Tandem Horner–Wadsworth–Emmons Olefination/Claisen Rearrangement/ Hydrolysis Sequence: Remarkable Acceleration in Water with Microwave Irradiation

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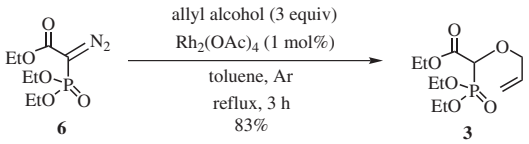
Dedicated to Professor Steven Ley on the occasion of his 60th birthday to acknowledge his friendship and his inspirational contributions to synthetic organic chemistry

Abstract: A tandem three-step, one-pot method for the conversion of aldehydes into β-substituted-2-oxohex-5-enoic acids **1** in good to excellent yield is described. The optimised sequence is carried out in water with microwave irradiation and involves sequential Horner–Wadsworth–Emmons (HWE) olefination, Claisen rearrangement and ester hydrolysis. The outcome of this domino sequence can be controlled by the temperature of the process.

Key words: tandem reactions, rearrangements, domino reactions, Wittig reactions, carboxylic acids

As part of a natural product programme, we required easy access to a range of homoallylic α-ketoacids **1**. We thought that Horner–Wadsworth–Emmons (HWE) olefination of aldehydes **2** with phosphonate **3** bearing an allyl group would produce 2-alkoxycarbonyl allyl vinyl ethers **4**, whose rearrangement should give esters **5** and hence acids **1**. Given our recent interest in tandem processes[2] we also envisaged that the sequence depicted in Scheme 1 could ultimately be carried out in a one-pot process.

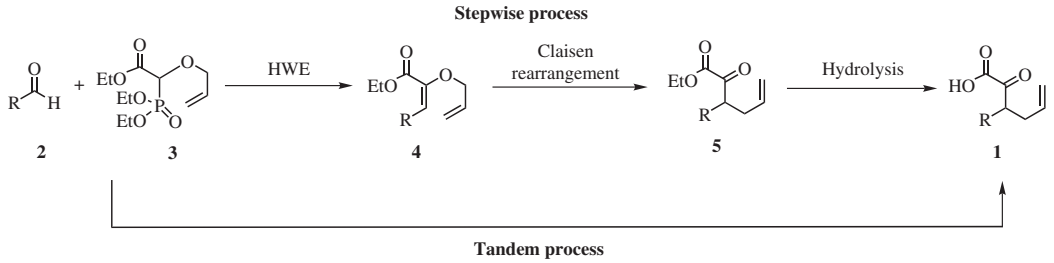
Of course, the Claisen rearrangement of allyl vinyl ethers is a well known process[3] but phosphorus-based olefination methods have not been widely used to access Claisen rearrangement precursors.[4,5] Moreover, the combination of these methodologies in a tandem fashion has been reported only rarely,[5] although recent examples have demonstrated the power of the methodology.[6] In order to explore the procedure for olefination/Claisen rearrangement depicted in Scheme 1, we first prepared the novel phosphonate **3**. Compound **3** was easily obtained on a multigram scale from diazophosphonate **6**[7] and allyl alcohol in a ruthenium-mediated[8] process (Scheme 2).



Scheme 2 Synthesis of phosphonate **3**.

With phosphonate **3** in hand, the viability of the stepwise and tandem methodology was explored using benzaldehyde as the model system (Scheme 3). First, HWE olefination was carried out under heterogeneous conditions in water, using a concentrated aqueous solution of K_2CO_3 as the base under the conditions developed by Villieras and co-workers.[9] The transformation proceeded at room temperature, affording 1,5-diene **4a** in 96% yield (*E:Z* = 1:1) after three hours. Diene **4a** underwent thermal rearrangement in toluene (120 °C, 6 h), affording racemic ester **5a** in 83% yield. Finally, saponification of **5a** using aqueous K_2CO_3 then gave acid **1a** in 87% yield. Ketoacid **1a** was crystalline and X-ray crystallographic analysis[10] confirmed the proposed structure (Figure 1).

