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Palladium catalyzed reductive decarboxylation of allyl α-alkenyl-β-ketoesters. A new synthesis of (*E*)-3-alkenones

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Abstract—The reductive decarboxylation of α-alkenyl derivatives of allyl-β-ketoesters was achieved by use of palladium(0) catalyst generated in situ from $Pd(OAc)_2$ and PPh_3, with triethylammonium formate as the hydride source, in THF. The reaction proceeds smoothly and cleanly, with linear alkenyl derivatives of allyl-β-ketoesters, to afford (*E*)-3-alkenones in good to excellent yields (73–92%) and high stereoselectivity (>98%).

β-Ketoesters and their α-substituted derivatives are important starting materials in organic synthesis and are extensively used for the preparation of a variety of ketones. This conversion is achieved either by the classical sequence of alkaline hydrolysis, acidification and thermal decarboxylation or by a direct decarboalkoxylation procedure.[1] However, these procedures usually require harsh conditions and sometimes the transformation is not easy, especially with α-substituted and α,α-disubstituted β-ketoesters, although some methods for smooth decarboxylation have been reported.[2]

An elegant method for the cleavage of β-ketoesters to give alkylated ketones appeared in 1985 with the introduction of palladium catalysts.[3] Extensive studies on palladium catalyzed reactions of allylic compounds, via π-allyl palladium complexes, led to synthetically useful catalytic reactions of allyl β-ketoesters offering new synthetic methodologies for their decarboxylation, not attainable by conventional routes. There are representative reports on the transformation of allyl β-ketoesters to (a) α-alkyl ketones by decarboxylation–hydrogenolysis; (b) α,β-unsaturated ketones by decarboxylation–dehydrogenation; (c) γ,δ-unsaturated ketones by decarboxylation–allylation and (d) α-methylene ketones by decarboxylation–deacetoxylation. All these types of palladium catalyzed reactions of allyl β-ketoesters have recently been reviewed by Tsuji.[4]

During the course of our studies directed towards the synthesis of (*E*)-2-alkenones[5] by decarboxylation of a β-keto acid, the problem of decarboxylation of α-alkenyl β-ketoesters was encountered. These derivatives, products of a Knoevenagel condensation of a β-ketoester with an aldehyde, could not be decarboxylated by conventional techniques. In this context, the possibility of applying the palladium catalyzed hydrogenolysis of allyl α-alkenyl-β-ketoesters was examined, expecting the formation of the corresponding α,β-unsaturated ketone. For this transformation, allyl α-isopentenyl acetoacetate **2c**, the product of the condensation of allyl acetoacetate and isovaleraldehyde, was chosen as the model (see reaction above Table 1).

Thus a solution of substrate **2c** (1 mmol), a catalytic amount of $Pd(OAc)_2$ (2.5 mmol %) and PPh_3 (5 mmol %), in the presence of triethylammonium formate (2.0 mmol), in THF was left overnight at room temperature. After a simple work up and rapid column chromatography on silica gel, (*E*)-6-methyl-4-hepten-2-one **3c** was obtained in 82% yield.

This unexpected result prompted us to study the above transformation using different α-alkenyl derivatives of allyl β-ketoesters, in order to establish the generality of the procedure as a new synthetic method for the synthesis of β,γ-unsaturated ketones.

To the best of our knowledge, the catalytic transformation of β-ketoesters or derivatives into β,γ-unsaturated

