

Isomerization Studies. 4. Isomerization of Acyl Halides in the Presence of Palladium Catalysts

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The direct catalytic isomerization of acyl halides to their α -branched isomeric counterparts has been studied. For example, when nonanoyl chloride is heated at 150 °C in the presence of PdBr₂ catalyst, a mixture of 2-methyloctyl, 2-ethylheptyl, and 2-propylhexyl acyl chlorides is obtained. Reaction parameters are very critical in determining the nature and type of products obtained from this isomerization process. At reaction temperatures up to 220 °C, other products obtained from the reaction in varying amounts are either a monoene or alkyl halide having one less carbon atom than the starting acyl halide. The addition of a phosphine ligand to the catalyst system or the introduction of unsaturation in the acyl halide results in a suppression of the isomerization reaction.

The decarbonylation of acid halides and aldehydes with transition metal catalysts has been demonstrated to be a synthetically useful reaction.² When acid chlorides with no β -hydrogen atoms are decarbonylated, alkyl chlorides are the major products, whereas when acid chlorides containing a β -hydrogen atom are decarbonylated, olefins are the primary products.^{2,3} Higher aliphatic acyl chlorides and bromides are decarbonylated in high yields when they are heated above 200 °C in the presence of a catalytic amount of selected palladium catalysts.^{4,5} On the other hand, the carbonylation of olefins to acids or esters has been accomplished with these same palladium catalysts when the reactions are performed in the presence of hydrogen halides. Accordingly, the mechanism of both the carbonylation and decarbonylation reactions with palladium catalysts have been postulated to proceed via the same pathway.⁴ In view of the foregoing, it seemed plausible that under the proper reaction conditions a palladium catalyst might effect the decarbonylation-carbonylation of acid chlorides in one step. One result of such a reaction, which may have synthetic utility, would be the conversion of a normal chain acid chloride into an isomeric α -branched chain counterpart or vice versa. It is the purpose of this report to describe the development of a catalyst system which does achieve such a skeletal isomerization.

As previously noted,^{4,5} acyl halides containing an available β -hydrogen atom, when heated in the presence of selected transition metal catalysts, readily undergo decarbonylation-dehydrohalogenation to a monoene, having one less carbon atom than the starting acyl chloride. Carbon monoxide and hydrogen chloride are also produced. For example, heating palmitoyl chloride at 220 °C in an open flask in the presence of palladium acetylacetonate (expt 1, Table I) resulted in the quantitative formation of pentadecene. As reported for stearoyl chloride,⁵ the olefin formed had its double bond randomly distributed within the internal positions of the hydrocarbon chain with no indication of branching of the hydrocarbon backbone. In contrast to the above, when the decarbonylation of palmitoyl chloride was carried out in a sealed reactor under similar reaction conditions (Table I) decarbonylation was incomplete, and the product mixture was more complex. Treatment of the latter mixture with methanol gave the expected pentadecene and residual methyl palmitate and two additional groups of products. One group was identified as being a mixture of secondary C₁₅ alkyl chlorides, whereas the other was identified as a mixture of isomeric α -branched C₁₆ methyl esters. Alkyl chloride formation is probably the result of the addition of hydrogen chloride to the first formed product, pentadecene, since with an increase in reaction time the amounts of both alkyl chloride and alkene increased (expt 2 and 3, Table I). On the other hand, lowering the reaction temperature to 150 °C resulted in an increased yield of isomeric C₁₆ acid chlorides and eliminated alkyl

chloride formation (expt 4, Table I). A similar result was obtained when the identical reaction was carried out in an open flask at 150 °C, rather than a sealed reactor (expt 5, Table I). Therefore, we concluded that the formation of α -branched acid chlorides from normal chain isomers was a result of a skeletal isomerization process and not a carbonylation reaction and that a sealed system was not required to achieve such a transformation.

In view of the above, a more extensive examination of this isomerization reaction as regards to catalyst composition, acid chloride structure, and reaction temperature and time was undertaken. The objective of this phase of the study was to determine the optimum conditions for the isomerization of normal chain acid chlorides into their isomeric α -branched chain counterparts and at the same time to avoid formation of decarbonylation products.