We next focused our attention on the development of a tandem procedure. Given the success of the aqueous HWE process, we attempted to carry out the three-step se-



Scheme 1 Stepwise thermal transformation vs. tandem three-step, one-pot HWE olefination/Claisen rearrangement/hydrolysis sequence to prepare α-ketoacids **1**.

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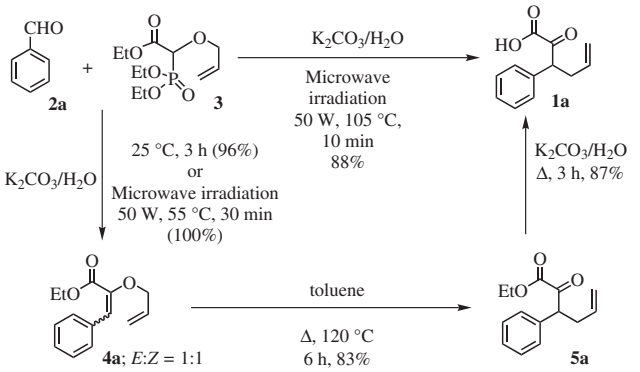


Scheme 3 Stepwise conventional vs. tandem microwave-mediated transformation.

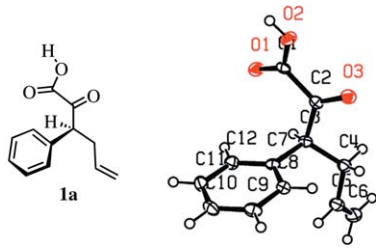


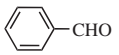
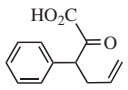
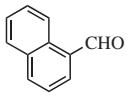
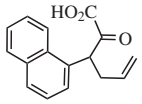
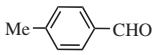
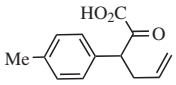
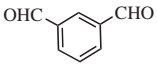
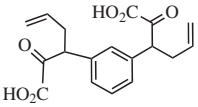
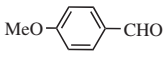
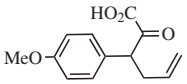
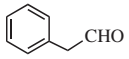
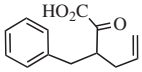
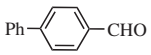
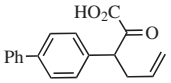
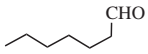
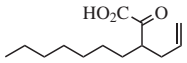
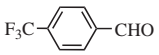
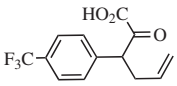
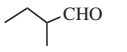
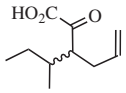
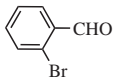
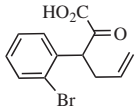
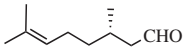
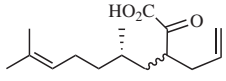
Figure 1 ORTEP plot of α-ketoacid (±)-**1a** (50% probability thermal ellipsoids).

quence in one-pot fashion in water. Unfortunately, using conventional heating, high temperature and prolonged reaction times are required, which precludes a clean transformation. However, we were delighted to discover that microwave irradiation (50 W) of an equimolecular, heterogeneous mixture of benzaldehyde and allyl phosphonate **3** in aqueous K_2CO_3 heated to 105 °C over ten minutes produced ketoacid **1a** directly in an excellent 88% overall yield.

In addition to the simplicity and efficiency of the tandem process, a further advantage is that the aqueous reaction conditions ensure an extremely simple purification procedure: extraction of the crude mixture with CH_2Cl_2 removes all of the organic by-products, and acidification with 10% HCl allows the acid **1a** to be extracted into EtOAc (leaving phosphorus by-products in the aqueous layer). It is noteworthy that the progress of the process can be controlled by adjustment of the reaction temperature in the microwave reactor. The sequence stops after the HWE olefination (quantitative) on heating to 55 °C at 50 W for 30 minutes, a significant rate enhancement compared to the standard thermal process (Scheme 3).

