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FACILE SYNTHESIS OF 3,4-DIHYDRO-4,4-DIMETHYL-2H-PYRAN-2-ONE VIA PALLADIUM CATALYZED TERMINAL OXIDATION OF 3,3-DIMETHYL-4-PENTENOATES

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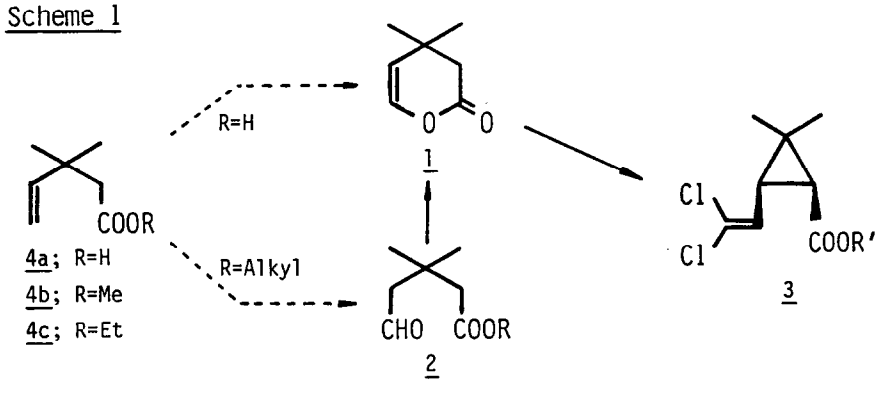
Abstract: Selective terminal oxidation of 3,3-dimethyl-4-pentenoates does occur under chloride-free Wacker conditions [$Pd(OAc)_2/O_2$] in AcOH to give 5-acetoxy-3,3-dimethyl-4-pentenoates (7) and their analogues (2, 8) in good yields. Successive cyclization of 7 and 8 at vapor phase pyrolysis on SiO_2 affords 3,4-dihydro-4,4-dimethyl-2H-pyran-2-one (1).

Among numerous routes[1] for synthetic pyrethroid insecticides such as 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylates (**3**), 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**1**) has been thought to be one of the most hopeful key compounds for the stereoselective synthesis of more active *cis*-isomers. However, lack of a facile path to dihydropyranone **1** has impeded this route. The existing way to **1** from 3,3-dimethyl-4-pentenoates (**4**) consists of a thorny one; *i.e.*, photochemical addition of thiophenol in the presence of BPO, chlorination by N-chlorosuccinimide, and oxidation using excess of copper(II) salts to give 3,3-dimethyl-5-oxopentanoates (**2**), followed by cyclization by phosphorus pentoxide.[1a]

Scheme 1



Here, we would like to report a new and convenient synthetic route to the key intermediate **1** from **4** using palladium catalyzed aerobic oxidation, followed by cyclization catalyzed by solid acid.

Palladium-copper catalyzed oxidation of 1-alkenes (Wacker reaction) is well-known to be a useful method for the synthesis of 2-alkanones.[2] If the selectivity of the reaction were reversed, one can easily expect that 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one could be obtained from 3,3-dimethyl-4-pentenoic acid (**4a**) by oxidative cyclization at the terminal carbon, or terminal oxidation of C-C double bond of esters (**4b** and **4c**) giving the corresponding aldehydes (**2**) or their synthons as shown in Scheme 1. According to this strategy, we examined

palladium-catalyzed oxidation of acid (**4a**) and esters (**4b** and **4c**) under a variety of Wacker conditions reported before.

In the case of acid **4a**, we could not obtain desired six-membered ring lactone nor 3,3-dimethyl-5-oxopentanoic acid (**2a**) under any conditions employed. Instead, five-membered ring lactone[3] or 3,3-dimethyl-4-oxopentanoic acid (**6a**) was formed in moderate yields. For example, when 3,3-dimethyl-4-pentenoic acid (**4a**) was treated under typical Wacker conditions ($PdCl_2$-$CuCl_2$/O_2/DMF-H_2O/r.t.~60 °C), β,β-dimethyl-γ-methylidene-γ-lactone (**5**), was obtained in 56 % yield.

