Tetrahedron Letters, Vol.32, No.11, pp 1433-1436, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Efficient synthesis of pseudoionone by oxidative decarboxylation of allyl β-ketoesters

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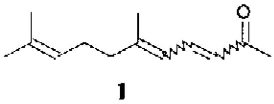
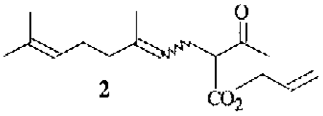
Summary : The palladium catalyzed oxidative decarboxylation of allyl β-ketoesters is used, in mild conditions, to synthesize efficiently pseudoionone from technical grade myrcene.

Recently we have developed a new industrial process for production of pseudoionone **1**, an important intermediate in the synthesis of vitamin A[2], via an oxidative decarboxylation of allyl β-ketoesters[1]. The decarboxylation-dehydrogenation of disubstituted allyl β-ketoesters is catalysed by palladium[3] ; we thought that it could efficiently be applied to the mixture of α-monosubstituted allyl β-ketoesters **2** and **3** to give mainly pseudoionone isomers.



1

Mixture of isomers



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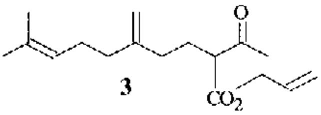
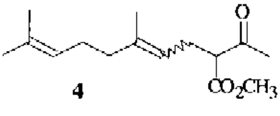


3

E/Z : 70/30 (^{1}H NMR analysis)

Compounds **2** and **3** can be prepared in two steps using technical grade myrcene as starting material[4]. When technical grade myrcene was reacted with methyl acetoacetate in the presence of a water soluble rhodium complex in a biphasic system, [(RhCl(I)(COD)$_2$ / tris (sodium-3-sulfophenyl)phosphine, TPPTS) ; H_2O ; CH_3OH ; Na_2CO_3], a very good selectivity was obtained. Products **4** and **5** were isolated in 97% yield (conversion of myrcene : 98%).



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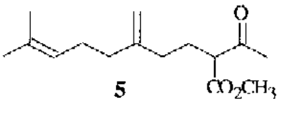
E/Z : 70/30 (^{1}H NMR analysis)



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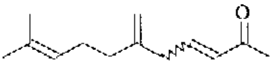
4/5 : 45/55 (GC analysis)

The water-soluble system (Rh(I)/TPPTS) selectively catalyzes many condensations under very mild conditions[5]. The ester interchange of **4** and **5** with allyl alcohol (Na, 5% mol, 90°C/ 6h) gave the allyl β-ketoesters **2** and **3** in 81% isolated yield (conversion of mixture **4** and **5** : 95%). Ratio **2/3** : 45/55 by GC analysis.

The mixture of **2** and **3** was transformed into the pseudoionone isomers **1** and **6** via an oxidative-decarboxylation reaction ; compounds **7** and **8** were also identified[6]. Surprisingly, we did not obtain any α-allyl ketones (**9** and **10**) although other groups have reported the formation of similar products[3]. The results are summarized in the Table.



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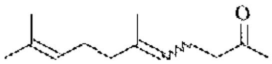

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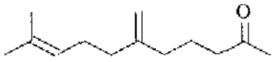
E/Z : 70/30 (^{1}H NMR analysis)



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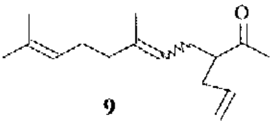

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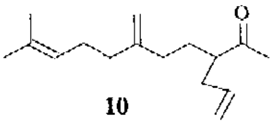

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Good yields and high selectivities were obtained with the use of nitriles and dinitriles as solvent. The reaction occurs at room temperature in dinitriles (entries 5 to 7). In mononitriles, higher temperatures are required. For example, the conversion is not complete after 24h in acetonitrile at room temperature.

A complete isomerisation of the mixture **1** and **6** to the mixture of stereoisomers **1**, necessary before acidic cyclisation to β-ionone[2], was obtained by a standard method[7] (iodine, 1% mol in N-methyl-2-pyrrolidone). The by-products **7** and **8** are valuable in the synthesis of vitamin E [8]. When allyl ester **2** E [9] was reacted with $Pd(OAc)_2$ (1% mol.) in acetonitrile (reflux, 1h30), compounds **1** and **7** E were obtained in 93% yield (conversion of **2** E : 98%). Ratio **1/7** E = 91/ 9 by GC analysis. The formation of **9** was not detected.

We intend to exploit this methodology in the design and synthesis of terpenoids and new classes of organic intermediates[5].

