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Deconjugative alkylation/Heck reaction as a simple platform for dihydronaphthalene synthesis

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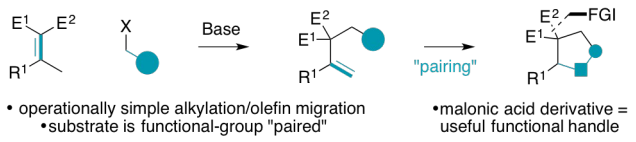
A simple platform for carbocycle synthesis by Knoevenagel adduct deconjugative alkylation/Heck reaction is described. Deconjugative alkylation of Knoevenagels adducts is two-fold synthetically enabling because (1) C–C bond formation is operationally simple due to the ease of Knoevenagel adduct carbanion generation and (2) results in alkene migration, which poises the substrate for cyclization. Furthermore, the *gem*-dinitrile moiety serves as a functional group for synthetic manipulation.

Introduction

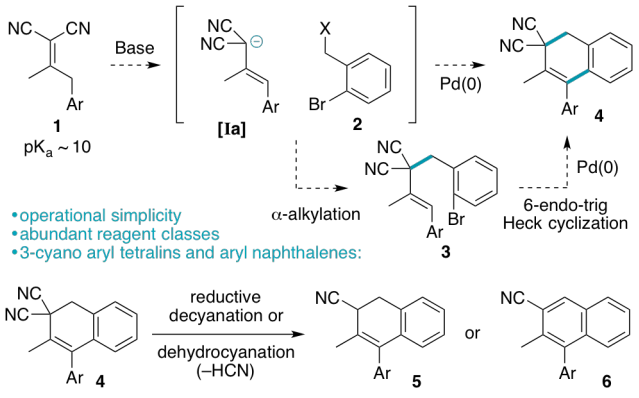
Knoevenagel adducts have attractive chemical attributes. They are prepared from abundant ketones and malonic acid derivatives by an eco-friendly condensation reaction.[1] Of specific interest to this work, they have highly acidic γ-C–H bonds, which allow for operationally simple activation to their respective allyl carbanions for coupling reactions.[2–4] Upon deconjugative alkylation (γ-deprotonation/α-alkylation),[2] the alkylidene-olefin cannot re-conjugate unlike *mono*-electron-withdrawing group analogues (*i.e.* when E^2 = H) (Scheme 1). A synthetic platform that takes advantage of the dual nature of deconjugative alkylation (C–C bond formation and olefin migration) for carbocyclization *via* a broadly defined "pairing" reaction has the potential to be a straightforward approach to the synthesis of useful chemical architectures. On this line, the malonic acid moiety, which is critical for implementing the chemistry, is situated within the carbocycle and would serve as a useful functional group for further manipulation to target structures.

Scheme 1. General strategy for carbocycle synthesis



We[4] recently disclosed that Knoevenagel adducts can behave as trimethylenemethane dipole surrogates for reaction with electrophiles and nucleophiles in a 3-component fashion.

In continued studies, we reasoned that aryl acetone-derived Knoevenagel adducts **1** and *o*-bromo-benzylic electrophiles **2** could react as described in Scheme 1 to yield useful cyclic scaffolds. As described in Scheme 2, Knoevenagel adduct **1** could undergo directed deconjugative alkylation (by deprotonation of the most acidic γ-C–H as shown to **Ia**)[2] with *o*-bromo-benzylic electrophiles **2** yielding **3**. The deconjugative alkylation process directly pairs the substrate for intramolecular Heck cyclization, ideally favouring a less common 6-*endo*-*trig*[5–7] reaction pathway (over 5-*exo*-*trig*) to yield aryl dihydronaphthalene **4** (Scheme 2). Notably, related aryltetralins and naphthalenes have significant biological activities and medicinal relevance.[8–12] If achieved, the proposed tetralin scaffolds **4** will bear a *gem*-dinitrile moiety, which will allow for access to unexplored nitrile-containing aryl tetralin analogues **5** and **6** by utilization of reductive[13,14] or dehydrocyanation protocols.[15,16] From a medicinal chemistry perspective, nitrile inclusion would be beneficial for the following reasons: (a) a nitrile is sterically small (A value = 0.17), (b) has noted metabolic stability, (c) changes the lipophilicity of the molecule, and (d) is isosteric to a halogen.[17]



