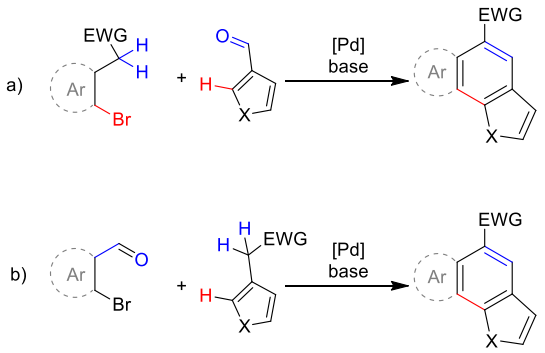
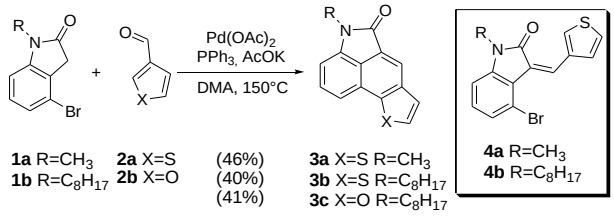


Figure 1. Strategies for cross-Aldol-DHA annulation reactions. EWG = Electron-withdrawing group. X = Sulfur or Oxygen.

As part of our continuing interest in isatin derivatives as new π-systems for organic electronics,[6c,12] we initially investigated the reaction of *N*-methyl-4-bromooxindole **1** (derived from isatin by reduction at its C3 carbonyl) and 3-formylthiophene or 3-formylfuran **2**, to form annulated products **3** (Scheme 1). This reaction is schematically shown as option *a)* in Figure 1. Using catalytic $Pd(OAc)_2$, KOAc and dry DMF at 150°C in moderately dilution conditions (200 mM), we were pleased to isolate the desired compound, **3a** (Scheme 1), after purification by flash column chromatography, albeit in relatively low yield (26%). A screening of catalysts, bases and reaction conditions

(Table S1) afforded an improved yield of 46% when using PPh_3 as the ligand and dry DMA as the solvent at 150°C.

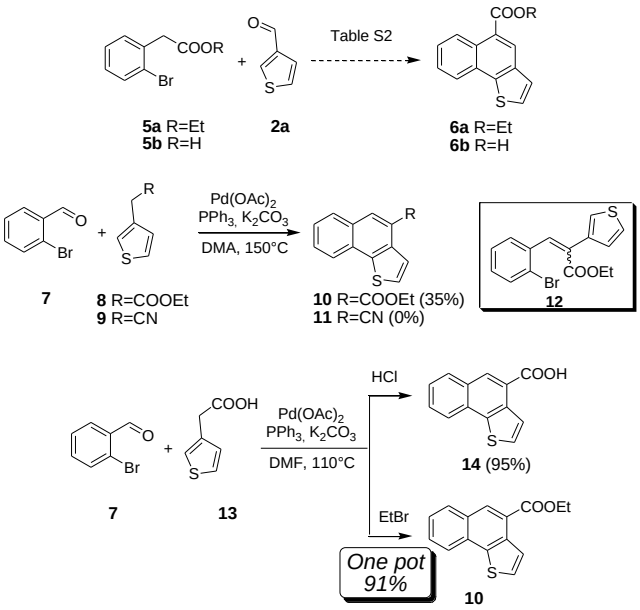
Scheme 1. Synthesis of thiophene-and furan-fused compounds 3



Compound **3a** was characterized by X-ray crystallography, NMR and UV/Vis spectroscopy, and cyclic voltammetry (Figures S1-S4). Compounds **4a** and **4b** were also isolated and characterized in the same reactions (20-30% yields), appearing as single stereoisomers in the ^{1}H NMR spectra. Although the precise stereochemistry of the carbon-carbon double bond in either **4a** or **4b** could not be unequivocally determined, it is likely to be the *E*-configuration, unfavorable for subsequent cyclization. We did not observe C5 arylation byproducts in the crude reaction mixtures.

To demonstrate the scope of our cross-Aldol-DHA strategy, we evaluated the use of simplified, commercially available reagents, in conjunction with route *a)* depicted in Figure 1.

