ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 3121–3123

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# Tandem reaction of 3-hydroxyhexa-4,5-allenic esters: a novel access to diversely substituted 2*H*-pyran-2-ones and indenes†

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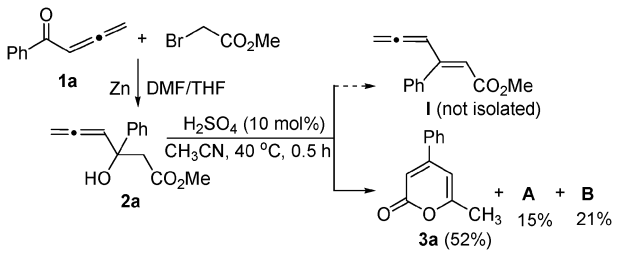
***Received 12th January 2012, Accepted 30th January 2012***
**DOI: 10.1039/c2cc30247k**



**A highly efficient synthesis of diversely substituted 2*H*-pyran-2-ones and indenes through Brønsted acid promoted tandem reaction of the readily obtainable 3-hydroxyhexa-4,5-allenic esters under extremely mild conditions has been developed.**

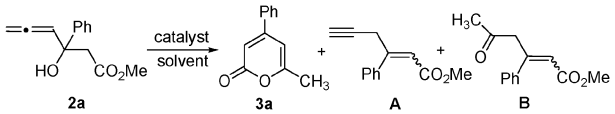
Allene derivatives are powerful synthetic intermediates toward a plethora of important organic compounds and frequent building blocks of natural products.[1] In this regard, 2,4,5-trienoates are the core substructure of some sex pheromones of male dried bean beetles.[2] As a continuation of our research in allene chemistry,[3] we envisioned a synthetic pathway toward 2,4,5-trienoate through dehydration of 3-hydroxyhexa-4,5-dienoate. For this purpose, 3-hydroxy-3-phenylhexa-4,5-dienoate (**2a**), prepared from 1-phenylbuta-2,3-dien-1-one (**1a**) and methyl 2-bromoacetate, was treated with $H_2SO_4$ (10 mol%) in $CH_3CN$ until a complete consumption of **2a** (0.5 h). From the resulting mixture, three products were isolated but none of them was the desired 2,4,5-trienoate (**I**). Instead, they were identified as 6-methyl-4-phenyl-2*H*-pyran-2-one (**3a**), methyl 3-phenyl hex-2-en-5-ynoate (**A**) and methyl 5-oxo-3-phenylhex-2-enoate (**B**) with yields of 52%, 15% and 21%, respectively (Scheme 1).

Although the desired 2,4,5-trienoate was not obtained, the result is interesting since it offers a novel approach toward 2*H*-pyran-2-ones. 2*H*-Pyran-2-ones are versatile synthetic building blocks and frequent backbones of compounds found in bacteria, fungi, plants, and animals. Many compounds with the α-pyrone moiety have shown antimicrobial, antineoplastic, and anti-HIV effects.[4,5] As a result, synthetic approaches to α-pyrones have been extensively investigated.[6–11] However, efficient protocols without using sophisticated catalysts/reagents and accomplished under mild conditions are still highly desirable.




