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PREPARATION OF α-METHYLENE KETONES BY THE PALLADIUM-CATALYZED DECARBOXYLATION-DEACETOXYLATION OF ALLYL α-ACETOXYMETHYL-β-KETO CARBOXYLATES UNDER MILD CONDITIONS

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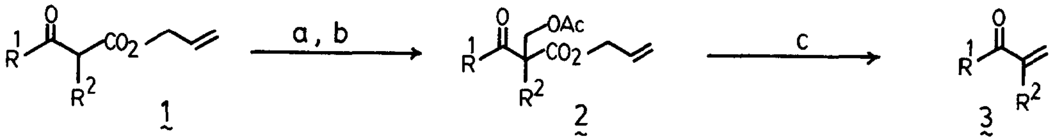
Summary; α-Methylene ketones are prepared in high yields by the palladium-catalyzed decarboxylation-deacetoxylation of allyl α-acetoxymethyl-β-keto carboxylates. The reaction proceeds rapidly at room temperature under neutral conditions in acetonitrile.

α-Methylene ketones are present in some natural products which exhibit high anti-tumor activity, and their efficient synthetic methods are strongly desirable. α-Methylene ketones are highly reactive and undergo facile Michael-type reaction, and hence their preparation in high yields must be carried out under extremely mild conditions. A number of preparative methods are known.1) However, further improvement is still required in these reactions, particulary in their yields. We now wish to report a new preparative method for α-methylene ketones in high yields under extremely mild conditions. We have been working on the palladium-catalyzed reactions of allyl β-keto carboxylates, and discovered three reactions, namely, 1. intramolecular decarboxylation-allylation to give α-allyl ketones,2,3) 2. decarboxylation-dehydrogenation to give α,β-unsaturated ketones,4,5) and 3. decarboxylation-hydrogenolysis to give α-alkyl ketones.6) In our continuing work on the palladium-catalyzed reactions of allyl β-keto carboxylates, we have discovered a new preparative method for α-methylene ketones **3** from allyl α-acetoxymethyl-β-keto carboxylates **2**. As shown in the following scheme, the present method is based on the three-step reactions starting from allyl β-keto carboxylates.

As the first step, hydroxymethyl group was introduced into allyl β-keto carboxylates **1** by the reaction with aqueous formaldehyde using $KHCO_3$ as a base. The reaction proceeds nearly quantitatively, and is much better than the reaction of formaldehyde with simple ketones. Then the hydroxy group was acetylated to give allyl α-acetoxymethyl-β-keto carboxylates **2**. Finally, **2** were treated with a $Pd_2(dba)_3\cdot CHCl_3$-PPh_3 catalyst in acetonitrile at 20-25°C. The reaction proceeds rapidly and α-methylene ketones **3** were obtained in high yields:

<SCHEME 1>

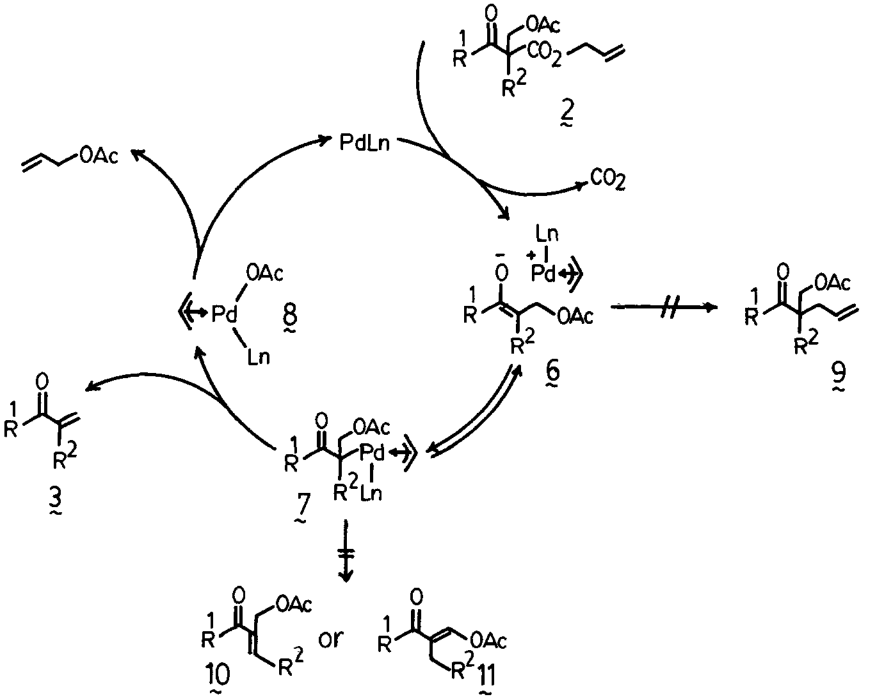


a) H_2CO, $KHCO_3/H_2O$-allyl alcohol-THF b) Ac_2O, Py.
c) $Pd_2(dba)_3\cdot CHCl_3$, PPh_3/MeCN, 20-25°C