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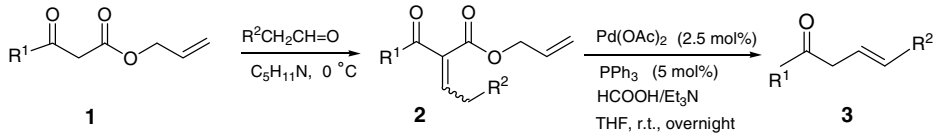
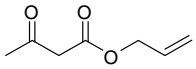
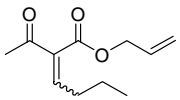
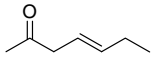
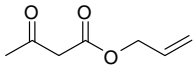
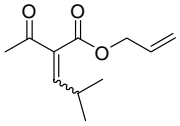
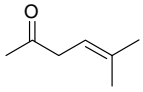
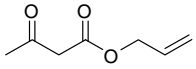
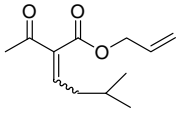
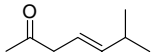
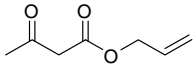
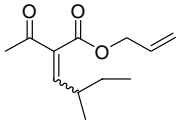
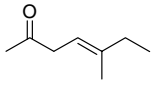
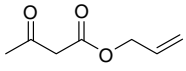
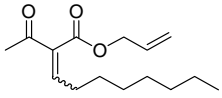
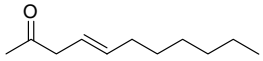
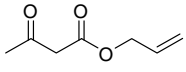
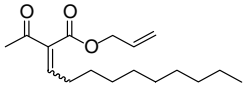
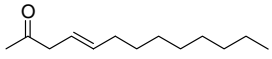
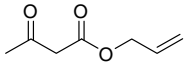
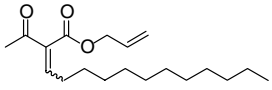
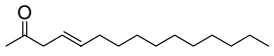
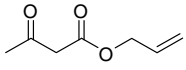
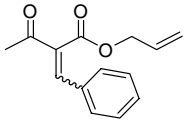
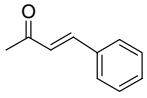
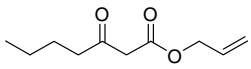
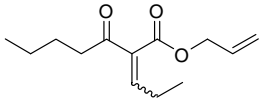
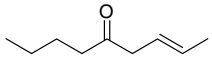
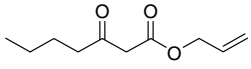
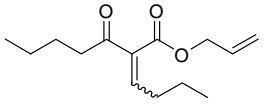
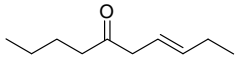
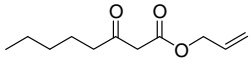
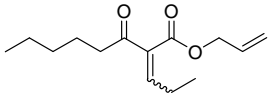
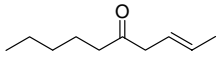
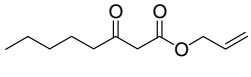
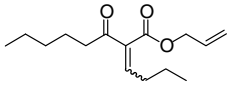
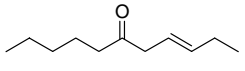
Table 1. Preparation of allyl α-alkenyl-β-ketoesters and their decarboxylation to (*E*)-3-alkenones



Entry	Allyl β-ketoester **1**	Condensation product **2**	Yield (%)	Decarboxylation product **3**	Yield (%)	Lit.[a]
a			81		73	16
b			75		44[b]	17
c			78		82	18
d			84		35[c]	19
e			92		83	20
f			87		86	7b
g			85		90	—
h			73		35[d]	5
i			84		86	21
j			90		88	—
k			86		84	—
l			91		92	—

[a] Spectral data of the reported compounds are in accord with those of the literature cited below.
[b] Mixture of 5-methyl-4(*E*)-hexen-2-one **3b** and 5-methyl-3(*E*)-hexen-2-one in a 1:1 ratio (GC–MS analysis).
[c] Mixture of 5-methyl-4(*E*)-hepten-2-one **3d**, 5-methyl-4(*Z*)-hepten-2-one and 5-methyl-3(*E*)-hepten-2-one in a 1:1:2 ratio (GC–MS analysis).
[d] Contains 17% of 4-phenyl-2-butanone (ratio 1:1, GC–MS analysis).

ketones has not yet been reported. Taking into account the easy preparation of the required starting α-alkenyl-allyl-β-ketoesters through the Knoevenagel condensation of a β-ketoester with an aldehyde,[6] their transformation into β,γ-enones should be synthetically very attractive.