Scheme 2. General hypothesis for carbocycle synthesis

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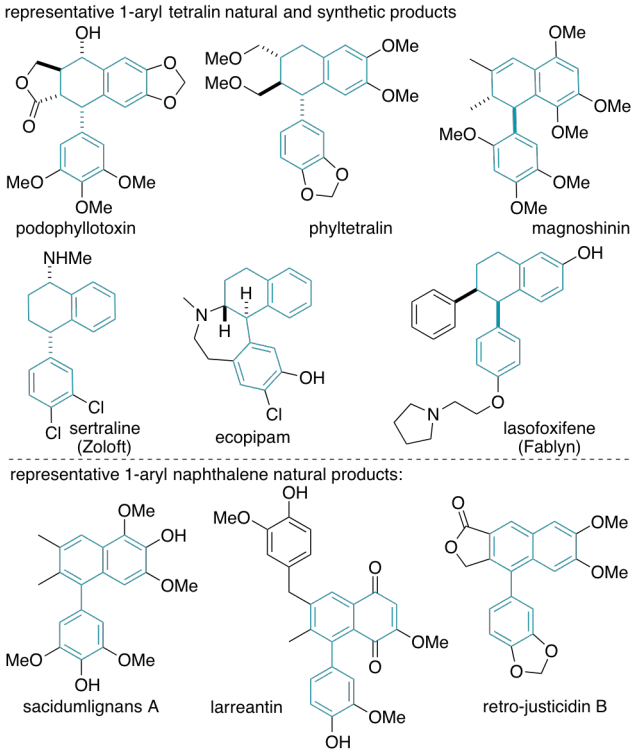
Related bicyclic scaffolds are commonly prepared by intramolecular Friedel-Crafts alkylation with a benzylic electrophile, or by a Diels-Alder cycloaddition of *o*-xylylenes generated from various precursors.[18-20] The former route is considered biomimetic.[19] Alternatively, 1-arylation of preformed bicycles (tetralins, naphthalenes, or related) is also common by organometallic addition, C–H arylation, or other methods.[21] There are other unique cyclization strategies,[22] however, of interest to the work herein, is aryl tetralin synthesis by intramolecular Heck cyclization,[5d,7] which is poorly examined.

Figure 1. Natural products and synthetic molecules of interest to this study



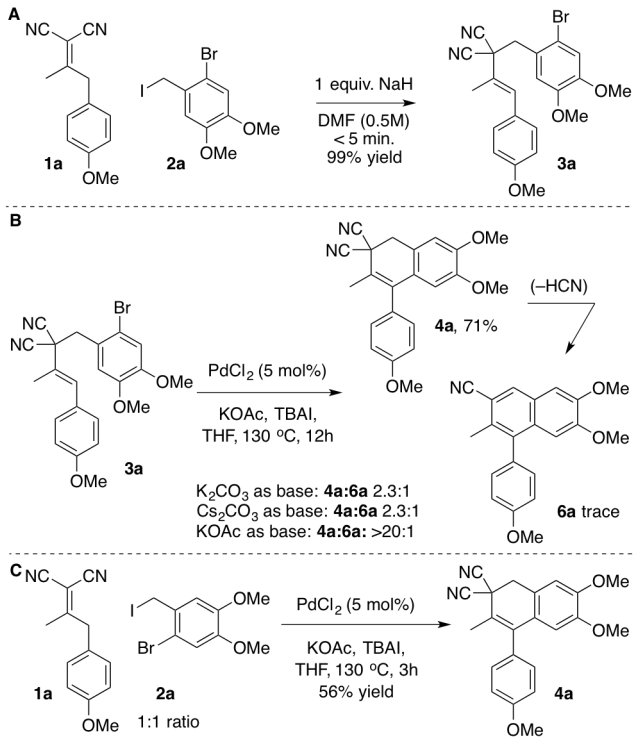
The proposed strategy is a unique platform for tetralin synthesis, utilizes abundant reagent classes as sole carbon sources (ketone + malononitrile = Knoevenagel adduct; benzylic electrophiles), has the potential to be operationally simple due to the ease of Knoevenagel adduct anion generation, and would result in structurally unique 3-cyano aryl dihydronaphthalenes **5** and aryl naphthalenes **6**. For these reasons we wished to examine the possibility of this hypothesis.

