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A one-pot synthesis of α-formyl-α-allylacetates via nucleophilic catalysis

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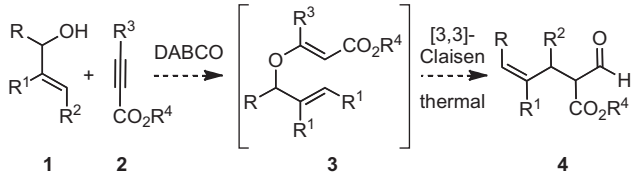
ABSTRACT

A step-economical one-pot nucleophilic catalysis/thermal Claisen-rearrangement protocol for the direct synthesis of α-formyl-α-allylacetates from allylic alcohols and activated alkynes has been developed. The product α-formyl-α-allylacetates were further reacted in situ to give either protected enol ethers or β-hydroxy-4-pentenoates.

α-Formyl-α-allylacetates are found in a number of biologically active natural products[1] and are important intermediates in the synthesis of peptide inhibitors,[2] as well as biologically active uracils[3] and pyrimidines.[4] These compounds are challenging substrates to synthesize via conventional enolate chemistry due to their propensity to undergo dimerization reactions and multiple allylations.[5,6] The most common method for α-formyl-α-allylacetate formation is via formylation of a γ,δ-unsaturated ester,[2] which itself must be synthesized. Thus, a more step-economical method to these important compounds from commercial starting materials would be highly beneficial. A one-pot synthesis would be an ideal approach as it minimizes the transfer of material and avoids the purification steps.[7,8] α-Formyl-α-allylacetates can be formed in a one-pot nucleophilic addition/Claisen-rearrangement process (Scheme 1).[9,10] This efficient method for the synthesis of α-formyl-α-allylacetates would be step-economical and limit the overall production costs in terms of time, expense and waste. Thus, addition of allyl alcohols **1** to activated ynones **2**, promoted by a nucleophilic catalyst (DABCO), would result in the formation of allyl vinyl ethers **3**. Subsequent thermal Claisen rearrangement of dienes **3** would give α-formyl-α-allylacetates **4**. Herein, we report a novel one-pot procedure based on this approach for the synthesis of α-formyl-α-allylacetates as well as their subsequent in situ derivatization to either protected enol ethers or β-hydroxy-4-pentenoates.

The formation of allyl vinyl ethers[11,12] from the addition of allyl alcohols to activated alkynes was initially investigated. Importantly, the conditions need to be viable under the subsequent thermal rearrangement conditions (vide infra). Building on the initial



Scheme 1. Proposed one-pot synthesis of α-formyl-α-allylacetates.

work of Inanaga et al.,[13] a number of researchers have employed a nucleophilic catalysis approach, notably the use of trialkyl phosphines,[14] DMAP,[15] and *N*-methylmorpholine,[16] for the formation of allyl vinyl ethers from allylic alcohols and activated alkynes. In our previous work on the one-pot nucleophilic catalysis / thermal rearrangement approach towards the synthesis of highly substituted pyrroles from oximes and activated alkynes, it was found that DABCO[17] was the best catalyst for processes that required heating.[18] Thus, the reaction of both primary and secondary allyl alcohols **1** with ethyl propiolate (**2a**) in CH_2Cl_2 at rt in the presence of 10 mol % DABCO gave the desired allyl vinyl ethers **3** in moderate to good yields (Scheme 2).[19] The only exception was triene **3g**, which was produced in a yield that was too low to be synthetically useful in a one-pot process. All of the vinyl ethers **3** were isolated as the *E*-isomer as determined by their $^3J_{HH}$ coupling constants.

