Tetrahedron Letters No. 39, pp 3741 - 3744. 0040-4039/79/0922-3741$02.00/0

APPLICATION OF PALLADIUM CATALYSES TO A SIMPLE SYNTHESIS OF (±)-PYRETHROLONE

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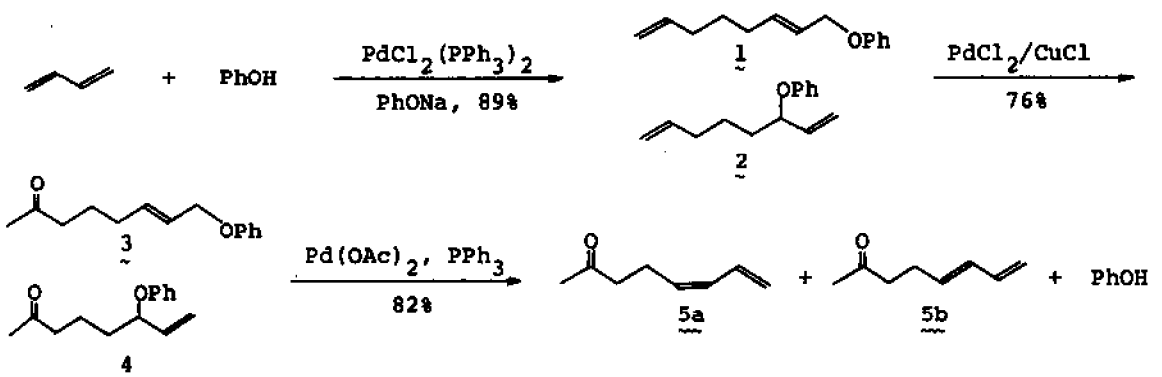
Summary: By sequential application of three palladium catalyzed reactions, namely, palladium catalyzed telomerization of butadiene with phenol, oxidation of terminal olefin of the telomer to methyl ketone, and palladium catalyzed elimination of phenol, an *E* and *Z* mixture of 5,7-octadien-2-one was prepared in a high yield. This compound was converted to an *E* and *Z* mixture of pyrethrolone. The *Z* form of pyrethrolone was separated from the *E* isomer by selective adduct formation of the latter with tetracyanoethylene.

Palladium compounds catalyze a variety of useful organic reactions, which have been successfully applied to efficient syntheses of a number of natural products. For example, we have recently synthesized 12-acetoxy-1,3-dodecadiene, an insect sex pheromone, from a butadiene telomer applying the palladium catalyzed diene formation.[1] We now wish to report a simple synthesis of pyrethrolone by applying three different palladium catalyzed reactions. They are telomerization of butadiene,[2] oxidation of terminal olefins to methyl ketones,[3-5] and conjugated diene formation from allylic ethers.[6] Pyrethrolone (8a) is an alcoholic component of naturally occurring pyrethroids. Syntheses of pyrethrolone and its analogues have been carried out by Crombie and coworkers.[7,8] The key intermediate in their synthesis is [*Z*]-5,7-octadien-2-one (5a). However, a good synthetic method for this important intermediate has not been explored. We have synthesized this dienone in three steps from easily available butadiene using palladium catalysts as shown by the following scheme.

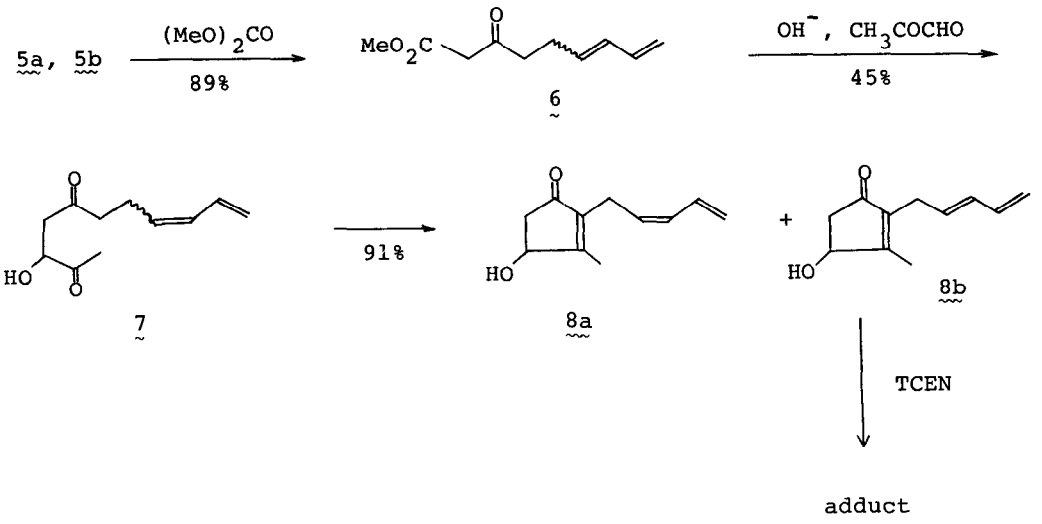


The first step is the palladium catalyzed telomerization of butadiene. Based on Smutny's procedure,[9] reaction of butadiene (33 ml) with phenol (9.4 g, 0.1 mol) was carried out in benzene at 60° in the presence of $PdCl_2(PPh_3)_2$ (350 mg, 0.5 mmol) and sodium phenoxide (300 mg, 2.6 mmol) to give a mixture of 1-phenoxy-2,7-octadiene (1) and 3-phenoxy-1,7-octadiene (2) in a ratio of 7 : 1. (18.0 g, 89%). These isomers (1 and 2) need not be separated, because they give the same diene mixture in the third step.