Development and Scope of the Strategy

We chose to examine Knoevenagel adduct **1a**, prepared from *p*-methoxyphenylacetone and malononitrile by the Cope-Knoevenagel procedure,[1c] and *o*-bromobenzyl iodide **2a,** prepared from commercial 6-bromoveratraldehyde, as our initial reagents for formal [3+3]-cyclization (Scheme 3). To begin, we examined the deconjugative alkylation[2] reaction and found the reaction was high yielding under standard alkylation conditions (NaH, DMF). Notably, the Knoevenagel adduct's aromatic group directs the deprotonation allowing for the desired styrene-moiety to be synthesized upon α-benzylation.

We next examined the key intramolecular Heck cyclization and found that "Jeffery" conditions[23,24] worked best with an optimized yield of 71% for dihydronaphthalene **4a** (Scheme 3B). We were pleased with this result as relatively inexpensive $PdCl_2$ (5 mol%) could be used as a catalyst in the presence of TBAI as an additive. That said, a variety of other conditions were attempted and are summarized in the supporting information. In brief, it appears that in our hands various Pd-phosphine catalyst-combinations were poorly reactive and only when ligandless conditions ("Jeffery conditions") were employed did we begin to observe the desired product **4a**. Interestingly, various bases were screened during the optimization and we observed byproduct cyanonaphthalene **6a** in some cases. The byproduct is derived from the product **4a** by a base-promoted dehydrocyanation.[15,16] For example, when the more basic carbonate bases (H_2O pK_a ~10) were used *in lieu* of KOAc (H_2O pK_a ~4), a significant amount of **6a** was observed (22% isolated yield). As the final point, we were also able to perform the γ-deprotonation/α-benzylation/Heck cyclization sequence in one-pot (56% yield from **1a** and **2a**). However, we ultimately decided to examine the scope over two steps as this yield was higher and isolation of benzylated intermediate **3** is simple.

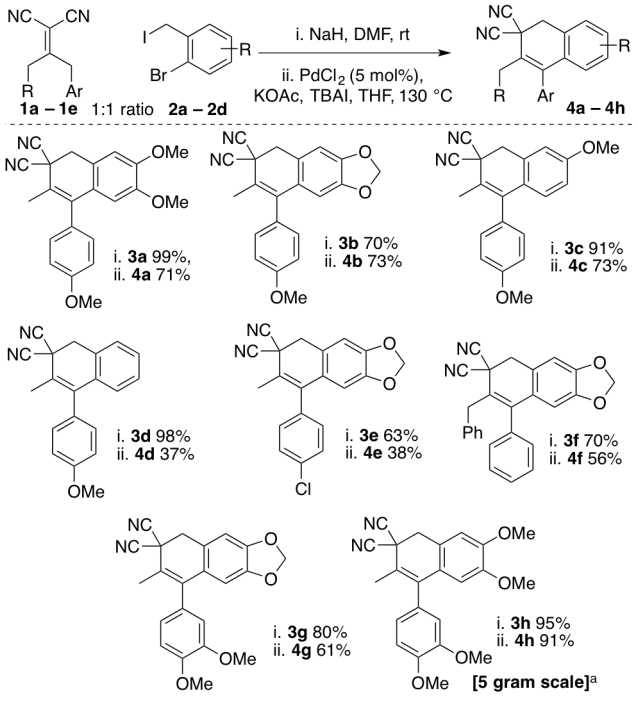
Scheme 3. Development of the formal [3+3] annulation strategy



