Tetrahedron Vol 39, No 23, pp 3991 to 3994, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00
Pergamon Press Ltd

REACTION OF CIS-CARVEOL WITH TRIPHENYLPHOSPHINE AND TETRACHLOROMETHANE: A NOTE ON THE MECHANISM OF THE LEE REACTION

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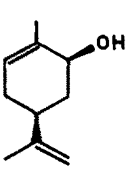
(*Received in the UK 24 February 1983*)

Abstract—The title reaction yielded trans-carvyl chloride **2** and pinol **3**. The formation of pinol and the specific rotation of the carvyl chloride are affected by the presence of acid. The implications of these findings on the understanding of the course of the reaction are discussed. Use of an acid scavenger is recommended in application of the PPh_3–CCl_4 reagent for acid sensitive compounds. A bimolecular, concerted group transfer mechanism (Scheme 2) is suggested for the decomposition of the intermediate alkoxytriphenylphosphonium halide **7**.

Trialkylphosphine-tetrahalomethane (R_3P–CX_4) is a versatile reagent, useful for halogenation of alcohols, dehydration of amides and for synthesis of compounds containing P–N linkage.[1] The reagent is considered to be very mild and essentially neutral and is used for halogenation of several sensitive compounds.[2] The reaction, sometimes referred to as the Lee reaction, is stereospecific, leading to halogenated compounds of opposite configuration to that of the parent alcohol[3] and in allylic systems, it is generally regioselective, substitution occurring essentially on the carbon atom bearing the hydroxyl group.[4]



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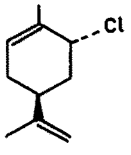

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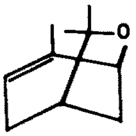

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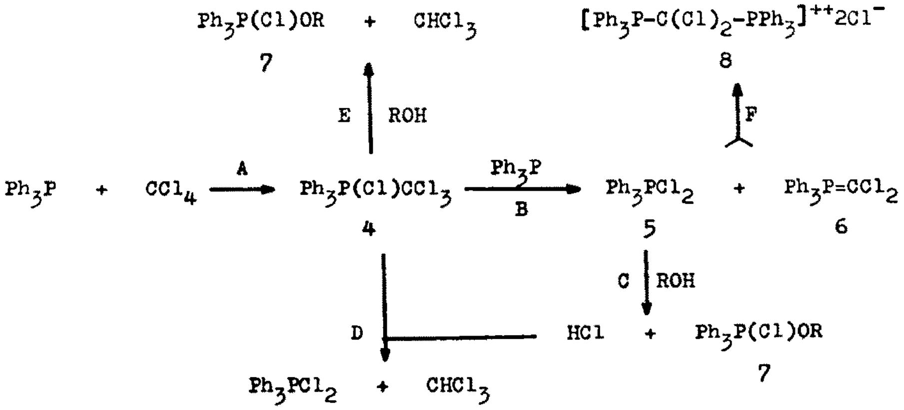
In connection with our work on the stereochemistry of the reaction of zinc salts with alkyl halides,[5] we needed an allylic halide of known stereochemistry and for this purpose, we used the above reaction with interesting results. cis-d-Carveol **1**,[6] was treated with PPh_3 and CCl_4 at 25° (48 hr) yielding trans-d-carvyl chloride (**2**, 45%), $[\alpha]_D + 92°$ (neat). The major product (55%) was identified as (−)-pinol **3**.[7] When the reaction was carried out at reflux, **2** and **3** were formed in the ratio 70:30; the specific rotation of **2** in this case was +170°. The reaction was examined under different conditions by varying the temperature, solvent and ratio of reactants; the results are summarized in Table 1.