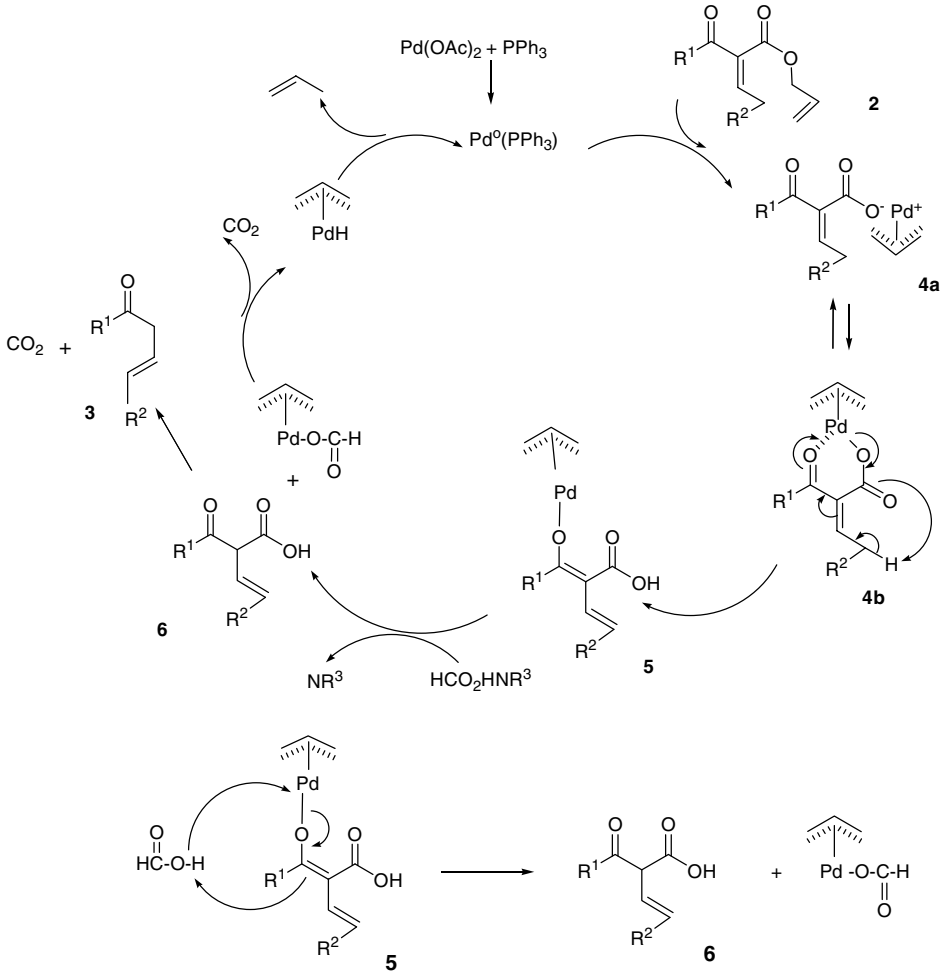
It is noteworthy that the synthesis of β,γ-unsaturated ketones poses a synthetic challenge, because of their occurrence in nature,[7] their physiological activity[8] and also their applicability as precursors for a variety of synthetic schemes.[9] In view of the synthetic importance of β,γ-unsaturated ketones, several synthetic approaches to these compounds have been reported.[10]

The allyl β-ketoesters required as starting materials in the present work, are, in general, commercial products. They can also be prepared in good yield, by reaction of the corresponding acid chloride with Meldrums's acid followed by alcoholysis with allyl alcohol[11] as well as by transesterification of the corresponding methyl or ethyl ester with an excess of allyl alcohol in the presence of dimethylaminopyridine[12] or zinc dust[13] as catalysts.

Knoevenagel condensation of allyl β-ketoesters with aldehydes,[14] in the presence of a catalytic amount of piperidine at 0 °C, gave the corresponding allyl α-alkenyl-β-ketoesters in good yield, as a mixture of (*E*)- and (*Z*)-isomers in an *E*/*Z* ratio of approximately 2/1, isolated from the crude product by rapid column chromatography on silica gel. A representative experimental procedure is reported[15] and the yields are summarized in Table 1.