We were pleased to find that a variety of substituted aryl tetralins **4a – 4h** could be prepared by the formal [3+3]-cyclization strategy (Scheme 4). Generally speaking the deconjugative benzylation reactions were excellent and the Heck reaction worked best when both aromatic rings were electron rich. For example, the yield was decreased for **4d** due to significant formation of its naphthalene byproduct (*via* dehydrocyanation). To reiterate, the electronics of the tetralin play a key role in favouring either product **4** or byproduct **6** under the reaction conditions. The reaction was not limited to arylacetone-derived Knoevenagel adducts as we were able to utilize a 1,3-diphenyl-ketone Knoevenagel adduct to prepare the tetralin **4f**. We also wished to explore the scalability. As is common with Jeffrey conditions, we were able to reduce the catalyst loading on the 5 gram scale when preparing tetralin **4h**.[24] Excitingly, the reaction works excellently on the large scale and ample material was prepared for further substrate processing.

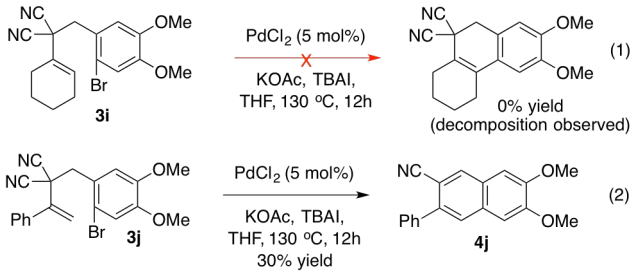
We also examined the cyclohexanone-derived substrate **3i** (eq. 1). Unfortunately, only decomposition was observed using the standard protocol. The acetophenone-derived molecule **3j** was a competent coupling partner, albeit in modest yield under the conditions optimized for arylacetone-derived substrates (eq. 2). Interestingly, the tetralin was not observed and we were only able to isolate the 2-phenylnaphthalene product **4j**. If further examined this could be a powerful strategy to prepare highly substituted naphthalenes from acetophenones, malononitrile, and benzylic electrophiles.

Scheme 4. Scope of 1-aryl tetralin synthesis

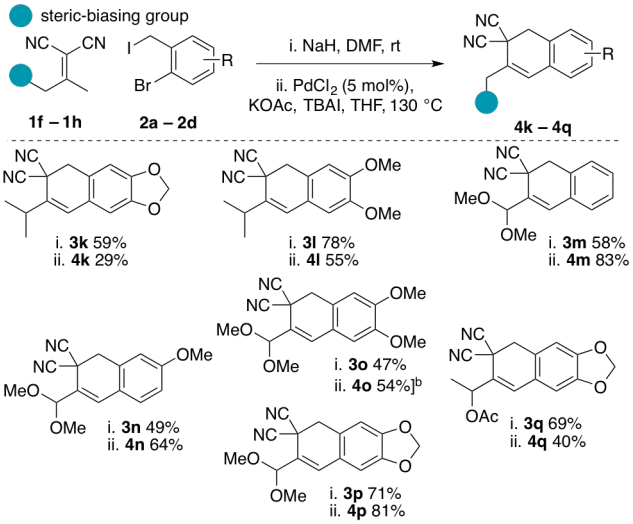


[a] $PdCl_2$ (2.5 mol%), KOAc (5 equiv.), TBAI (THF), THF (0.75M), 130 °C, 5

Considering the results from our initial scope studies (Scheme 4) and the results in equations 1 and 2, we wondered if the γ-deprotonation/α-alkylation could be directed by sterics to prepare other uniquely substituted tetralin cores (Scheme 5). In this regard we found that a variety of γ,γ-disubstituted Knoevenagel adducts could afford the desired tetralin products **4k – 4q** in modest to good yields. For example, products **4k – 4l** are derived from isopropyl methyl ketone, **4m – 4p** are derived pyruvaldehyde dimethyl acetal, and **4q** is derived from acetoin.