Drastic change of the selectivity accompanied by the conditions employed was observed in the reaction of esters (**4b** or **4c**). Under the conditions, where the chloride ion source is present in the reaction media, such as usual Wacker conditions, Murahashi's conditions,[4] and those employing $CuCl_2$ as oxidant, the corresponding methyl ketone, methyl 3,3-dimethyl-4-oxopentanoate (**6b**), was obtained from **4b**. On the other hands, selective terminal oxidation of **4b** did proceed under the chloride-free conditions. Thus, on using $Pd(OAc)_2$ and $Cu(OAc)_2$ as catalyst in AcOH at 10 atm of oxygen, methyl 5-acetoxy-3,3-dimethyl-4-pentenoate (**7b**),[5] methyl 3,3-dimethyl-5-oxopentanoate (**2b**), and its diacetylacetal (**8**) were obtained in 43, 4, and 7 % yields, respectively, without any formation of internally oxidated products. Though Henry *et al.* have reported that the addition of sodium acetate caused to increase the ratio of terminal acetoxylated product in the oxidation of 3,3-dimethyl-1-butene using benzoquinone as oxidant,[6] no change of the reaction rate and the product yields was observed in our systems as shown in Table. The reaction proceeds even at normal pressure of O_2, though the reaction rate clearly depends on O_2 pressure. To our surprise, esters **4b** and **4c** can be smoothly oxidized even in the absence of $Cu(OAc)_2$ as co-catalyst. This shows that Pd(0) species formed *in situ* can be easily reoxidized to Pd(II) by the action of oxygen molecule. Again, the chloride-free conditions are essential for the present regioselective oxidation. For,

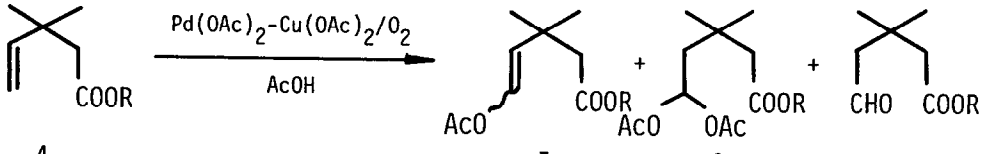


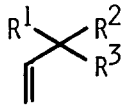
Table Aerobic Oxidation of 4

Run	R	$Pd(OAc)_2$ (mol%)	$Cu(OAc)_2$ (eq)	Additive (eq)	O_2 (atm)	Temp (°C)	Time (hr)	Yield(%)[a] 7	8	2
1	Me	4.5	0.2	-	10	100	8	43	7	4
2	Me	4.5	0.2	NaOAc(1)	10	100	8	44	4	5
3	Me	4.5	0.2	NaOAc(1)	1	100	24	24	3	3
4	Me	4.5	0.2	LiCl(1)	1	100	16	0	10	0
5	Me	4.5	0	-	10	100	4	46	5	3
6	Me	4.5	0	-	30	60	24	42	10	7
7	Me	2.0	0	-	50	80	22	63[b]	-	-
8	Me	0.5	0	-	30	100	24	35	2	4
9	Et	2.0	0	-	30	70	12	44	5	4

a) Yields were determined by GLC. *b*) Isolated yield.

addition of lithium chloride to the above reaction mixture suppressed the reaction, and we can identify only **8** (10%) from the complex mixture of the reaction products. Results are summarized in Table.

Next, we investigated the applicability of the present reaction for similar substrates (**9a-j**). However, only diethylamide **9j** underwent the selective terminal oxidation to afford N,N-diethyl-5-acetoxy-3,3-dimethyl-(*E*)-4-pentenamide in 45 % conversion yield as a single product, and others gave us complex reaction products. These results show us that not only steric effects of substituents at allylic position, but also the sort and location of functional groups play an important role in progress of the present oxidation.



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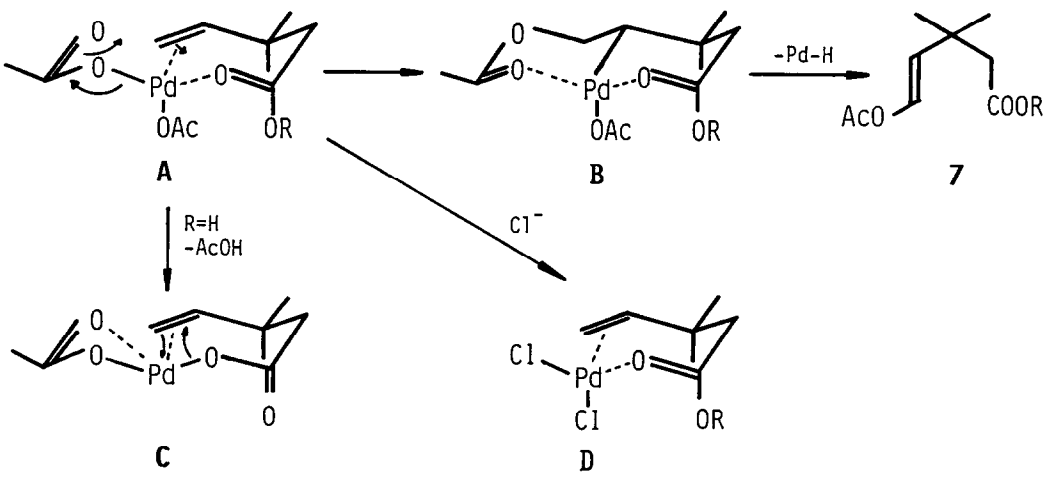
a; $R^1=R^2=H$, $R^3=CH_2COOMe$
b; $R^1=H$, $R^2=Me$, $R^3=CH_2COOEt$
c; $R^1=H$, $R^2=Ph$, $R^3=CH_2COOEt$
d; $R^1=R^2=R^3=Me$
e; $R^1=R^2=Me$, $R^3=CH_2CH_2OH$
f; $R^1=R^2=Me$, $R^3=CH_2CH_2OAc$
g; $R^1=R^2=Me$, $R^3=CH_2CH_2COOMe$
h; $R^1=R^2=Me$, $R^3=CH_2CH_2CN$
i; $R^1=R^2=Me$, $R^3=CH_2CONHMe$
j; $R^1=R^2=Me$, $R^3=CH_2CONEt_2$