**Scheme 1** Unexpected formation of α-pyrone **3a**.

**Table 1** Optimization studies for the formation of **3a**[a]




| | | | | | Yield[b] (%) | | |
|---|---|---|---|---|---|---|---|
| Entry | Acid | Solvent | $T$/°C | $t$/h | **3a** | **A** | **B** |
| 1 | $H_2SO_4$ | $CH_3CN$ | 40 | 0.5 | 52 | 15 | 21 |
| 2 | $H_2SO_4$[c] | $CH_3CN$ | 40 | 0.5 | 56 | 12 | 23 |
| 3 | $H_2SO_4$ | $CH_3CN$ | 60 | 0.5 | 61 | 10 | 19 |
| 4 | $H_2SO_4$ | $CH_3CN$ | 40 | 1 | 72 | Trace | 15 |
| 5 | $H_2SO_4$ | $CH_3CN$ | 40 | 2 | 73 | Trace | 13 |
| 6 | $H_2SO_4$ | THF | 40 | 1 | 30 | 10 | 35 |
| 7 | $H_2SO_4$ | $CH_3OH$ | 40 | 1 | 26 | 23 | 25 |
| 8 | $H_2SO_4$ | $CH_2Cl_2$ | Reflux | 0.5 | 86 | Trace | Trace |
| 9 | $H_2SO_4$ | $CH_2Cl_2$ | rt | 0.5 | 85 | Trace | Trace |
| 10 | TsOH | $CH_2Cl_2$ | rt | 1 | 36 | Trace | 35 |
| 11 | $BF_3{\cdot}Et_2O$ | $CH_2Cl_2$ | rt | 1 | 32 | 31 | 26 |
| 12 | $RuCl_3{\cdot}nH_2O$ | $CH_2Cl_2$ | rt | 1 | 21 | 10 | 10 |
| 13 | $FeCl_3{\cdot}6H_2O$ | $CH_2Cl_2$ | rt | 1 | 32 | 20 | 35 |

[a] Reaction conditions: **2a** (1 mmol), acid catalyst (0.1 mmol). [b] Isolated yields. [c] 0.2 mmol of acid were used.

Thus, exhaustive studies on reaction conditions for the formation of **3a** were conducted (Table 1). After some trial and error, the optimal conditions were identified as follows: 10 mol% of $H_2SO_4$ in dichloromethane at rt for 0.5 h. Under such conditions, **3a** was obtained in 85% yield.

With the optimized conditions in hand, we screened a range of 3-hydroxyhexa-4,5-dienoates to probe the scope of this reaction. It turns out that substrates prepared from aryl substituted allenic ketones with various substituents on the aryl ring undergo this reaction smoothly with good to excellent yields (Table 2, entries 1–13). The presence of an electron-withdrawing or electron-donating group on the aryl ring slightly affects the reactivity. The reaction is found to be also compatible with substrates prepared from diaryl or alkyl, aryl

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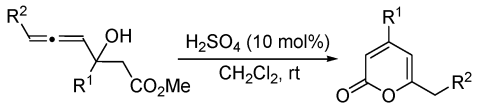
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and NMR spectra. See DOI: 10.1039/c2cc30247k

**Table 2** Synthesis of 4,6-disubstituted 2*H*-pyran-2-ones[a]




**2** **3**

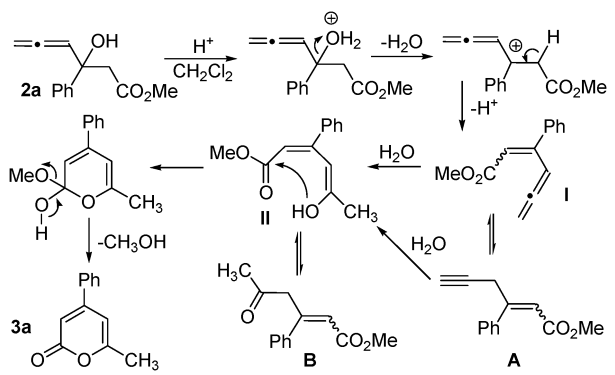
| Entry | $R^1$ | $R^2$ | **3** | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Ph | H | **3a** | 85 |
| 2 | *p*-Cl–$C_6H_4$ | H | **3b** | 86 |
| 3 | *p*-Br–$C_6H_4$ | H | **3c** | 88 |
| 4 | *o*-Cl–$C_6H_4$ | H | **3d** | 78 |
| 5 | *o*-Br–$C_6H_4$ | H | **3e** | 81 |
| 6 | *p*-$CH_3$–$C_6H_4$ | H | **3f** | 84 |
| 7 | *m*-$CH_3$–$C_6H_4$ | H | **3g** | 82 |
| 8 | *o*-F–$C_6H_4$ | H | **3h** | 83 |
| 9 | *m*-F–$C_6H_4$ | H | **3i** | 81 |
| 10 | *p*-$CH_3O$–$C_6H_4$ | H | **3j** | 80 |
| 11 | *o*-$CH_3O$–$C_6H_4$ | H | **3k** | 75 |
| 12 | *m*,*p*-di-$CH_3O$–$C_6H_3$ | H | **3l** | 76 |
| 13 | *p*-NC–$C_6H_4$ | H | **3m** | 90 |
| 14 | Ph | Ph | **3n** | 82 |
| 15 | Ph | *p*-F–$C_6H_4$ | **3o** | 86 |
| 16 | *p*-$CH_3$–$C_6H_4$ | Ph | **3p** | 80 |
| 17 | *p*-$CH_3$–$C_6H_4$ | *p*-F–$C_6H_4$ | **3q** | 79 |
| 18 | *p*-Cl–$C_6H_4$ | Ph | **3r** | 80 |
| 19 | $CH_3$ | Ph | **3s** | 82 |
| 20 | $CH_3$ | *p*-F–$C_6H_4$ | **3t** | 81 |

