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A deconjugative alkylation/Diels-Alder cycloaddition strategy to synthesize 2-substituted bicyclic scaffolds

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ABSTRACT

Knoevenagel adducts derived from α,β-unsaturated aldehydes and a malonic acid derivative can undergo deconjugative alkylation using dienophile-functionalized alkyl iodides. The single step reaction is two-fold significant: (a) The electron-deficient diene (α,β-unsaturated aldehyde Knoevenagel adduct) is deconjugated from the esters, resulting in an electronically neutral diene and (b) tethers the diene and dienophile, which allow for intramolecular cycloaddition to bicyclic systems bearing a malonic acid derivative at the 2-position. The sequence thus converts simple reagents into natural product relevant bicyclic scaffolds. We also disclose an unexpected Diels-Alder cycloaddition/aromative C–C cleavage reaction that results due to the malonate's location at the 2-position.

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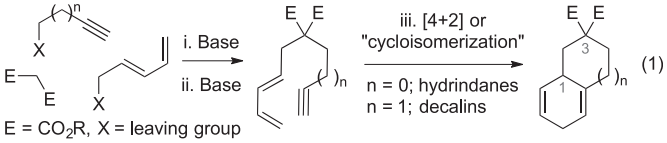
1. Introduction

Intramolecular Diels-Alder cycloaddition is a useful strategy for the synthesis of bicyclic carbon frameworks.[1] The assembly of tethered diene-dienophile paired substrates can be accomplished in a variety of ways, but one common strategy centers about nucleophilic substitution of malonate anions with diene- and dienophile-containing electrophiles (eq. (1)).[2] The caveat with this strategy is that the carbocycle prepared will bear a malonate functional group at the 3-position, which may or may not be desired depending on the target structure (eq. (1)).[3] In this regard, Dudley recently described a simple protocol that circumvents the malonate functional group and directly installs a gem-dimethyl moiety, a common fate of the malonate group, at this position.[3] Nonetheless, α,α-disubstitution of malonate with electrophiles containing unique π-systems serves as the standard synthetic strategy to prepare substrates for intramolecular Diels-Alder[2] and cycloisomerization.[4,5] This disconnection results in common electrophiles that can be attached to the malonate under simple and mild conditions due to mild malonate carbanion generation (malonate DMSO pK_a ~16).



(1)

What if one wished for the malonate functional group to be at the 2-position of the bicyclic framework? As shown in Fig. 1, there are numerous hydrindane, decalin, and related natural products that contain substitution at the 2-position.[6] Potentially, a malonic acid derivative at this location could be used as a handle to install natural product-relevant functionality and other diversity elements by functional-group interconversion, decarboxylation,[7a,b] decarboxylative coupling.[7c] Using the same general strategy of coupling diene- and dienophile-containing electrophiles to a central malonate carbon as described in eq. (1) would require the coupling of 1-halo- (or pseudohalo)-1,3-diene **A** *via* metal-catalysis analogous to malonate arylation (eq. (2)).[8]

Although 1-halo- (or pseudohalo)-1,3-dienes and related structures are competent reagents for cross-coupling reactions with organometallic nucleophiles (*e.g.* Grignard and Suzuki reagents),[9] malonate dienylation *via* an analogous enolate dienylation[10] is not a common strategy for construction of such chemical motifs. 2,4-Dienyl-1-malonates are rare but can be

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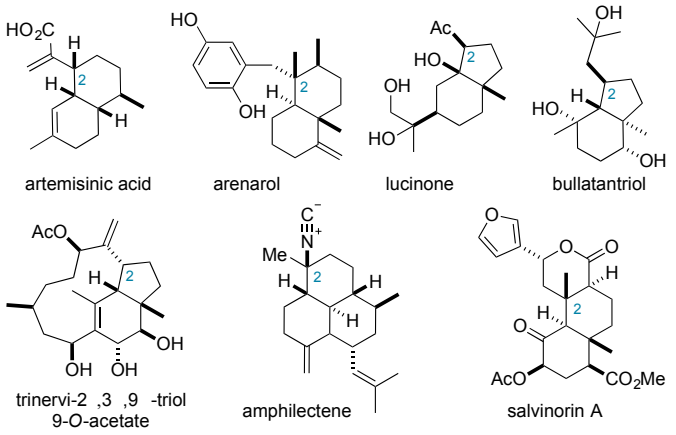
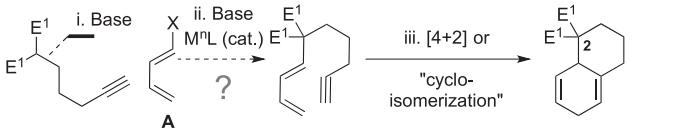
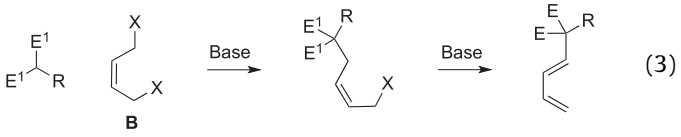


Fig. 1. Representative 2-substituted decalins and hydrindanes.

