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Facile Synthesis of α-Keto Acids and Esters by Palladium-Catalyzed Decarboxylation Reactions of Diallyl α-Oxalcarboxylates

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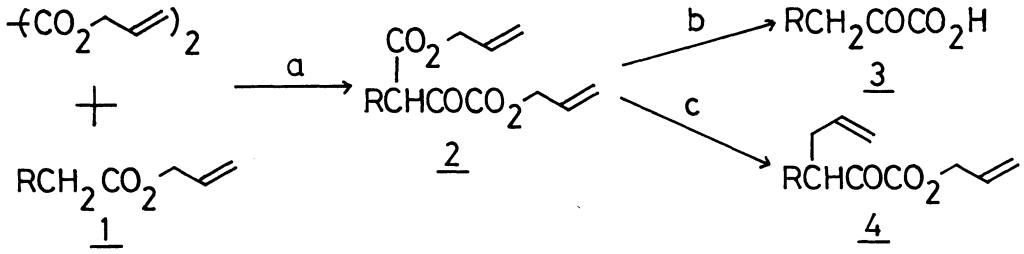
Reaction of diallyl α-oxalcarboxylates with formic acid in the presence of palladium catalyst gave α-keto acid in good yields. When the reaction was carried out without formic acid, decarboxylation-allylation took place to give allyl β-allyl-α-keto carboxylates.

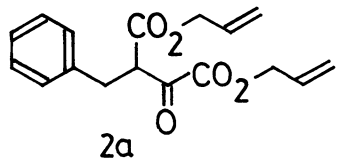
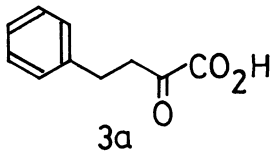
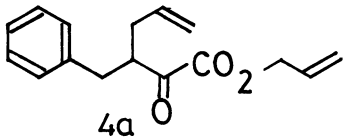
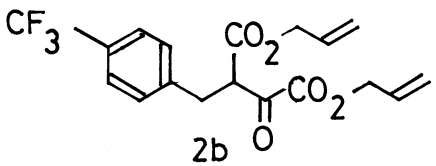
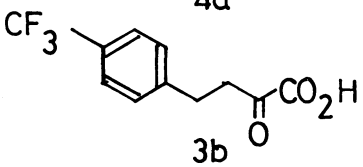
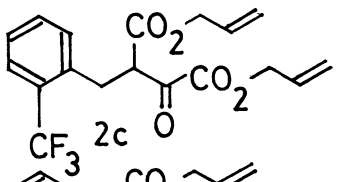
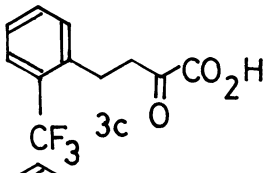
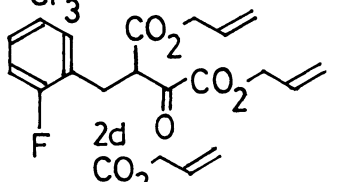
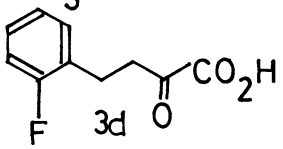
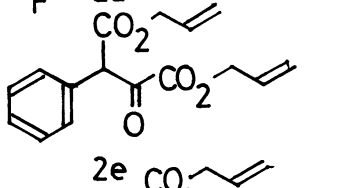
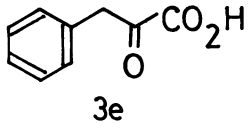
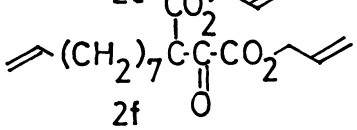
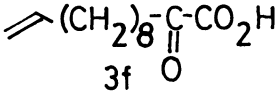
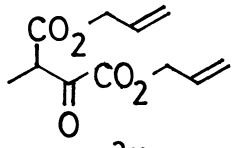
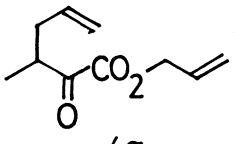
Development of practical synthetic methods for various α-keto acids[1] is of current interest because α-keto acids are important for synthesis of biologically active compounds. Among the various synthetic methods of α-keto acids, hydrolysis of α-oxalcarboxylates followed by subsequent decarboxylation is known as one of the most useful synthetic methods.[2] However, the decarboxylation usually requires strong acids such as concentrated hydrochloric acid. We have reported that decarboxylation reaction of allyl β-keto carboxylates to give the corresponding ketones proceeds with ease under mild conditions using formic acid in the presence of palladium catalyst.[3] In this paper we wish to report a facile decarboxylation reaction of diallyl α-oxalesters to α-keto acids using palladium catalyst. Decarboxylation-allylation of diallyl oxalcarboxylate to β-allyl-α-keto esters is also carried out using palladium catalyst.[4]