Carvyl chloride and pinol are formed in almost equal amounts at 25° in both CCl_4 and CH_3CN (Table 1, entries 1 and 7) and at reflux temperature of the solvent, the ratio is 70:30 (entries 4 and 8). Apparently, **2** and **3** are forming competitively, halogenation being faster at higher temperatures. Steric factors being favorable, pinol obviously is formed by intramolecular addition of the hydroxyl group to the isopropenyl moiety; this reaction must be catalysed by the hydrogen chloride formed in the reaction. The HCl is detectable[8] within 10 min after mixing the reagents and is present throughout the reaction. This and the fact that pinol was formed even when 0.2 equiv of PPh_3 are used (entry 2) should caution against use of this reaction in case of acid-sensitive compounds. The formation of pinol was completely prevented by use of 1 equiv of pyridine which acted as an acid scavenger (entry 5). The stereo- and regio-chemistry of the Lee reaction has been demonstrated[9] to be essentially unaffected by different solvents but the

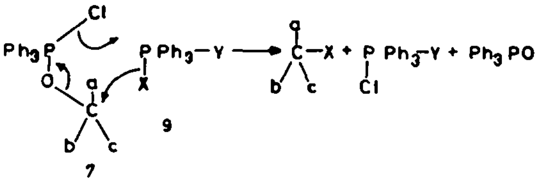


Scheme 1.

Table 1. Results of the reaction of cis-d-carveol with PPh_3 and CCl_4 under different conditions

Entry	Carveol	PPh_3	CCl_4	Pyridine	Solvent	Temp. °C	Time hr	Ratio 2:3	$[\alpha]_D$ of 2
	(-------- molar	equivalents	--------)						
1	1	1.3	10	-	-	25	48	45:55	+ 92°
2	1	0.2	10	-	-	25	incomplete	45:55	-
3	1	1.3	10	-	-	50	16	62:38	+ 114°
4	1	1.3	10	-	-	75	2	70:30	+ 170°
5	1	1.6	10	1	-	75	2	100:0	+ 178°
6	1	2.1	10	1	-	25	140	100:0	+ 225°
7	1	1.6	1.6	-	CH_3CN	25	5	55:45	+ 1°
8	1	1.6	1.6	-	CH_3CN	80	0.25	72:28	+ 14°
9	1	1.6	1.6	1	CH_3CN	25	24	0:0	-
10	1	1.6	1.6	1	CH_3CN	80	8	0:0	-

specific rotation of **2** now obtained in the reaction varied widely depending on the solvent and temperature. An understanding of the stability of asymmetric allylic halides under the conditions of the reaction was essential to draw meaningful conclusions from the results in Table 1. While the product was invariably trans-carvyl chloride[10] thus confirming the stereospecificity of the reaction, the degree of its racemization varied considerably under different conditions (Table 2). The lower specific rotation of the product obtained at lower temperatures (in CCl_4) may now be understood as due to the longer reaction times, necessitating longer exposure to HCl. Similarly, the trans-carvyl chloride formed in CH_3CN is racemic due to its rapid racemization in presence of HCl in this solvent. Understandably the reaction of carveol with PPh_3 and CCl_4 in presence of pyridine and at room temperature gave carvyl chloride with the maximum specific rotation, though it took considerably long period (Table 1, entry 6). The specific rotation of **2** is calculated according to Brewster's rule[11] to be +294°; considering the fact that the starting material is of about 80% stereochemical purity, the observed rotation of the product is in agreement with the structure assigned.



Scheme 2.

Considerable amount of work has been done on the mechanism of the various steps involved in the Lee reaction (Scheme 1).[1] Formation of trichloromethyltriphenylphosphonium chloride **4** in CCl_4 (reaction A) is slow and once formed, it reacts rapidly with excess PPh_3 yielding triphenylphosphine dichloride **5** and dichloromethylenetriphenylphosphorane **6** (reaction B). **5** and **6** can react together (reaction F) leading, ultimately, to inert products. In presence of an alcohol both **4** and **5** could react to give the alkoxytriphenylphosphonium chloride **7** (reaction C and E), but **4** is generally considered to be the "phosphorylating agent". Since our

Table 2. Racemization of (+) trans-carvyl chloride under different conditions

Entry	Solvent	Temp °C	Time hr	Extent of Racemization
1	CCl_4	25	16	0
2	CCl_4	75	2	16
3	CCl_4-Py(5%)	25	16	0
4	CCl_4-Py (5%)	75	2	33
5	CCl_4-HCl (trace)	25	16	20
6	CCl_4-HCl (trace)	75	2	45
7	CH_3CN	25	16	0
8	CH_3CN	80	6	50
9	CH_3CN-HCl (trace)	25	5	86
10	CH_3CN-HCl (trace)	80	0.5	84

results have shown that HCl is present throughout the reaction and since the acid, being more proton-active than the alcohol, could readily decompose a species of the type **4** to give **5** and $CHCl_3$ (reaction D), we suggest that **5** could be the main phosphorylating agent leading to the formation of **7**.