Thus, the sequential three-step process gave an overall yield of 69% with a combined reaction time of 12 hours, compared to the tandem process which gives 88% yield in a single operation lasting ten minutes. The aqueous medium employed for the tandem sequence presumably assisted the sigmatropic rearrangement via the well-known

Table 1 Tandem Microwave-Assisted HWE–Claisen–Hydrolysis to Give Ketoacids **1**

Entry	Aldehyde	Product	Yield (%)	Entry	Aldehyde	Product	Yield (%)
1			88	7			94
2			83	8			58[b]
3			53 71[a]	9			86
4			64	10			74
5			93	11			67[c]
6			78	12			75[c]

[a] HWE olefination carried out for 12 h at r.t. prior to microwave irradiation.
[b] Phosphonate **3** (3 equiv) used and HWE olefination carried out at r.t. for 12 h prior to microwave irradiation.
[c] Diastereomeric (1:1) mixtures.

hydrophobic acceleration effect,[11] as well as effecting the in situ hydrolysis of the intermediate α-ketoester.

Having established an effective tandem protocol on the model system, we investigated the scope and limitations of the method (Table 1). The results clearly show that the method is particularly efficient for aryl aldehydes (entries 1–8). The reaction is compatible with both electron-donating (entries 2 and 3) and electron-withdrawing (entries 4–6) functional groups on the aromatic core. The method is also applicable to hindered aromatic substrates (entries 6 and 7) and to bifunctional aryl aldehydes (entry 8). Aliphatic aldehydes are also suitable substrates (entries 9–12), even when highly enolisable (entry 9). The method is highly selective for aldehydes as ketones (e.g. acetophenone, cyclobutanone, cyclopentanone) do not react under these conditions. It should be noted that, in certain examples (e.g. entry 3), improved yields were obtained if the olefination reaction was allowed to reach completion prior to microwave irradiation.

In conclusion, we have developed a technically simple method for the synthesis of racemic 3-functionalised-2-oxohex-5-enoic acids **1** in good to excellent yields through a tandem three-step transformation involving HWE olefination, Claisen rearrangement and hydrolysis carried out in water under mild microwave-mediated conditions. We are currently applying this methodology in natural product synthesis.

One-Pot Microwave-Assisted Reaction; General Procedure

To a microwave tube containing benzaldehyde (63 μL, 0.53 mmol) and phosphonate **3** (150 mg, 0.53 mmol), was added a 10 M aqueous solution of K_2CO_3 (12 equiv). The heterogeneous mixture was efficiently stirred and irradiated in a CEM focused microwave (Discovery model) operating at 50 W at 105 °C for 10 min. The crude material was diluted with water and extracted with CH_2Cl_2 (3 × 10 mL). The aqueous layer was acidified with 10% HCl solution (20 mL) and extracted with EtOAc (5 × 10 mL). The EtOAc layer was washed with water and brine (15 mL), dried ($MgSO_4$), the solvent was removed under reduced pressure, affording **1a** (115 mg, 88% yield) as a waxy viscous solid; mp 64–65 °C.

IR (film): 3430, 1725, 1519, 1258 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.59 (m, 1 H, C4-CH_a), 2.85 (m, 1 H, C4-CH_b), 4.68 (t, *J* = 7.6 Hz, 1 H, C3-CH), 5.02 (m, 1 H, C6-CH_a), 5.07 (m, 1 H, C6-CH_b), 5.7 (m, 1 H, C5-CH), 7.25–7.4 (m, 5 H, Ph), 8.9 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.8, 51.9, 117.7, 128.1, 129.0, 129.1, 134.4, 134.8, 160.3, 194.5.

HRMS–CI: *m/z* [M + NH_4^+] calcd for $C_{12}H_{16}NO_3$: 222.11302; found: 222.11302.

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(10) Crystallographic data for **1a** can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. CCDC reference number: 255362. Selected crystallographic data: $C_{12}H_{12}O_3 \cdot C_{12}H_{12}O_3$ (dimer), M = 408.44, crystal system: Monoclinic, a = 16.103 (4), b = 5.4841 (12), c = 23.444 (5) Å, U = 2058.3 (8) $Å^3$, T = 115 (2) K, space group P2 (1)/c, Z = 8, μ = 0.094 mm^{-1}, 11027 reflections measured.
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