[a] Reaction conditions: **2** (1 mmol), $H_2SO_4$ (0.1 mmol), $CH_2Cl_2$ (5 mL), rt, 0.5 h. [b] Isolated yields.

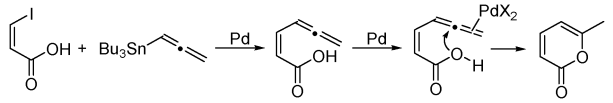
disubstituted allenic ketones (entries 14–20). Various functional groups such as methyl, methoxy, halides and cyano are well tolerated with the reaction conditions.

Based on the above observations, a plausible pathway for the formation of **3a** is depicted in Scheme 2. Acid promoted dehydration of **2a** affords 2,4,5-trienoate **I** or alkyne **A**. Subsequent hydration of **I** or **A** gives an enol intermediate (**II**) or its ketone isomer **B**. Intramolecular transesterification of **II** affords α-pyrone **3a**. The proposal that **3a** could be formed through the separable alkyne **A** is confirmed by a separate experiment, in which **A** was treated with $H_2O$ in $CH_2Cl_2$ at rt for 0.5 h in the presence of $H_2SO_4$ (10 mol%) to give **3a** in 88% yield.[12]

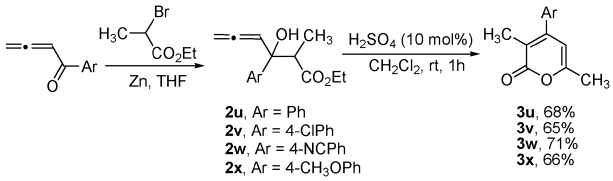
We noticed that Abarbri *et al.* have reported an efficient synthesis of α-pyrones by treating (*Z*)-α-iodovinylic acids with allenyl tributyltin (Scheme 3).[11] Although the key intermediates in Abarbri's process and our method are structurally similar, the



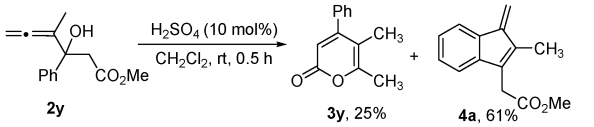

**Scheme 2** Plausible pathway for the formation of **3a**.




**Scheme 3** Abarbri's synthesis of α-pyrones *via* a hexa-2,4,5-trienoic acid intermediate.




**Scheme 4** Preparation of 3,4,6-trisubstituted α-pyrone **3u–3x**.



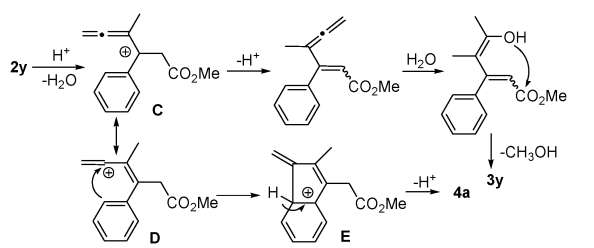

**Scheme 5** Reaction of **2y** and unexpected formation of **4a**.

two protocols are remarkably different in terms of substrates starting from, catalysts and reagents employed, as well as mechanistic pathways that involved.

