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NEW DIENE FORMATION BY ENE-TYPE CHLORINATION AND PALLADIUM CATALYZED DEHYDROCHLORINATION: SYNTHESIS OF CITRAL FROM DIPRENYL ETHER

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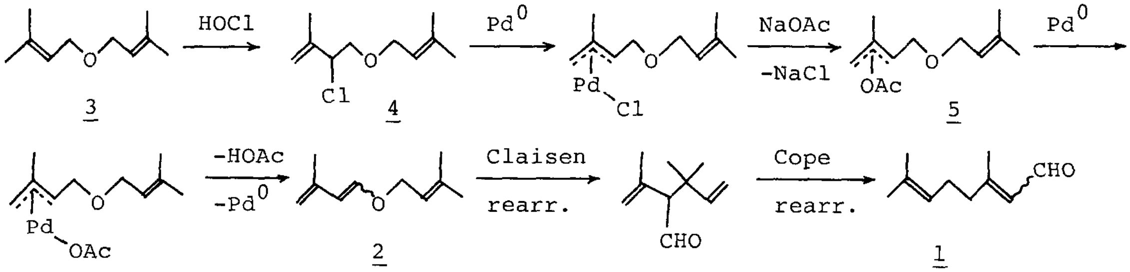
Abstract: Synthesis of citral from diprenyl ether is achieved by new diene forming reaction which consists of ene-type chlorination and palladium catalyzed dehydrochlorination.

Citral (1) which is an important compound in terpenoid industry as a starting material for the synthesis of ionones and vitamin A has been synthesized by a variety of methods.[1] Especially tandem Claisen and Cope rearrangement of 3-methyl-1,3-butadienyl prenyl ether (2) provides a straightforward route to 1,[2] but its synthetic utility is fairly diminished by troublesome handlings for the preparation of 3,3-dimethylacrolein and its diprenyl acetal.

Here we describe a new synthesis of 1 starting from diprenyl ether (3) which is a by-product of methylheptenone synthesis from prenyl chloride and acetone on a scale of several hundred tons per year. The key step of the synthesis is conversion of 3 into 2, and the formation of this diene system is achieved by a combination of ene-type chlorination and novel palladium catalyzed dehydrochlorination (Scheme 1).



Scheme 1 Synthesis of citral from diprenyl ether

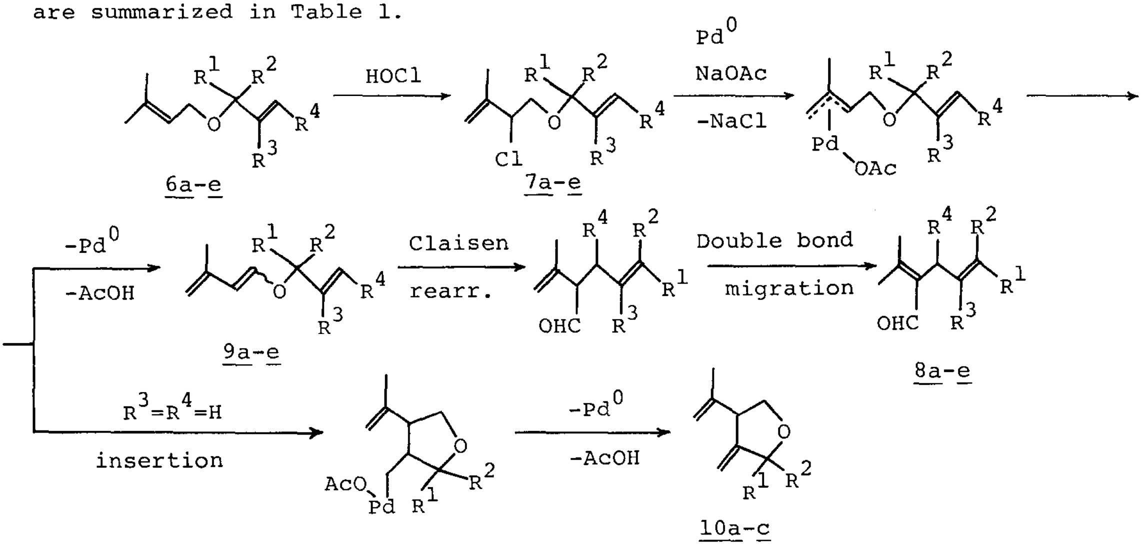
An excess amount of dry ice was added in portions to a mixture of a solution of 3 (23.2 g, 0.15 mol) in CH_2Cl_2 (600 ml) and a suspension of $Ca(OCl)_2$