The decarboalkoxylation procedure was applied to the series of allyl α-alkenyl-β-ketoesters in Table 1. The reaction was carried out under the typical conditions of reductive decarboxylation[3] in the presence of $Pd(OAc)_2$ and PPh_3 and an excess of triethylammonium formate under nitrogen, either at room temperature overnight, or at 50 °C for half an hour. The yields reported in Table 1 are for products purified by column chromatography on silica gel.[15]

The nature of the aldehyde used for the production of the starting allyl α-alkenyl-β-ketoesters, significantly affects the reactivity of these substrates towards the palladium catalyzed decarboalkoxylation. Thus, the reaction with substrate **2**, obtained by condensation of an allyl β-acetoacetate with an aldehyde unsubstituted in the α-position (entries a, c, e–g and i–l), proceeded smoothly and cleanly to give the corresponding β,γ-unsaturated



Scheme 1.

ketone **3** in good yield (73–92%) and high stereoselectivity (>98%). The trans-geometry was deduced from the characteristic absorption at 970 cm^{-1} in the IR as well as by comparison of their ^1H NMR and mass spectra with those reported in the literature (see Table 1). Minor amounts (<0.5%) of the corresponding α,β-unsaturated ketone or (*Z*)-β,γ-unsaturated ketone, as well as the fully saturated product, were detected by GC–MS analysis.

When substrate **2** was obtained by condensation of an allyl β-acetoacetate and an α-branched aldehyde (entries b and d), the decarboalkoxylation proceeded in lower yield (44% and 35%, respectively) and the selectivity of the reaction was poor. A considerable amount of the corresponding α,β-unsaturated ketone was present in the final product. Decarboxylation of substrate **3h**, which contains an aromatic ring (entry h), also needed forcing conditions and gave, in low yield (35%), α,β-unsaturated ketone and the reduced ketone in a 1/1 ratio. It must be noted that for the decarboxylation step, there was no need to separate the *E*- and *Z*-isomers of allyl α-alkenyl-β-ketoesters **2**. For example, when the *Z*- and *E*-isomers of substrate **2c** were separated by careful column chromatography on silica gel and separately subjected to the decarboxylation procedure, (*E*)-6-methyl-4-hepten-2-one **3c** was obtained in the same yield, and exactly the same purity, in both cases.

The formation of β,γ-unsaturated ketones from allyl α-alkenyl-β-ketoesters, by palladium catalyzed reductive decarboxylation, can be explained by the catalytic cycle presented in Scheme 1.

Oxidative addition of allyl α-alkenyl-β-ketoester **2** to the palladium(0) species formed in situ from $Pd(OAc)_2$ and PPh_3, affords a π-allylpalladium-β-ketocarboxylate complex **4a** initially, which is transformed to π-allylpalladium enolate **4b**.[3] The α-carbonyl group in π-allylpalladium-β-ketocarboxylate **4b** is activated by a chelating effect. An intramolecular proton transfer of the palladium complex **4b** gives **5**. Next, π-allylpalladium dienolate acid **5** (which cannot be decarboxylated), undergoes protonation from HCOOH to give β,γ-unsaturated keto acid **6**, which is finally decarboxylated to afford β,γ-unsaturated ketone **3** and π-allylpalladium formate. The latter, after decarboxylation and reductive elimination of the produced allylpalladium hydride, gives propene and regenerates the Pd(0) species, which enters a new catalytic cycle.

In conclusion, the reductive decarboxylation of allyl α-alkenyl-β-ketoesters by the use of $Pd(OAc)_2$ and PPh_3, followed by the addition of $HCOOH/Et_3N$ in THF, provides an efficient procedure for the preparation of linear (*E*)-3-alkenones. The attractive features of this new approach are: the readily accessible starting materials, the good yield, the high stereoselectivity of the products and the operational simplicity of the procedure. The reaction conditions are mild, preventing the inherent lability of the double bond undergoing prototropic rearrangement to produce conjugated isomeric ketones. Further studies are underway to apply this reaction in cyclic or polyfunctional substrates and also in the synthesis of natural products.