Having established an efficient and mild protocol toward 4,6-disubstituted 2*H*-pyran-2-ones, we moved forward to study the possibility of preparing 2*H*-pyran-2-ones with other substitution patterns. Firstly, reactions of **2u–2x** were studied (Scheme 4). From these reactions, 3,4,6-trisubstituted 2*H*-pyran-2-ones (**3u–3x**) were obtained in good yields.

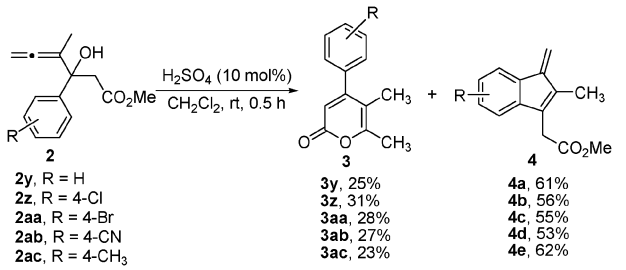
Next, from substrates with a methyl group on the internal position of the allene moiety (**2y**), 4,5,6-trisubstituted 2*H*-pyran-2-one (**3y**) was obtained but in low yield (Scheme 5). Interestingly, methyl 2-(2-methyl-1-methylene-1*H*-inden-3-yl)acetate (**4a**) was isolated along with **3y** in a yield of 61%. The structure of **4a** was established based on its MS and NMR spectra ($^1H$, $^{13}C$ and HMQC). A possible mechanism leading to **3y** and **4a** is described in Scheme 6. While acid promoted domino process *via* the initially formed carbocation **C** affords **3y**, the formation of **4a** is most likely through an intramolecular Friedel–Crafts reaction of carbocation **D**.[13] The presence of a methyl group makes this alternative route possible since it can stabilize **D** with the formation of a tetrasubstituted C–C double bond. Alternatively, a Nazarov pathway leading to **4a** cannot be eliminated.[14]

The unexpected formation of **4a** turns out to be very attractive since compounds with an indene core have been widely used as drug candidates and functional materials.[15] The generality of the above process was demonstrated with

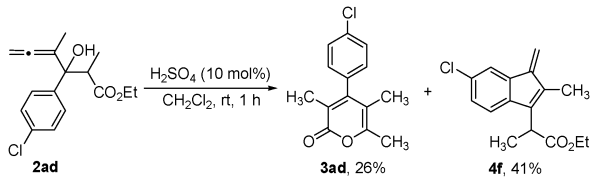



**Scheme 6** Plausible pathway for the formation of **4a**.




**Scheme 7** Preparation of 4,5,6-trisubstituted α-pyrones **3y–3ac** and indenes **4a–4e**.




**Scheme 8** Preparation of 3,4,5,6-tetrasubstituted α-pyrone **3ad** and indene **4f**.

substrates **2y–2ac**, from which, indenes (**4a–4e**) were obtained in reasonably good yields (Scheme 7). From these reactions, the corresponding 4,5,6-trisubstituted pyran-2-ones (**3y–3ac**) could also be obtained. As a further aspect, we were able to obtain a 3,4,5,6-tetrasubstituted 2*H*-pyran-2-one (**3ad**) together with indene **4f** from substrate **2ad** (Scheme 8).

In summary, we have developed a novel and easy-to-perform protocol for the preparation of 2*H*-pyran-2-ones through an acid-catalyzed domino reaction of 3-hydroxyhexa-4,5-dienoates. By tuning the substitution patterns of the substrates, 4,6-disubstituted and 3,4,6-trisubstituted α-pyrones can be synthesized with high efficiency. More interestingly, from substrates with a methyl group on the internal position of the allene moiety, indene derivatives could also be prepared together with 4,5,6-trisubstituted or 3,4,5,6-tetrasubstituted α-pyrones. With advantages such as readily available substrates, diversely substituted products, free of sophisticated catalysts or reagents, and extremely mild reaction conditions, this finding should be an important implication in heterocyclic chemistry and related areas. Further studies to expand substrate scope and have a possible deeper insight into the reaction mechanism are currently underway.

We are grateful to the National Natural Science Foundation of China (20972042, 21172057), Innovation Scientists and Technicians Troop Construction Projects (104100510019), PCSIRT (IRT1061) and 2012IRTSTHN006 for financial support.

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