The second phase of this work was directed towards the thermal rearrangement of allyl vinyl ethers **3** to α-formyl-α-allylacetates **4**. The temperature at which the thermal Claisen rearrangement of allyl vinyl ethers will proceed is highly dependent on the nature of the substituent on the alkene moiety.[10] Substrates that contained electron-withdrawing groups required higher temperatures.[20,21]

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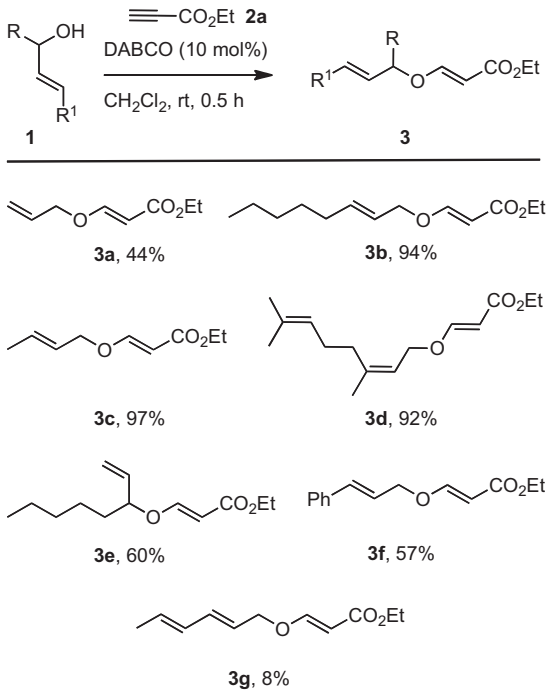
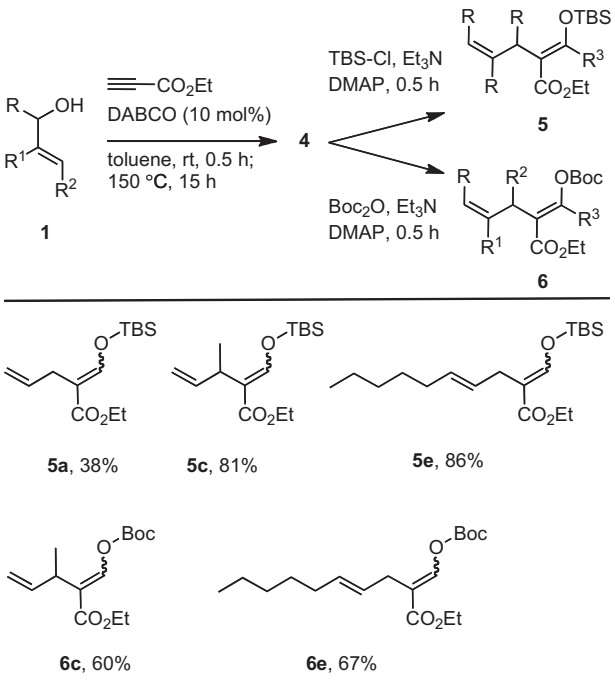


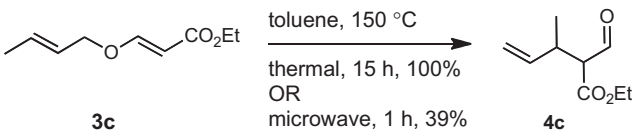
Scheme 2. Synthesis of allyl vinyl ethers **3** via nucleophilic catalysis.



Scheme 4. Synthesis of enol ethers **5** and **6**.

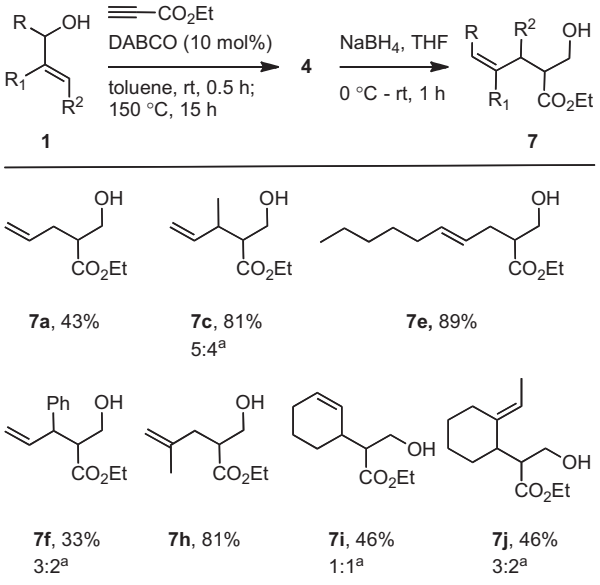
Therefore, we wanted to establish the minimum temperature for the rearrangement of allyl vinyl ethers **3** to aldehydes **4**. Thus, heating a solution of allyl vinyl ether **3c** to 150 °C in either an oil bath or in a microwave oven led to quantitative and 39% conversion to α-formyl-α-allylacetate **4c**, respectively (Scheme 3). While the thermal rearrangement was clean by ^{1}H NMR analysis, attempts to purify the microwave derived material by column chromatography (1:9 EtOAc/petrol with 1% Et_3N) resulted in complete degradation. In solution, α-formyl-α-allylacetates **4c** existed as a 1:1 mixture of keto-enol tautomers.