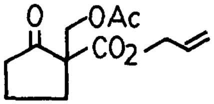
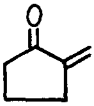
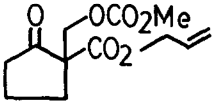
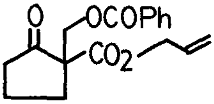
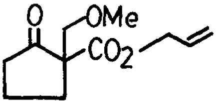
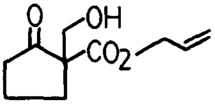
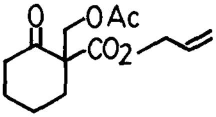
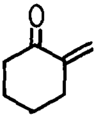
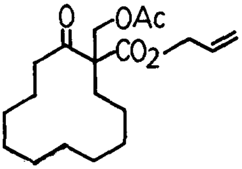
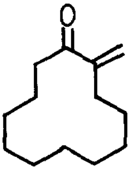
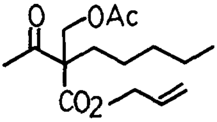
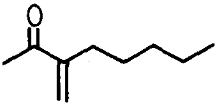
Some results are shown in <Table 1>. Acetonitrile is the best solvent for this reaction. In THF, α-allyl ketone **9** was obtained as a minor product.$^{2,3)}$ Other predictable by-products, enones **10** or **11**, formed by β-hydrogen elimination from $7^{4-6)}$ were not obtained at all. As for the leaving group, carbonates and benzoate are also acceptable ones. But methoxy and hydroxy groups are not suitable, which give α-allyl ketones as major products.

Generally reactions were carried out in the following way; A solution of **2** (1 mmol), $Pd_2(dba)_3\cdot CHCl_3$ (0.05 mmol), and PPh_3 (0.2 mmol) in acetonitrile (5 mL) was stirred for 10-20 min at 20-25°C under argon. After the reaction was complete (TLC and GLC analyses), α-methylene ketones were isolated by column chromatography on silica gel, preparative GLC, or distillation.

<SCHEME 2>



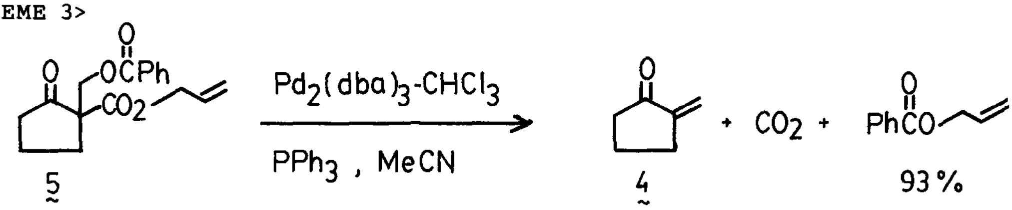
<TABLE 1> PREPARATION OF α-METYLENE KETONES

RUN	β-KETO ESTER	α-METHYLENE KETONE	YIELD(%)a)
1		 **4**	67 (93)
2		**4**	(94)
3		**4**	59
4		**4**	(4)b)
5		**4**	(4)c)
6			63 (100)
7			83
8			88

a) Isolated yields. GLC yields in parentheses. b) α-Allyl ketone was obtained (94%). c) α-Allyl ketone was obtained (72%).

The reaction can be explained by the following mechanism. Oxidative addition of allyl α-acetoxymethyl-β-keto carboxylates **2** to Pd(0) followed by decarboxylation affords (π-allyl)palladium enolate complex **6**, which is in equilibrium with C-bonded complex **7**. Then elimination of α-acetoxy group takes place to give α-methylene ketones **3** and (π-allyl)palladium acetate complex **8**. Finally, reductive elimination gives allyl acetate and regenerates the Pd(0) species. As a supporting evidence, allyl benzoate was obtained in 93% yield by the palladium-catalyzed reaction of allyl α-benzoxymethyl-β-keto carboxylate **5**.

<SCHEME 3>



The present method offers a facile and efficient preparative method for α-methylene ketones. Application of this enone formation to syntheses of natural products is in progress.

ACKNOWLEDGMENT:

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