synthesized by the following strategies: (a) allylic alkylation of mono-alkyl malonates with bis-electrophilic buten-1,4-diol derivatives **B** followed by vinylogous elimination (eq. (3)),[11] (b) allylic alkylation of mono-alkyl malonates with 1,3-silylated allyl acetate **C** followed by a Sakurai allylation/Peterson olefination sequence (eq. (4)),[12] and (c) deconjugative allylation of Knoevenagel adducts with allylic acetates **D** (eq. (5)).[13] It is important to point out that all of these strategies appear to be under examined with limited understanding of scope.[11–13]



(2)



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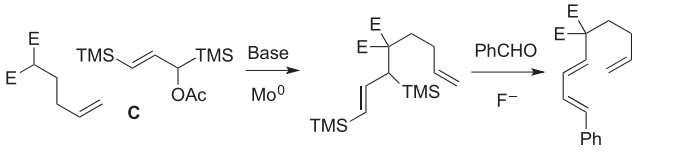

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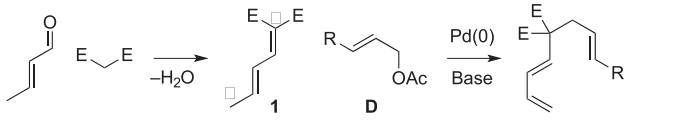
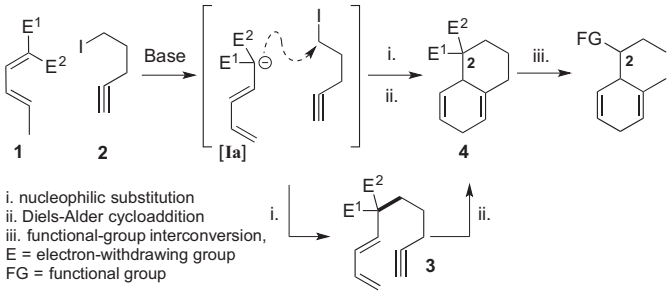


(5)

For our interest in developing a simple protocol to prepare substituted bicycloalkanes bearing a malonate at the 2-position, we ultimately decided to examine the deconjugation strategy in more detail (Scheme 1). Although the background provides precedence,[13] the authors, Sato and coworkers, only examined the scope of allylic acetates. Thus, the limitations of this reaction in terms of which Knoevenagel adduct and alkyl electrophiles are competent coupling partners is unknown. We propose that Knoevenagel adducts **1** derived from α,β-unsaturated aldehydes can serve as diene/malonate-anion equivalents [**Ia**] for coupling with dienophile-tethered alkyl iodides (**2**) yielding 2-functionalized carbocycles *via* ε-deprotonation/α-alkylation (to **3**) then Diels-Alder cycloaddition (to **4**). The strategy utilizes abundant carbon sources (malonic acid derivative + aldehyde = Knoevenagel adduct[14]; dienophile-tethered alkyl iodides) and has the potential to be operationally simple due to the ease of anion generation.[15] the overall strategy presented in Scheme 1 is under explored as a potentially simple and straightforward 2-step sequence toward bicycloalkanes.



Scheme 1. Synthesis of 2-substituted bicycloalkanes from Knoevenagel adducts and dienophile-tethered alkyl iodides.

Although ε-deprotonation/α-alkylation of Knoevenagel adducts is poorly examined,[13] it should be mentioned that deconjugation of related Knoevenagel adducts by a γ-deprotonation/α-alkylation strategy was classically studied by Cope[16] and has more recently found other applications,[17] including research of our own.[18]

2. Discussion

To begin our studies, we prepared a variety of Knoevenagel adducts **1a** − **1j** derived from commercially available α,β-unsaturated aldehydes and malonic acid derivatives by a standard protocol.[14] Molecules **1** were then reacted with an equivalent of potassium *tert*-butoxide and the alkyl iodides **1a** − **1c** in DMF to yield products **3**. We found that deconjugative alkylation by ε-deprotonation/α-alkylation was a selective transformation under these conditions producing a variety of diene/dienophile-paired substrates **3a** − **3l** in good to excellent yields as single alkene diastereomers. We were initially concerned of potential competing S_N2/E2 reactions as previous reports were limited to allylic alkylation,[13] however these pentadienyl anions appear to be competent nucleophiles.

There are several notable aspects relating to the alkylation step. First, Knoevenagel adducts **1e** − **1g** derived from citral were prepared as isomeric mixtures and contain nonequivalent ε-carbons. Under the standard conditions, deprotonation was selective for the least substituted ε-position (ε vs. ε′ deprotonation) resulting in products **3e** − **3g** in good yields as single isomers. During our studies on the alkylation of Knoevenagel adducts **1**, we realized that *E/Z* diene geometry can be controlled (Scheme 3). This is best presented through the comparison of Knoevenagel adducts **1a** and **1h** which differ by their substitution at the C−3 position. Upon ε-deprotonation, there are several possible anion-geometries including **[I-a]** and **[I-b]**. Using substrate **1a**, following alkylation, **3a** was observed having *E* olefin geometry. This is most likely sterically directed due to the significant difference in size of an H-atom *vs*. a vinyl group. Interestingly, **1h** through the same sequence results in **3h** having *Z* olefin geometry.

We next examined the Diels-Alder reaction for substrates **3** (Scheme 2). Fortunately, we found that thermal conditions were generally sufficient in promoting the intramolecular cycloadditions, although the reactions times were long (72 h). Under these