A typical procedure is as follows (entry 7) : under argon, a solution of 2.78g (10 mmol.) of the mixture of **2** and **3**, and 24 mg of $Pd(OAc)_2$ in 1,6-dicyanohexane (10 ml), was stirred 1h at 20°C. Brine was added and the resulting mixture was extracted with pentane. The organic layer was dried over $MgSO_4$; after evaporation a colorless oil was obtained (1.80g), 91% yield (**1** + **6**).

TABLE : Oxidative decarboxylation of the mixture of **2** and **3**.

Entry	Temperature °C	Catalyst % mol.	Time h	Solvent	Conversion % (c) (**2** + **3**)	Yield % (c) (**1** + **6**)	Selectivity % (c) (d) **1** / **6** / **7** + **8** / **9** + **10**
1	90	Pd(OAc)$_2$ 3.4	1	CH_3CN	100	88	46 / 32 / 22 / 0
2	80	" 1	2	"	"	90	48 / 33 / 19 / 0
3	"	"	"	C_6H_5–CN	"	89	48 / 40 / 12 / 0
4	"	Pd(DBA)$_2$ (e) 1	1	"	"	93	52 / 39 / 9 / 0
5	20	Pd(OAc)$_2$ 1	2	(a)	95	92	42 / 45 / 13 / 0
6	80	"	0.5	(b)	98	90	48 / 43 / 9 / 0
7	20	"	1	"	100	91	46 / 44 / 8 / 0

(a) 2-Methylglutaronitrile
(b) 1,6-Dicyanohexane
(c) From GC analysis with internal reference
(d) **7** / **8** = 10/90
(e) DBA : dibenzylideneacetone

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1) C. Mercier and G . Mignani, Rhône-Poulenc, French patent, R 89-08-317, (06.22.89).

2) O. Isler, Carotenoids, (1971), Birkaüser Verlag, Basel, Switzerland.

3) (a) I.Minami, M. Nisar, M. Yuhara, I. Shimizu and J. Tsuji, Synthesis, (1987), 992.

(b) Nippon Zeon, French patent, 2, 526, 420, (04.05.82).

4) A typical crude pyrolyzate contains 75-77 wt % myrcene, 9 wt% limonene, and a few percent of ψ-limonene and minor cracking products ; see reference [8] p. 726.

5) (a) D. Morel, Rhône-Poulenc, European Patent, 44, 771, (07.10.80).

(b) G. Mignani, C. Chevalier, F. Grass, G. Allmang and D. Morel, Tetrahedron Lett., (1990), 31, 5161 and references cited therein.

6) Mixture **2** and **3** : bp 125-127°C / 0.5 mmHg.
Mixture **4** and **5** : bp 217-218°C / 20 mmHg.
Mixture **7** and **8** : bp 155-156°C / 20 mmHg.
All new compounds were characterized by ^{1}H NMR and ^{13}C NMR and well as FTIR, mass spectroscopy and combustion analysis.

7) Y. Fujita , T. Onishi, K. Hino and T. Nishida, Tetrahedron Lett., (1980), 21, 1347.

8) Kirk-Othmer, Encyclopedia of Chemical Technology, 3d Edition, J. Wiley and Sons, (1980), 12, 709.

9) Synthesis of compound **2** E : To a solution of allyl acetoacetate (15.4g, 0.1 mol.) in THF (70 ml) 2.3g of sodium were added . The mixture was stirred 2h at room temperature. 17.5g (0.1 mol.) of geranyl chloride were added and the mixture was refluxed for 16h. Brine (100 ml) was added and the resulting solution was extracted with pentane. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, 26.1 g of an oil were obtained. The crude material was distilled under reduced pressure and 19.5g of **2** E were obtained (bp 128-131°C / 0.4 mmHg). Yield 70%.

Mass spectrum (CI) : (m/e) 278 (M^+), ^{1}H NMR (250 MHz, $CDCl_3$) : δ 2.16 (s, $-CO-CH_3$, 3H), 3.42 (t, J = 7Hz, $-CH-CO-$, 1H), 2.50 (t, J = 7 Hz, $C\underline{H}_2$ CH , 2H), 4.97 (t, J = 7Hz, $C=CH$, 2 x 1H), 5.83 (m, $C\underline{H}=CH_2$, 1H), 5.25 and 5.18 (2d, J = 17 Hz and 11 Hz, $-CH_2-CH=C\underline{H}_2$, 2 x 1H), 4.55 (d, J = 5 Hz, $-O-CH_2-$, 2H), 1.90 – 1.95 (m, $-CH_2-CH_2-$, 2 x 2H), 1.60, 1.55 and 1.52 (3s, CH_3-, 3 x 3H). FTIR (KBr) 1745 1720 cm^{-1} (ν – CO–), 1650 – 1630 cm^{-1} (ν C=C).

(Received in France 6 November 1990)