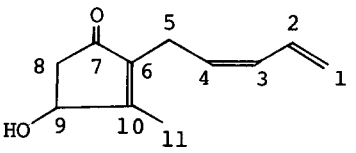
The mixture of telomers 1 and 2, without separation, was subjected to the palladium catalyzed oxidation.[5] A mixture of $PdCl_2$ (709 mg, 4.0 mmol), CuCl (3.96 g, 40 mmol), DMF (40 ml), and water (4 ml) was stirred under oxygen atmosphere for 1 h, and then the telomers (8.08 g, 40 mmol) were added. The mixture was stirred for 8 h at a room temperature. After the usual work-up, a mixture of 1-phenoxy-2-octen-7-one (3) and 3-phenoxy-1-octen-7-one (4) was isolated by distillation. (6.59 g, 76%, bp 120-125°/2.5 Torr). NMR (CCl_4): δ 1.35-1.90 (m, 2H), 2.00 (s, 3H, $COCH_3$), 1.90-2.50 (m, 4H), 4.45 (d, 2H, J = 4 Hz), 5.60-5.85 (m, 2H, olefinic), 6.55-7.65 (m, 5H, aromatic). The other double bond at C_1 of 2 was not oxidized under these conditions.

As the third palladium catalyzed reaction, the ketones 3 and 4 were subjected to elimination reaction of phenol to give terminal dienes 5a and 5b.[6] $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), and triphenylphosphine (262 mg, 1 mmol) were dissolved in dioxane (10 ml). The ketones 3 and 4 (2.18 g, 10 mmol) were added and the mixture was slowly refluxed with stirring for 1 h. After the usual work-up, the crude product was subjected to column chromatography to give 5,7-octadiene-2-one (1.02 g, 82%). NMR (CCl_4): δ 2.10 (s, 3H, $COCH_3$), 2.25-2.70 (m, 4H), 4.80-6.90 (m, 5H, olefinic). The dienone was a mixture of *Z* (5a) and *E* (5b) isomers and their ratio was determined by the following way. The separation of a *Z* isomer from a mixture of *Z* and *E* isomers of terminal dienes of some natural products has been carried out by Nesbitt *et al* utilizing selective adduct forming property of the *E* isomer with tetracyanoethylene (TCEN), leaving the *Z* isomer intact.[10] Thus chromatographic analyses before and after the addition of an excess TCEN to the dienone mixture showed that the dienone is a mixture of the *Z* (5a) and *E* (5b) isomers in a ratio of 31 : 69.[11]

Three step conversion of the dienones 5a and 5b (without separation) to pyrethrolone was carried out by following the Crombie's method[6,7] as shown below. Methyl 3-oxo-6,8-nonadienoate (6) was prepared in 89% yield by the reaction of methyl carbonate and the dienone 5. The keto ester 6, after hydrolysis, was converted to 3-hydroxy-8,10-undecadiene-2,5-dione (7) by the reaction of methylglyoxal in 45% yield. The final step is the base catalyzed aldol condensation to give pyrethrolone (8a, 8b) in 91%. NMR (CCl_4): δ 2.05 (s, 3H, $=CCH_3$), 2.30 (bs, 1H, COCH), 2.55 (d, 1H, J = 6 Hz, COCH-), 2.95 (m, 2H, $=CCH_2$-), 4.30 (bs, 1H, COH), 4.60 (m, 1H, CHO), 4.70-7.25 (m, 5H, olefinic); IR (film): 3400, 1695, and 1950 cm^{-1}; mass spectrum m/e 178 (M^+).



The pyrethrolone thus obtained was a mixture of *E* and *Z* isomers. The separation of the *Z* isomer from the mixture was carried out utilizing selective adduct forming property of the *E* isomer with tetracyanoethylene (TCEN) leaving the *Z* isomer intact.[10] The mixture of 8a and 8b (500 mg, 2.81 mmol) was added to a solution of tetracyanoethylene (384 mg, 3.0 mmol) in THF (4 ml) and the mixture was stirred at a room temperature under nitrogen for 48 h. Evaporation of the solvent, followed by column chromatographic separation of the reaction mixture afforded pure [Z]-pyrethrolone (8a) (148 mg). NMR (CCl_4): δ 2.20 (s, 3H, $=CCH_3$), 2.35-2.80 (m, 5H), 3.05 (m, 2H), 3.30-3.70 (m, 1H), 4.55-4.90 (m, 1H), 5.70-5.95 (m, 2H); IR (film): 3400, 1695, 1650, 910 cm^{-1}. The Z configuration was confirmed by comparison of its ^{13}C NMR spectrum with the reported one as shown in the next table. (ppm from TMS in $CDCl_3$)



	observed (*Z* form)	reported[12] (*Z* form)	observed (*E* form)
1.	118.17	118.1	115.98
2.	131.57	131.6	136.59
3.	130.15	130.2	132.06
4.	127.19	127.1	129.72
5.	21.64	21.6	25.92
6.	139.95		
7.	205.02		
8.	44.25		
9.	71.44		
10.	169.78		
11.	13.79		

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(Received in Japan 18 June 1979)