Catalyst composition was studied first. Changing the palladium catalyst ligand from acetylacetonate to chloride ion and heating at 150 °C for 5 h resulted in an undesirable increase in yield of pentadecene from palmitoyl chloride; compare expt 5 to 6, Table I. This result was in agreement with previous data which showed that palladium chloride is a very efficient decarbonylation catalyst.⁴ In contrast, palladium bromide catalyst gave less alkene formation and more isomerized acyl halide (expt 7, Table I). Even better yields of isomerized acid halides were obtained with the palladium bromide catalyst when the reaction was carried out at 130 °C (expt 8, Table I) instead of 150 °C.

Heating pelargonyl chloride with palladium bromide at 150 °C resulted in extensive decarbonylation (>60%) to C₈ alkene, whereas at 130 °C alkene formation was negligible compared to acid chloride isomerization (expt 9, Table I). Prolonging the reaction time to 18 h increased the amount of α -branched acid chlorides but also increased the amount of alkene formed (expt 10, Table I). The lower ratio of α isomers to normal isomer obtained with pelargonyl chloride compared to palmitoyl chloride is attributed to the larger number of isomers possible for the latter acid chloride. It is also apparent from the data in Table I that the α -branched acid chlorides undergo decarbonylation on prolonged heating.

Evidence that the isomerization process is a reversible process was obtained by heating α -methyloctanoyl chloride under the same reaction conditions used for the isomerization of pelargonyl chloride. The ratio of branched-chain isomers to straight-chain product was of the same order of magnitude when starting with either acyl halide; compare expt 10 and 11, Table I. The branched acid chloride, however, gave rise to more octene formation.

Introduction of a phosphine ligand into the palladium salts, e.g., bis(triphenylphosphine)palladium chloride [(C₆H₅)₃P]₂PdCl₂, completely suppressed the isomerization and decarbonylation reactions of palmitoyl chloride at both 130 and

Table I. Isomerization of Acid Chlorides with Pd Salts^a

Expt	Acyl halide	Registry no.	PdX ₂	Registry no.	Temp, °C	Time, h	% C _n H _{2n}	% RCl	% n-RCOCl ^{c,d}	% α-RCOCl ^{c,d}
1	CH ₃ (CH ₂) ₄ COCl	112-67-4	acac ^b	14024-61-4	220	1	100	6	47	27
2	CH ₃ (CH ₂) ₄ COCl	112-67-4	acac ^b	14024-61-4	220 ^e	2	20	18	15	15
3	CH ₃ (CH ₂) ₄ COCl	112-67-4	acac ^b	14024-61-4	220 ^e	5	52		44	43
4	CH ₃ (CH ₂) ₄ COCl	112-67-4	acac ^b	14024-61-4	150 ^e	5	13		39	47
5	CH ₃ (CH ₂) ₄ COCl	112-67-4	acac ^b	14024-61-4	150	5	14		9	28
6	CH ₃ (CH ₂) ₄ COCl	112-67-4	Cl	7647-10-1	150	5	63		13	55
7	CH ₃ (CH ₂) ₄ COCl	112-67-4	Br	13444-94-5	150	5	32		12	60
8	CH ₃ (CH ₂) ₄ COCl	112-67-4	Br	13444-94-5	130	5	28		55	58
9	CH ₃ (CH ₂) ₇ COCl	764-85-2	Br	13444-94-5	130	5	2		32	54
10	CH ₃ (CH ₂) ₇ COCl	764-85-2	Br	13444-94-5	130	18	10		25	54
11	CH ₃ (CH ₂) ₇ C(CH ₃)HCOCl	43152-88-1	Br	13444-94-5	130	18	21		92	81
12	CH ₂ =CH(CH ₂) ₆ COCl	27236-80-2	Br	13444-94-5	110 ^f	18	8g		81	4
13	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ COCl	112-77-6	Br	13444-94-5	150	5	15g			

^a Mole ratio of acid chloride to palladium catalyst of 100:1. ^b acac = acetylacetonate. ^c n-R normal isomer; α-R = α-branched isomers. ^d Determined as methyl ester. ^e Reaction run in sealed reactor. ^f At 150 °C for 18 h formed >90% alkene. ^g Diene formation C_nH_{2n-2}.