Scheme 5. Sterically-biased formal [3+3]-cyclizations



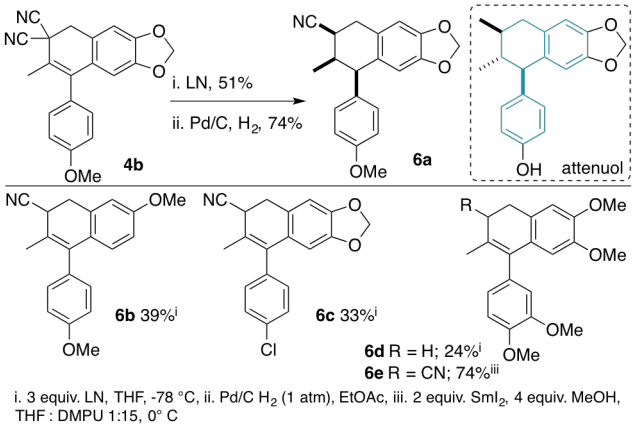
Having established that a variety of tetralin cores bearing a *gem*-dicyano group can be prepared, we next examined two different strategies to mono-decyanate the scaffolds; reductive decyanation[13,14] and base-promoted dehydrocyanation (E2 reaction) (Schemes 6 and 7, respectively).[15,16] We were able to realize a reductive decyanation reaction yielding 3-cyano aryl tetralins when using either lithium naphthalenide[14c] (LN) or samarium(II) iodide[14e] (SmI_2) (Scheme 6). Using LN, mono-decyanation was observed on a variety of scaffolds (**4b**, **4c**, **4e**) preparing cyanotetralins **6a – 6c.** One outlier substrate was **4h**, where decyanation conditions using LN produced only double decyanation product **6d** in modest yield. At this point, other reductive conditions were examined and we found that SmI_2[16e] was an excellent reagent for mono-decyanation of these substrates producing **6e** in 74% isolated yield.

The molecules prepared in Scheme 5 are unnatural nitrile-containing analogues of attenuol (Scheme 5),[23] magnoshinin (Figure 1),[24] and other related 2,3-dimethyl aryl tetralins.[25] Such natural products have a variety of biological activities.[23-25]

Replacement of a methyl group with a nitrile is unprecedented both naturally and synthetically but could have interesting effects on structure-activity relationships.[15]

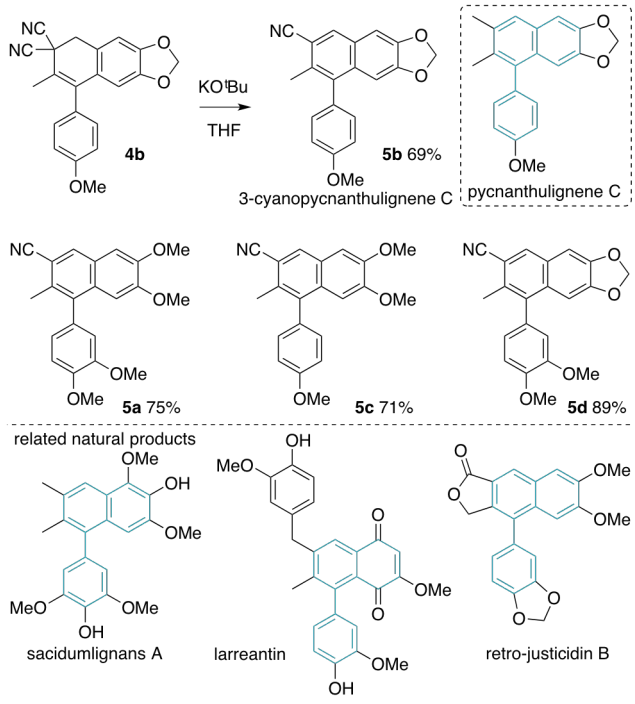
The second decyanation reaction examined was base-promoted dehydrocyanation leading to 3-cyano aryl naphthalenes **5a** – **5d** (Scheme 7).[27,28] Cyanide is not a common leaving group, but due to the aromaticity driving force, the reaction was found to be facile under simple conditions (1.1 equiv. KO^{t}Bu, THF, 0 °C). As above, the synthetic strategy results in medicinally relevant cyano-containing analogues of 1-aryl naphthalene natural products. The parent 1-aryl-napthalene core is found in many bioactive natural products.[27,28]