Acknowledgement

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15. (a) *Representative experimental procedure and spectral data for entry c, Table 1*; *allyl 6-methyl-3-hepten-2-one-3-carboxylate* (**2c**): To a mixture of allyl-acetoacetate (2.28 g, 16 mmol) and isovaleraldehyde (1.45 g, 16.8 mmol) at ice-bath temperature, piperidine (one drop) was added. The reaction mixture was stirred at 0 °C for 4 h, a saturated aqueous solution of NH_4Cl (10 ml) was added and the total was extracted with diethyl ether

(3×25 ml). The organic phase was washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by rapid preparative chromatography on silica gel (elution: petroleum ether–ether 8:1) to give allyl 6-methyl-3-hepten-2-one-3-carboxylate (**2c**) (2.62 g, 12.5 mmol, yield 78%) as a mixture of *E*- and *Z*-isomers. Careful flash chromatography of the (*E*) and (*Z*)-mixture of **2c** (0.2 g) on silica gel (elution: petroleum ether–ether 25:1) gave pure (*E*)-**2c** (0.105 g) followed by a mixture (0.030 g) and finally pure (*Z*)-**2c** (0.047 g) (elution: petroleum ether–ether 10:1). Compound (*E*)-**2c**: IR (CCl_4): 1712, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.91 (6H, d, $J = 6.6$ Hz), 1.78 (1H, m), 2.13 (2H, m), 2.34 (3H, s), 4.66 (2H, dt, $J_1 = 5.8$, $J_2 = 1.4$), 5.26 (1H, m), 5.35 (1H, m), 5.82–6.02 (1H, m), 6.95 (1H, t, $J = 7.8$); ^{13}C NMR ($CDCl_3$, 50 MHz): 22.6 (2C), 28.5, 31.4, 38.4, 65.8, 118.8, 131.8, 136.1, 148.5, 164.3, 201.2; MS *m*/*z* (relative intensity): 210 (M^+, 1), 195 (3), 169 (6), 137 (8), 127 (8), 110 (14), 82 (10), 43 (100).

Compound (*Z*)-**2c**: IR (CCl_4): 1729, 1696, 1638, 1618 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (6H, d, $J = 6.7$ Hz), 1.80 (1H, m), 2.18 (2H, m), 2.28 (3H, s), 4.70 (2H, dt, $J_1 = 6.0$ Hz, $J_2 = 1.5$Hz), 5.25 (1H, m), 5.40 (1H, m), 5.80–6.05 (1H, m), 6.85 (1H, t, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): 22.6 (2C), 27.1, 28.4, 39.0, 66.0, 119.3, 131.7, 137.6, 148.0, 166.4, 195.1; MS *m*/*z* (relative intensity): 210 (M^+, 1), 195 (3), 169 (6), 137 (8), 127 (8), 110 (14), 82 (10), 43 (100). (b) *Reductive decarboxylation of* **2c**; *synthesis of 6-methyl-4-hepten-2-one* **3c**: To a stirred solution of palladium acetate (11 mg, 0.05 mmol) and Ph_3P (26 mg, 0.1 mmol) in anhydrous THF (3 ml), in a dry flask under nitrogen were added in one portion HCOOH (0.18 ml, 4 mmol) and Et_3N (0.83 ml, 5 mmol) in anhydrous THF (2 ml), at room temperature. The mixture was vigorously stirred and allowed to react with a solution of allyl-6-methyl-3-hepten-2-one-3-carboxylate **2c** (0.420 g, 2 mmol) in dry THF (1 ml). The reaction mixture was stirred for 30 min at 50 °C or at room temperature overnight. The mixture was passed through a short silica gel column and washed with ether. The filtrate was washed with a solution of 5% $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on SiO_2 (elution: petroleum ether–ether 10:1) to afford 6-methyl-4-hepten-2-one **3c** (0.205 g, yield 82%) as a colourless oil; IR (CCl_4): 1720, 1630, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.99 (6H, d, $J = 6.6$), 2.15 (3H, s), 2.25 (1H, m), 3.1 (2H, d, $J = 5.6$), 5.5 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): 22.3 (2C), 29.3, 31.1, 47.6, 118.8, 142.3, 207.7; MS *m*/*z* (relative intensity): 126 (M^+, 2), 108 (10), 93 (3), 83 (2), 71 (3), 69 (3), 55 (18), 43 (100).

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