Scheme 2. Efficient construction of naphthothiophene-fused compounds

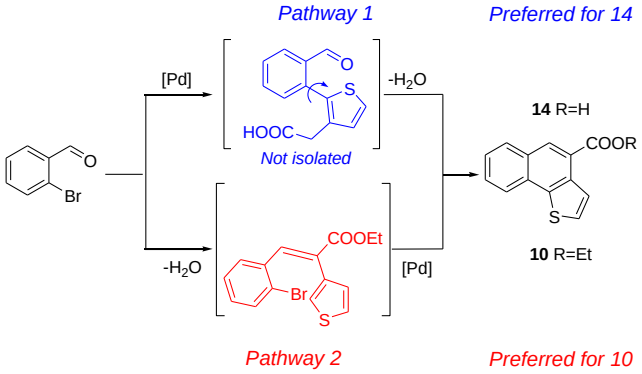


The reaction of ethyl 2-bromophenylacetate **5a**, or the corresponding acid **5b**, and 3-formylthiophene **2a** (Scheme 2), when screened under a variety of conditions (Table S2), did not afford the desired product **6**, with essentially only baseline material stuck to the chromatographic support detected. Both electronic and steric effects are likely responsible for the different outcomes of reactions of aldehyde **2a**. The starting amide used in the synthesis of **3** enjoys aromatic stabilization when deprotonated, whereas the conjugate base of the ester in the attempted synthesis of **6** may be more prone to side reactions. Additionally, a highly stereoselective preference for the formation of the *E*-intermediate alkene formed in the Aldol reaction could play a role since would inevitably preclude cyclization in the subsequent DHA.

Reversing the positions of nucleophilic and electrophilic elements of the cross-Aldol reaction (Pathway *b)* in Figure 1), by using 2-bromobenzaldehyde **7** and ethyl 3-thiopheneacetate **8**, produced **10** (Scheme 2) in 35% yield after reaction optimization (Table S3). GC-MS experiments on the crude reaction mixture revealed the presence of byproduct **12**, wherein the Aldol condensation had occurred without subsequent DHA. Furthermore, in the case of cyano substituted substrate, **9**, none of the desired product **11** is detected. Gratifyingly, using 3-thiopheneacetic acid **13** in place of the corresponding ester (**8**) produced **14** in nearly quantitative yield after acidification and simple filtration. The reaction could be carried forward, bypassing the isolation of **14**, by the addition of ethyl bromide at room temperature one pot, giving π-extended annulated ester **10** in 91% after purification by column chromatography.

In case of substrate **13**, the cross-Aldol intermediate byproduct was not observed in the crude reaction mixture. Control experiments in the absence of the Pd(II) catalyst and the phosphine, with all other conditions equal, revealed that reactants **7** and **8**, produce **12** in 43% yield. The major stereoisomer could be separated by careful column chromatography. NOESY NMR spectroscopy confirmed this to be the (*E*)-**12** adduct (Figures S5-S8). Furthermore, the stereopure compound did not show any sign of (*E*)-(*Z*) interconversion (Figure S9) upon heating at 110˚C in DMSO-d_6 for 48 h, and, when subjected to DHA conditions, afforded compound **10** in good yields. The control reaction between **7** and **13**, followed by esterification with ethyl bromide, gave no cross-Aldol product, with the reaction containing unreacted **7** and esterification of **13** to afford **8**. On the basis of all the above data, we propose the mechanism illustrated in Scheme 3. It is clear that the different electron-withdrawing abilities of cyano, ester, and carboxylate groups (Hammett's σ_p = 0.66, 0.45 and 0.00, respectively)[13] influence the acidity of the neighboring α-hydrogens lowering the rate of the Aldol condensation with respect to the DHA, and promoting the synthetic Pathway 1 instead of 2.