Having demonstrated the feasibility of both of the proposed steps independently, a one-pot synthesis of α-formyl-α-allylacetates from allyl alcohols and ethyl propiolate was investigated. As the purification of α-formyl-α-allylacetates **4** proved to be problematic (vide supra), the product aldehydes were converted into enol ethers. Thus, the reaction of allyl alcohols **1** with ethyl propiolate (**2a**) gave α-formyl-α-allylacetates **4** (Scheme 4). Addition of TBS-Cl[22] or Boc_2O[23] to the reaction mixture resulted in the formation of enol ethers **5** or **6**, respectively. Several features of the one-pot method are noteworthy. It was found that a 0.5 h mixing of the reagents at room temperature prior to increasing the temperature to 150 °C was necessary in order to form the α-formyl-α-allylacetate. This method proved to be very expedient for both primary and secondary alcohols. Additionally, slightly better yields were obtained using the TBS-protocol. For example, subjection of **1e** and **2a** to the optimized conditions gave either enol ether **5e** or **6e** depending on the trapping agent that was employed. All of the enol ethers **5** and **6** were isolated as a single geometric isomer, though the configuration of the isomer was not determined.

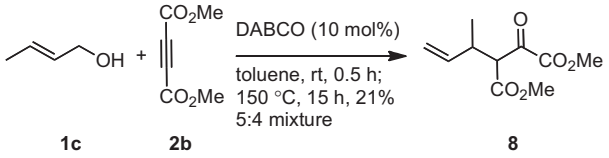


Scheme 3. Thermal vs. microwave rearrangement of allyl vinyl ether **3c**.

Having demonstrated the feasibility of the one-pot synthesis of protected α-formyl-α-allylacetates, the synthesis of a series of reduced β-hydroxy-4-pentenoate derivatives **7** was also investigated.[24] This one-pot process involved an initial 1,4-addition followed by a thermal Claisen rearrangement and in situ reduction of the α-formyl-α-allylacetate. Thus, subjection of allyl alcohols **1** and ethyl propiolate (**2a**) to the standard conditions followed by solvent exchange and reduction with $NaBH_4$ gave β-hydroxy-4-pentenoates **7** in moderate to good yields (Scheme 5).[25] The products of both primary **7a**,**c**,**f**,**h**,**i** and secondary alcohols **7e**,**j** were amenable to this process. Cyclic alcohols **1i**,**j** were also subjected to the three-step process to give alcohols **7i**,**j** in moderate yields. β-Hydroxy-4-pentenoates **7c**,**f**,**i**,**j** were formed as inseparable mixtures of diastereomers due to facile epimerization prior to reduction.



Scheme 5. One-pot synthesis of β-hydroxy-4-pentenoates **7**. [a]Ratio of two inseparable diastereoisomers.



Scheme 6. Synthesis of dimethyl 2-(but-3-en-2-yl)-3-oxosuccinate (**8**).