a) allyl alcohol, NaH in THF.
b) Pd-PPh_3 catalyst, HCO_2H, Et_3N in dioxane.
c) Pd-PPh_3 catalyst in THF.

Scheme 1.

Table 1. Palladium-catalyzed decarboxylation of diallyl α-oxalcarboxylates

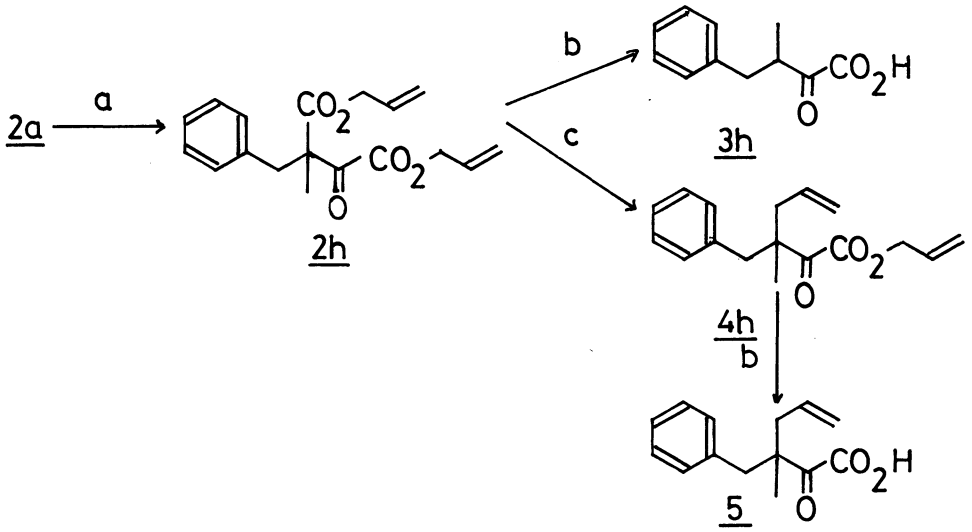
Run	Diallyl oxalcarboxylate	Method[a)]	Product[5)]	Yield[b)]
1	 2a	A	 3a	88
		B	 4a	83
2	 2b	A	 3b	68
3	 2c	A	 3c	79
4	 2d	A	 3d	69
5	 2e	A	 3e	64
6	 2f	A	 3f	88
7	 2g	B	 4g	98

a) A:$Pd_2(DBA)_3CHCl_3$ (1 mol%), PPh_3 (1 mol%), HCO_2H (10 equiv.), Et_3N (10 equiv.) in dioxane at room temperature.
B:$Pd_2(DBA)_3CHCl_3$ (1 mol%), PPh_3 (1 mol%) in THF under reflux.

b) Isolated yield.

The procedures for preparation of α-keto acids and esters are shown in Scheme 1. The diallyl α-oxalesters, 2a-2g, were obtained in good yields (57-88%) from the corresponding allyl esters 1 by reaction with diallyl oxalate using sodium allyloxide (2 equiv.) in THF at room temperature. In a typical experiment for the conversion of α-oxalcarboxylates 2 to α-keto acids 3, a mixture of HCO_2H (10 equiv.) and Et_3N (10 equiv.) was added to a solution of $Pd_2(DBA)_3CHCl_3$ (1 mol%) and PPh_3 (1 mol%) in dioxane (30 ml) at room temperature. To the solution was added diallyl α-oxalhydrocinnamate 2a (3.3 mmol) and the mixture was stirred for 8 h at room temperature. Saturated aqueous $NaHCO_3$ was added to the solution and the resulting basic solution was extracted with ether to removed non-acidic compounds. The aqueous solution was acidified with dilute hydrochloric acid and the organic acid was extracted with ether. The extract was concentrated and the residue was chromatographed on silica gel using a mixture of hexane-ether (80/20) as an eluent to give the α-keto acid 3a in 88% yield. The keto acid 3a was characterized after esterification with diazomethane. Me ester of 3a ; ^1H NMR (60 MH_Z, CCl_4) δ 7.09 (5H, s), 3.70 (3H, s), and 2.70-3.18 (4H); ^{13}C NMR (90 MH_Z, $CDCl_3$) δ 192.9 (s), 161.2 (s), 139.9 (s), 128.4 (d), 128.2 (d), 126.3 (d), 52.8 (q), 40.9 (t), 28.9 (t). Both hydrogenolysis of the allyl ester to acid and decarboxylation of the carboxylic group substituted at α-position of the ketones took place to give the α-keto acid 3a in the reaction of 2a. Similarly diallyl oxalcaboxylates 2b-2g were converted to the corresponding α-keto acids 3b-3f. (Table 1, Method A)