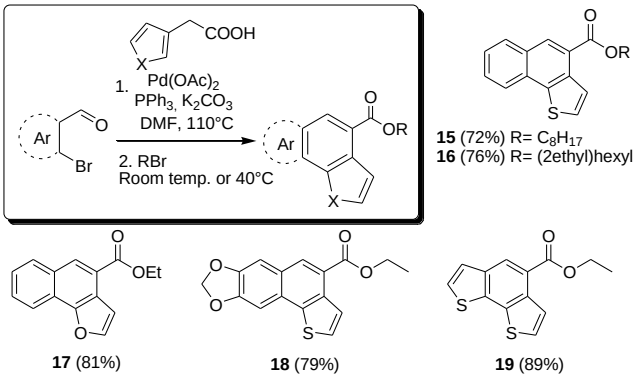
Scheme 3. Competing cross-Aldol and DHA Pathways



The possibility of the carboxylate functionality present in the reagent **13** to coordinate intramolecularly the Pd(II) catalyst, to form the Ar-Pd-OOCR group attacking the CH in a metallocyclic intermediate, is highly unlikely by geometrical considerations. Furthermore, control experiments with **7** and **13**, with all other conditions equal except increasing amounts of pivalic acid (up to 100% mol with respect to the starting materials), had only minor effects on the yield of compound **10** (yields dropped from 91% to 80%). Pivalic acid is known to coordinate to Pd(II) and should compete with the carboxylic acid functionality of **13**. The intermediate in Pathway 1 could not be isolated.

In order to investigate the general utility of the domino DHA and cross-Aldol strategy, so successful in the case of **13**, we extended our procedures to the synthesis of compounds **15-19** (Scheme 4).

Scheme 4. Synthesis of compounds 15-19 with the optimized DHA-Aldol cascade protocol



The introduction of long side chains that are often needed to impart solubilty, is equally efficient and, by adding other alkyl-bromides, **15** and **16** are produced in good yields. The introduction of a furan ring instead of thiophene occurred smoothly to produce **17** (Figures S10-S11). Also important is that the introduction of electron rich functional groups in the aryl-aldehydes worked equally well to efficiently produce **18** and **19**. It is worth noting that **10** was previously reported as byproduct of the catalytic cyclization *via* ruthenium-carbene/oxidation, following a complex procedure.[14] Compound **19**, is an interesting and promising building block for organic photovoltaic (OPV) devices, has been previously reported by Kirner *et. al.*[15] using a seven-step synthetic sequence rather than our single step sequence from commercially available materials. Additionally a comparison between E-factors[16] calculated for the last synthetic step of our synthetic route relative to the published route showed a 98% and 90% reduction for **10** and **19**, respectively (see Supporting Information).

In conclusion, we have developed an efficient methodology for the annulation of heteroaryl building blocks. Our method is a single step one pot method that provides for polycyclic extended π-systems with pendant carboxylate or ester groups for use in developing chromophores and organic electronic materials. Previously known compounds are produced in dramatically simplified procedures. Our annulations appear to work equally well for furan and thiophene compounds. Our strategy paves the way for efficient syntheses of other dithiophene, difuran or mixed thiophene-furan π-extended annulated monomers, through easily scalable procedures, and may find utility in creating industrially relevant OPV materials.

ASSOCIATED CONTENT

Supporting Information

Additional experimental details and Tables about synthetic routes. Additional Figures about UV-Vis spectroscopy, cyclic voltammetry and X-Ray crystallography for compound **3a**. Copies of ^{1}H, ^{13}C NMR, ESI-MS and GC-MS spectra for new compounds.

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Notes

The authors declare no competing financial interests.

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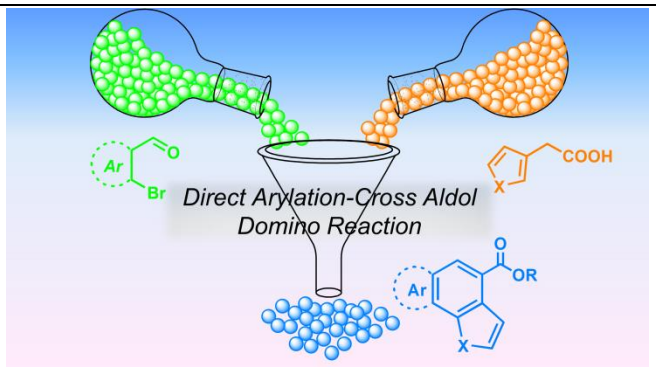

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