The importance of the route A → B → C → D (Scheme 1) is demonstrated when carveol remained unaffected on treatment with PPh_3 and CCl_4 in CH_3CN–pyridine (Table 1, entries 9 and 10). Interestingly, in the absence of pyridine, the reaction is about 10 times faster in CH_3CN than in CCl_4 (compare entries 1 and 7 and 4 and 8). It is unlikely that reaction E is affected by pyridine. That the reactions A and B are also unaffected by pyridine is proved by the formation of α, α-dichlorotoluene and 2′, 2′-dichlorostyrene on reacting benzaldehyde with PPh_3 and CCl_4[12] in presence of pyridine. The PPh_3Cl_2 formed in reaction B is consumed in reaction of the type F, which appears to be fast in CH_3CN.[13] The excess PPh_3Cl_2 required for reaction C is not formed as reaction D is blocked. The extremely slow reaction of carveol with PPh_3–CCl_4–pyridine at room temperature (Table 1, entry 6) and the requirement of at least 2 equivalents of PPh_3 also show that reaction E is not the main phosphorylating step. It is known[14] that preformed **5** reacts with alcohols to give products similar to those obtained with the PPh_3–CCl_4 reagent.[15]

We now wish to avail this occasion to comment, based mainly on the enormous amount of experimental data already on record, on another aspect of the reaction, namely the mode of decomposition of the intermediate alkoxytriphenylphosphonium chloride **7**. The relevant features of the reaction can be summarized thus:[16,17] (i) the intermediacy of **7** in the reaction is firmly established; (ii) the formation of **7** is 60 times faster in CH_3CN than in CCl_4; (iii) the intermediate decomposition occurs with predominant inversion ofconfiguration and in allylic systems, the substitution is essentially on the α-carbon atom; (iv) the decomposition of **7** is slower in hindered alcohols; (v) the decomposition is first order in CCl_4 and second order in CH_3CN; (vi) when the reaction was carried out in CH_3CN in presence of thiocyanate ion, a mixture of alkyl halide and alkyl thiocyanate was formed; and (vii) the isotope effect k_H/k_D for the reaction is 1.05. Points iv, v and vii are held against the unimolecular, thermal pericyclic, four-centre ($\sigma 2s + \sigma 2a$) decomposition of **7**, suggested by Aneja *et al.*[18] Very recently, Slagle *et al.*[17] suggested an ion pair cluster intermediate which, again, cannot satisfactorily account for the points v and vii. Also, the ion pair mechanism fails to explain the regioselectivity in allylic systems even in dipolar solvents.[9] We have recently suggested ion quadruplets, akin to ion pair clusters, as intermediates in nucleophilic substitution of tertiary alkyl halides by moderately electrophilic metal salts.[5] We have also demonstrated that no regio- or stereo- selectivity exists in the substitution at allylic center under the conditions most suitable for formation of ion quadruplets (i.e. in solvents of low dielectric constant and at low temperatures). Thus, (+)-trans-carvyl chloride, obtained above, gave a racemic mixture of cis- and trans-carvyl acetates (1:3) when treated with zinc acetate in acetic acid[5] or in chloroform and pyridine.[19] at room temperature.