When the reaction was carried out without formic acid, decarboxylation-allylation took place to give allyl β-allyl-α-keto carboxylates. Thus, reaction



a) MeI, K_2CO_3 in acetone.
b) Pd-PPh_3 catalyst, HCO_2H, Et_3N in dioxane.
c) Pd-PPh_3 catalyst in THF.

Scheme 2.

of 2a (2.0 g, 6.6 mmol) in the presence of $Pd_2(DBA)_3CHCl_3$ (1 mmol) and PPh_3 (8 mmol) in THF (40 ml) at 65 °C for 3 h gave the allyl β-allyl-α-keto carboxylate 4a in 83% yield. By a similar procedure, 2g was converted to the corresponding allyl β-allyl-α-keto caboxylate 4g. Although it is known that alkylation of α-keto esters is difficult, the present palladium-catalyzed allylation provides a useful method for introduction of allyl group at β-position of α-keto esters. Furthermore, active hydrogens of α-oxalesters can be replaced easily with various electrophiles under weak basic condition. Therefore, synthesis of an α-keto ester having quarternary carbon at β-position is possible by introduction of alkyl group before the palladium-catalyzed allylation (Scheme 2). Methylation of 2a to 2h was carried out using methyl iodide and K_2CO_3 in acetone under reflux in 99% yield. Palladium-catalyzed decarboxylation of 2h with HCO_2H gave β-methylhydrocinnamic acid (3h) in 91% yield. Also, decarboxylation-allylation of 2a to 4h was carried out in 73% yield. The keto ester 4h was converted to the acid 5 with HCO_2H in 91% yield using palladium catalyst. 5 ; ^1H NMR (60 MH_Z, CCl_4) δ 9.12 (1H, s), 6.82-7.40 (5H, m), 4.80-6.04 (3H, m), 1.63-3.90 (4H, m), 1.14 (3H, s); ^{13}C NMR (90 MH_Z, $CDCl_3$) δ 199.7 (s), 162.4 (s), 136.2 (s), 132.6 (d), 130.2 (d), 128.1 (d), 126.7 (d), 119.4 (t), 51.0 (s), 43.4 (t), 41.8 (t), 20.4 (q). As shown above, various β-substituted hydrocinnamic acids or esters (3h, 4a, 4h, and 5) were prepared from 2a, which indicates the usefulness of this reaction.

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5) All keto acids in Table 1 were characterized after conversion to their corresponding methyl or ethyl esters. ^{13}C-NMR spectra of 3b-3f are as follows: Et ester of 3b; δ 194.2 (s), 160.9 (s), 143.8 (s), 128.6 (d), 125.6 (d), 39.4 (t), 28.7 (t). Et ester of 3c; δ 193.8 (s), 161.3 (s), 138.5 (s), 132.0 (d), 130.9 (d) 130.8 (d), 126.6 (d), 118.4 (s), 40.0 (t), 25.8 (t). Et ester of 3d; δ194.2 (s), 161.0 (s), 161.0 (d J_{CF}=245.4 MH_Z), 130.5 (s), 128.1 (d), 124.0 (d), 115.7 (d), 114.8 (d), 38.4 (t), 22.6 (t). Me ester of 3e; δ 166.5 (s), 139.0 (s), 129.8 (s), 128.3 (d), 127.8 (d), 111.1 (d), 53.2 (q). Me ester of 3f; δ 194.1 (s), 161.5 (s), 52.7 (q), 39.3 (t), 29.4 (t), 29.3 (t), 28.9 (t), 23.0 (t).

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