(active Cl 60%, 17.9 g, 0.075 mol) in water (200 ml).[3] Usual work-up of the reaction mixture provided the chloroether 4 in 65% yield after distillation (b.p. 72-74°C / 1.7 torr).[4]

Attempts for dehydrochlorination of 4 with basic reagents were unsuccessful.[5] Use of $Pd(OAc)_2$-PPh_3, which was reported to eliminate acetic acid from allylic acetates,[6] also resulted in recovery of 4. However, addition of NaOAc caused smooth reaction: Heating of 4 (9.44 g, 50 mmol) with $Pd(OAc)_2$ (0.01 g, 0.05 mmol), PPh_3 (0.50 g, 2.0 mmol) and NaOAc (4.92 g, 60 mmol) at 150°C for 3.5 h under reduced pressure (100 torr) afforded 1 in 66% yield (E:Z = 59:41) after work-up followed by distillation (b.p. 50-52°C / 1.0 torr).

Figure 1 shows a correlation betweem product distribution and reaction time. The three isomeric acetates 5 (pri.-E:pri.-Z:sec. = 39:18:43 after 15 min.) were observed as primary products. These acetates may be formed *via* the π-allylic palladium chloride, since the rate of substitution became much slower in the absence of the palladium complex. Thus the mechanism of this dehydrochlorination is supposed as shown in Scheme 1.

Then, we applied the diene forming reaction to a variety of prenyl ethers 6a-e in order to examine the effect of substituent (Scheme 2). The results are summarized in Table 1.



Scheme 2 Application of the diene forming reaction

Ene-type chlorination occurred selectively at the prenyl group to provide the chloroethers 7a-e.[7] Palladium catalyzed dehydrochlorination of 7a-e gave the α,β-unsaturated aldehydes 8a-e which were formed by Claisen rearrangement of the corresponding dienyl ethers 9a-e followed by double bond migration.[8] Interestingly, the cyclic ethers 10a-c were obtained from the chloroethers 7a-c having vinyl group.[8,9] Presumably these cyclic ethers are formed by intramolecular insertion as shown in Scheme 2.

In conclusion, it is proved that the present diene forming reaction developed in the course of the synthesis of citral is effective for converting prenyl group into 3-methyl-1,3-butadienyl group even in the presence of other less substituted allylic moieties. Application to the synthesis of natural products, coupled with intramolecular Diels-Alder reaction, is now in progress.

References and Notes:

1. G. Saucy, R. Marbet, H. Lindlar, O. Isler, *Helv. Chim. Acta,* 42, 1945 (1959). H. Pauling, D. A. Andrews, N. C. Hindley, *ibid.,* 59, 1233 (1976).
2. USP 4,016,212; 4,073,811; 4,123,464 (Hoffmann La Roche). USP 3,965,193; 4,021,411; 4,058,536 (BASF).
3. S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, J. Wolinsky, *Tetrahedron Lett.,* 21, 441 (1980).
4. 4: NMR ($CDCl_3$, HMS) δ 1.65 (s, 3H); 1.74 (s, 3H); 1.81 (s, 3H); 3.62 (d, J = 6.9 Hz, 2H); 4.00 (d, J = 7.5 Hz, 2H); 4.50 (t, J = 6.9 Hz, 1H); 4.96 (m, 1H); 5.07 (s, 1H); 5.20 (m, 1H) ppm.
   IR (film) 1120, 1080 (C-O); 905 ($C{=}CH_2$); 790 (C-Cl) cm^{-1}.
   MASS m/e (rel. int.) 69 (100), 41 (65), 53 (38), 173 (5, M^+-Me).
5. The results are summarized in the following table.