To explain the various features of the Lee reaction, we now propose a bimolecular, symmetry allowed, six-center ($\sigma 2s + \sigma 2a + \sigma 2a$) group transfer mechanism as depicted in Scheme 2. The inversion at C_α,[3] steric suppression of the speed of the reaction[16] and regioselectivity in allylic systems[9] are now readily comprehensible. Added anions may exchange with the halogen prior to the group transfer reaction yielding mixtures of products, as has been observed in CH_3CN.[17] The difference in kinetics of the reaction in different solvents[17] can be explained by noting that the decomposition kinetics were measured with respect to the concentration of the alkoxytriphenylphosphonium chloride **7**. In CCl_4, the formation of **7** itself is slow and this reacts with excess PPh_3Cl_2 (**9**, X = Y = Cl). In CH_3CN, on the other hand, formation of **7** is so fast[17] that PPh_3Cl_2 is consumed and now **9** (Y = OR) in Scheme 2 is another molecule of **7**, thus showing second order kinetics. The concerted mechanism now proposed is also consistent with the small isotope effect observed earlier for the reaction,[16] which indicates a nearly balanced bond-breaking and bond-making process.

EXPERIMENTAL

B.ps are uncorrected. Optical rotations are obtained using a Perkin–Elmer 243 polarimeter at 589 nm. ^1H NMR spectra were recorded in CCl_4 on a Varian 390 (90 MHz) instrument using TMS as internal standard. GLC was carried out using a column (3 mm ID × 2 m) packed with 10% Carbowax 20 M on Chromosorb W; temp. 120–8–200°; carrier gas, N_2; 30 ml/min; detector, TCD.

cis-d-Carveol. Carvone ($[\alpha]_D + 55°$, 10 g) in anhydrous ether was treated with $LiAlH_4$ according to the procedure described by Garver *et al.*[6] yielding cis-d-carveol **1**, (8 g) $[\alpha]_D + 30°$ (neat).

Reaction of carveol with PPh_3 and CCl_4: cis-d-Carveol (**1**; 10 mmol) in CCl_4 (10 ml) was treated with PPh_3 (13 mmol). The reaction mixture was stirred until TLC showed complete disappearance of carveol. The mixture was treated with hexane (20 ml), filtered and the solvent was evaporated. The product was then distilled under reduced pressure using a Vigreux column yielding two fractions. The first fraction was a colorless liquid with a camphoraceous odour, b.p. 35°/1.5 mm; ^1H NMR (CCl_4): δ 1.13 (3H, s), 1.26 (3H, s) , 1.67 (3H, br), 2.20 (5H, br), 3.90 (1H, m) and 5.17 (1H, m) $[\alpha]_D - 79°$ (neat); identified as pinol (**3**)[6]. Carvyl chloride (**2**) was obtained as the second fraction, b.p. 67–69°/1.5 mm, ^1H NMR (CCl_4): δ 1.83 (3H, s), 1.80 (3H, s), 4.40 (1H, d, J = 3 Hz), 4.77 (2H, s) and 5.67 (1H, br). The specific rotation of **2** and the relative proportions of **2** and **3** (as determined by GC) formed under different conditions are given in Table 1.

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[7] Pinol, considered to be a useful, chiral NMR solvent, was earlier prepared by intramolecular oxymercuration of cis-carveol followed by reduction (see ref 6).

[8] The HCl was detected by withdrawing 1 ml of the vapor above the reaction mixture and dissolving it in distilled water; this solution had acidic pH and gave a white precipitate with $AgNO_3$–HNO_3 solution.

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[10] Cis- and trans-carvyl chlorides are distinguishable by their ^1H NMR spectra. The cis isomer showed an olefinic methyl signal

at δ 1.77 and the allylic $\underline{\text{CH}}$Cl as a very broad signal at δ 4.50; other signals are as for trans-carvyl chloride (see Experimental).

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[13] That reaction F is competitive in CH_3CN medium even in the absence of pyridine is indicated by the requirement of at least 1.6 equivalents of PPh_3 for completion of the reaction (Table 1).

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[15] In fact, cis-d-carveol, when stirred at room temperature with PPh_3Cl_2 in CCl_4-pyridine (36 hr) gave trans-d-carvyl chloride, $[\alpha]_D + 176°$ in 85% yield. A major hurdle in industrial application of the very versatile laboratory reagent, PPh_3-CCl_4, is that there is no economical method for regeneration of spent PPh_3. Since the recovered PPh_3PO can be easily converted to PPh_3Cl_2 by phosgene, the present inference regarding the active species, namely PPh_3Cl_2, should help general application of this well studied reaction in both laboratory and industry (see ref. 1b, p 423).

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