Additionally, this method was extended to the synthesis of dimethyl 2-(but-3-en-2-yl)-3-oxosuccinate (**8**) via the reaction of (*E*)-2-buten-1-ol (**1c**) with dimethyl acetylenedicarboxylate (**2b**) using the standard protocol. Diester **8** was isolated in moderate yield as a 5:4 mixture of diastereomers (Scheme 6).[26]

In conclusion, we have developed a simple one-pot approach to the synthesis of α-formyl-α-allylacetates as well as their protected enol ether or β-hydroxy-4-pentenoate derivatives based on a novel nucleophilic catalysis/thermal rearrangement protocol.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.035.

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19. *Typical procedure for the synthesis of allyl vinyl ether* **3**: To a stirred solution of geraniol (**1d**, 0.48 mL, 2.64 mmol) and DABCO (27 mg, 0.24 mmol) in dry CH_2Cl_2 (10 mL) at rt was added ethyl propiolate (**2a**, 0.25 mL, 2.40 mmol) dropwise over 10 min and the resultant mixture was stirred for 0.5 h at rt. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (15:1 petrol/EtOAc) to give ethyl 3-{[(*E*)-3,7-dimethylocta-2,6-dien-1-yl]oxy}acrylate (**3d**, 0.64 g, 92%) as a colourless oil.
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22. *Typical procedure for the synthesis of TBS-enol ethers* **5**: To a stirred solution of (*E*)-2-buten-1-ol (**1c**, 0.19 mL, 2.2 mmol) and DABCO (22 mg, 0.2 mmol) in dry toluene (2 mL) at rt was added ethyl propiolate (**2a**, 0.20 mL, 2.0 mmol) dropwise over 10 min and the resultant solution was stirred for 0.5 h at rt. The mixture was heated to 150 °C for 15 h, cooled to rt and DMAP (25 mg, 0.2 mmol), Et_3N (0.34 mL, 2.4 mmol) and TBS-Cl (332 mg, 2.2 mmol) were added. The mixture was stirred for 3 h at rt. H_2O (20 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give ethyl 2-{[(*tert*-butyldimethylsilyl)oxy]methylene}-3-methylpent-4-enoate (**5c**, 460 mg, 81%) as a brown oil.
23. *Typical procedure for the synthesis of Boc-enol ethers* **6**: To a stirred solution of 2-buten-1-ol (**1c**, 0.19 mL, 2.2 mmol) and DABCO (22 mg, 0.2 mmol) in dry toluene (2 mL) at rt was added ethyl propiolate (**2a**, 0.20 mL, 2.0 mmol) dropwise over 10 min and the resultant solution was stirred for 0.5 h at rt. The mixture was heated to 150 °C for 15 h, cooled to rt and DMAP (24 mg, 0.2 mmol), Et_3N (0.28 mL, 2.0 mmol) and Boc_2O (0.87 g, 4.0 mmol) were added. The mixture was stirred for 3 h at rt. H_2O (20 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give ethyl 2-{[(*tert*-butoxycarbonyl)oxy]methylene}-3-methylpent-4-enoate (**6c**, 350 mg, 60%) as a colourless oil.
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25. *Typical procedure for the synthesis of β-hydroxy-4-pentenoates* **7**: To a stirred solution of 2-buten-1-ol (**1c**, 0.084 mL, 1.1 mmol) and DABCO (11 mg, 0.1 mmol) in dry toluene (2 mL) at rt was added ethyl propiolate (**2a**, 0.10 mL, 1.0 mmol) dropwise over 10 min and the resultant solution was stirred for 0.5 h at rt. The mixture was heated to 150 °C for 15 h, cooled to rt and the solvent was removed under reduced pressure. THF (2 mL) was added to the residue and the mixture was cooled to 0 °C. $NaBH_4$ (57 mg, 1.5 mmol) was added portionwise and the resultant mixture stirred for 1 h at rt, cooled to 0 °C and quenched with H_2O (3 mL). H_2O (15 mL) was added and the the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (2:1 petrol/EtOAc) to give ethyl 2-(hydroxymethyl)-4-methylpent-4-enoate (**7c,** 166 mg, 81%) as a brown oil as an inseparable 5:4 mixture of diastereomers.
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