Scheme 6. Reductive decyanation produces nitrile-containing analogues of aryl tetralin natural products



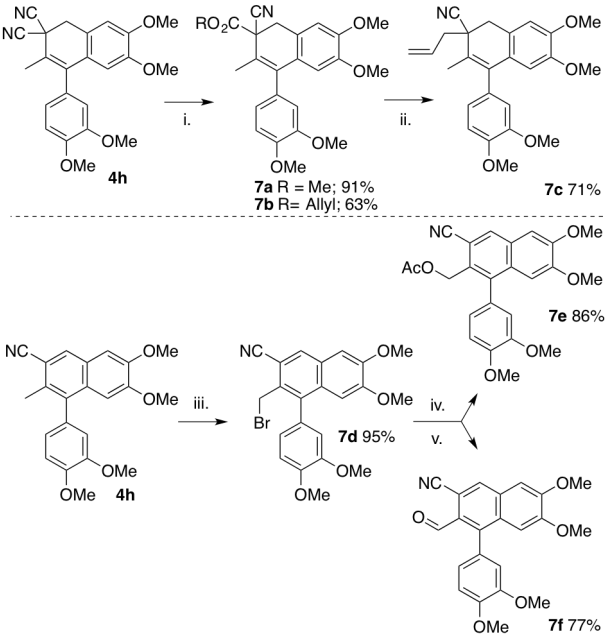
i. 3 equiv. LN, THF, -78 °C, ii. Pd/C H_2 (1 atm), EtOAc, iii. 2 equiv. SmI_2, 4 equiv. MeOH, THF : DMPU 1:15, 0° C

Scheme 7. Retro-hydrocyanation produces nitrile-containing analogues of aryl naphthalene natural products



The *gem*-dinitrile moiety could also react with alcohols under Pinner reaction[29] conditions to yield cyanoacetic esters **7a** and **7b** following hydrolysis (Scheme 8). Notably, synthesis of the allyl cyanoacetate **7b** allowed us to utilize decarboxylative allylation (DcA) to install an allyl group onto scaffold **7c**.[30] We also examined oxidative protocols for the naphthalene scaffolds and found that radical benzylic bromination to **7d** was high yielding. The halogen could then serve as a functional handle for the incorporation of nucleophiles (*e.g.* acetate, **7e**) or allow further oxidation to an aldehyde (the Sommelet protocol was utilized, **7f**).[31]

Scheme 8. Other scaffold manipulations



i. MeOH or AllylOH, 10 equiv. K_2CO_3, 0 °C, 5 min., ii. $Pd(PPh_3)_4$ (1 mol%), Tol, 60 °C, 3h, iii. NBS (10 equiv.), AIBN (0.1 equiv.), CCl_4, 90 °C, 1h, iv. K_2CO_3 (4 equiv.) AcOH (4 equiv.), DMF, rt, v. hexamethylenetetramine (1.5 equiv.), $CHCl_3$, 63 °C, 40 min. AcOH

Conclusions

We have devised a platform for carbocycle synthesis that utilizes Knoevenagel adducts as conjunctive reagents. Knoevenagel adducts can react with *bis*-electrophilic *o*-bromobenzyl iodides allowing for formal [3+3]-cyclization by deconjugative benzylation then 6-*endo*-*trig* Heck cyclization. The developed cyclization uses abundant carbon-sources, is operationally simple, and yields useful carbocyclic frameworks. We describe the synthesis of previously unknown 3-cyano aryl tetralin and naphthalenes, which are being analysed for biological activity. Future synthetic efforts are aimed at designing related cyclization reactions for Knoevenagel adducts based on the general reaction protocol outlined in Scheme 1.

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