Reagent	Solvent	Temperature (°C)	Time (h)	Conversion of 4* (%)	Selectivity*(%) 2	1
DBU	DMF	160	1	100	0	0
$CaCO_3$	DMF	160	1	0	-	-
KOH	EtOH	70	2	56	28	0

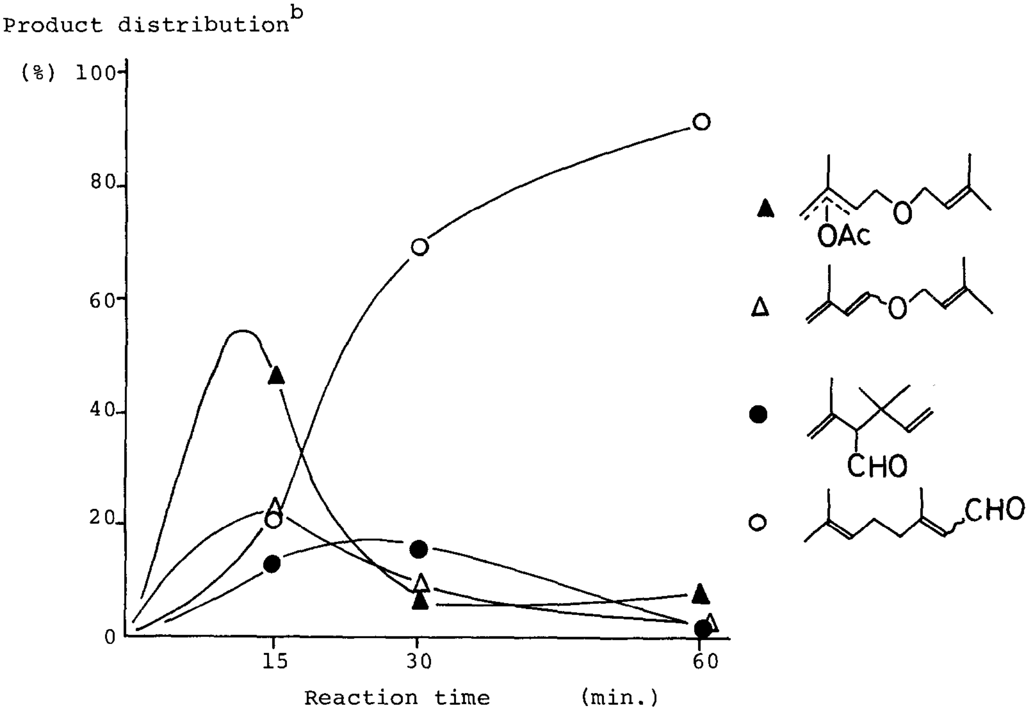
* Determined by GLC analysis.

6. J. Tsuji, T. Yamakawa, M. Kaito, T. Mandai, *Tetrahedron Lett.,* 2075 (1978).
7. The structures were confirmed by NMR and IR spectra.

Chloroether	7a	7b	7c	7d	7e
b.p. (°C/torr)	92-93/20	80-84/19	98-99/19	88-92/20	79-81/18

8. All compounds gave satisfactory NMR, IR and MASS spectra.
9. 10a: ^{1}H-NMR ($CDCl_3$, HMS) δ 1.24 (s, 6H); 1.59 (d, J = 0.9Hz, 3H); 3.29-3.99 (m, 3H); 4.75 (m, 4H) ppm.
   ^{13}C-NMR ($CDCl_3$, TMS) δ 18.5, 27.0, 28.4, 52.6, 68.2, 82.2, 104.6, 113.7, 143.5, 158.0 ppm.
   IR (film) 1050 (C-O), 890 ($C{=}CH_2$) cm^{-1}.
   MASS m/e (rel. int.) 137 (100), 43 (78), 107 (68), 152 (2,M^+).

Figure 1 Correlation between product distribution and reaction time.[a]



[a] The reaction was carried out at 150°C / 100 torr using $Pd(OAc)_2$ (1 mol%) and PPh_3 (4 mol%).

[b] Represented by relative peak areas of the products, which were determined by GLC analysis (2 m column of Polyethylene Glycol 20M, 5% on Chromosorb W, 60-80 mesh).

Table 1 Results of the reactions of the prenyl ethers 6a-e.[a]

Prenyl ether	R^1	R^2	R^3	R^4	Yield (%) of 7	8	10
6a	Me	Me	H	H	71	40	44
6b	Me	H	H	H	74	35	26
6c	H	H	H	Me	71	33	0
6d	H	H	Me	H	65	38	0
6e	H	H	H	H	73	18	19

[a] The palladium catalyzed dehydrochlorinations were conducted at 150°C under slightly reduced pressure (>200 torr) using $Pd(OAc)_2$ (1 mol%) and PPh_3 (4 mol%), and the yields were not optimized.

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