We can propose the following Scheme as a plausible mechanism. Pentenoate (**4b** or **c**) occupies two coordination sites of palladium acetate by π-electrons of carbon-carbon double bond and lone pair electrons of carbonyl oxygen (complex **A**), and then acetate on palladium atom migrates to terminal carbon atom of pentenoate (*cis*-attack)[7] to give bicyclic intermediate **B**. The data in Run 1 and 2 show that external *trans*-attack[7] can be slower than *cis*-attack. Successive β-elimination of H-Pd(OAc) from **B** affords the product **7**. While, in the case of acid **4a** (R=H), complex **A** may be turned into complex **C** by elimination of acetic acid, followed by preferable intramolecular cyclization resulting in the formation of 5-membered lactone (5) or its analogues. Further, chloride ion in the reaction media might

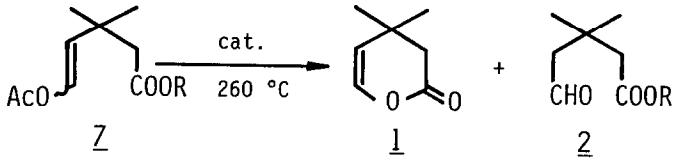
Scheme 2



replace acetate on palladium (complex **D**), and make *cis*-attack of acetate impossible any longer. Steric effects of substituents at allylic position are not clear now, and further mechanistic studies must be required for their clarification.

Typical procedure is as follows. A mixture of $Pd(OAc)_2$ (2 mol%), methyl 3,3-dimethyl-4-pentenoate (**4b**) (50 mmol), and AcOH (150 ml) in a 200 ml stainless steel autoclave was heated at 80 °C for 22 h under O_2 pressure (50 atm) with stirring. After the solvent was removed under reduced pressure, the residue was extracted with Et_2O-10 % $NaHCO_3$ aq. Distillation of ethereal solution under reduced pressure afforded methyl 5-acetoxy-3,3-dimethyl-4-pentenoate (**7b**) in 63 % yield.

Compounds **7** and **8** thus obtained can be easily converted to **2** by acid-catalyzed alcoholysis in excellent yield. Furthermore, vapor phase pyrolysis of compounds **7** and **8** in flow system on solid acid such as silica gel or alumina gives us 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**1**) directly in good yield in addition to aldehyde **2**.



7 1 2

1) R=Me, SiO_2	63%	
2) R=Et, SiO_2	68%	
3) R=Et, Al_2O_3	39%	20%

Mechanistic studies and further application of the present terminal oxidation reaction for organic synthesis are underway.

References and Notes

1) For example, a) USP 4235780 (1980): b) D. Arlt, M. Jautelat, and R. Lautzsch, Angew. Chem. Int. Ed. Engl., 20, 703 (1981): c) T. Aratani, Y. Yoneyoshi, and T. Nagase, Tetrahedron Lett., 23, 685 (1982): d) K. Matsui, A. Negishi, Y. Takahatake, K. Sugimoto, T. Fujimoto, T. Takashima, and K. Kondo, Bull. Chem. Soc. Jpn., 59, 221 (1986).

2) J. Tsuji, Synthesis, 1984, 369.

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4) T. Hosokawa, T. Ohta, and S. Murahashi, J. Chem. Soc. Chem. Commun., 1983, 848.

5) Bp 57 °C/0.04 mmHg. ^{1}H-NMR ($CDCl_3$, TMS) (*E*)-form δ 1.18 (s, 6H), 2.05 (s, 3H), 2.27 (s, 2H), 3.60 (s, 3H), 5.55 (d, J=12 Hz, 1H), 7.07 (d, J=12 Hz, 1H). (*Z*)-form δ 1.26 (s, 6H), 2.13 (s, 3H), 2.46 (s, 2H), 3.63 (s, 3H), 4.80 (d, J=7.5 Hz, 1H), 6.88 (d, J=7.5 Hz, 1H).

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