Table II. Product Distribution of Isomerized Acyl Chlorides^{a,b}

Starting n-RCOCl	% α-CH ₃	% α-C ₂ H ₅	% α-C ₃ H ₇	% normal
CH ₃ (CH ₂) ₇ COCl	29	17	15	39
CH ₃ (CH ₂) ₅ CHCOCl	35	23	20	22
CH ₃ (CH ₂) ₁₄ COCl	14	8	33 ^c	45

^a Determined by GLC of methyl esters. ^b Mole ratio of acid chloride to PdBr₂, 100:1 reaction run for 5 h at 130 °C. ^c Composition includes α-C₄H₉, α-C₅H₁₁, and α-C₆H₁₃ isomers.

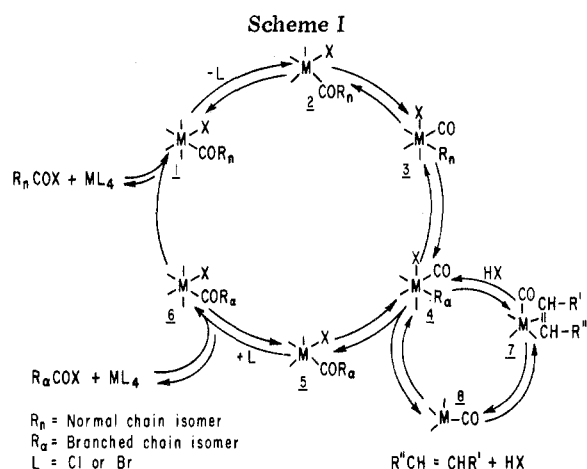
150 °C, whereas at higher temperatures decarbonylation to alkene occurred. This deleterious effect of phosphines on the isomerization of acid chlorides was further demonstrated by admixture of triphenylphosphine to the palladium bromide catalyst. This completely inhibited the isomerization of palmitoyl chloride at 150 °C, yielding only the starting acyl chloride. Substitution of a rhodium metal catalyst (RhCl₃) for the palladium catalyst did not produce any isomerization reaction, and the starting acyl chloride was recovered. This result is to be contrasted with the extensive use of the former transition metal as a decarbonylation catalyst at elevated temperatures.⁶

As observed with triphenylphosphine, the presence of an olefinic linkage in the acid chloride molecule also suppressed the isomerization reaction. For example, with the terminal alkene 11-undecenoyl chloride, no α isomers are observed and for the internally unsaturated acid chloride oleoyl chloride, only 4% α isomers are produced (expt 12 and 13, Table I). Attempts to increase the yields of α-branched acid chlorides for the latter two examples by raising reaction temperature or increasing reaction times resulted only in the increased formation of dienes.⁷ That the double bond must be contained within the acid chloride molecule in order to effectively inhibit the isomerization reaction was demonstrated by heating pelargonoyl chloride with PdBr₂ in the presence of either added octene-1 or octadiene. The results were similar to those obtained when no added unsaturates were present.

Insight as to the isomeric composition of the acid chlorides produced during the course of the isomerization process was obtained by the combined use of GLC and mass spectrometry. For the C₉ acid chlorides, GLC of the esterified reaction products indicated the presence of three α-branched methyl esters in addition to methyl pelargonate. The percentage distribution of this mixture of isomeric C₉ methyl esters is given in Table II. Identification of individual isomers was made from an examination of their mass spectra, more specifically by comparison of their McLafferty rearrangement ions.⁸ For example, in the spectrum of methyl α-methyl octanoate this rearrangement ion is found at *m/e* 88 (base peak), thus confirming that the methyl substituent is α to the carbomethoxy function. Similarly, the α-ethyl heptanoate and α-propyl hexanoate isomers were identified by the appearance of McLafferty rearrangement ions at *m/e* of 102, 144 and 116, 130, respectively. Analysis of the palmitoyl chloride isomerization product was conducted in the same manner (Table II). A major difference in this example, however, was the formation of a larger number of α-branched isomers. Although GLC indicated that only three isomers were formed, mass spectrometry established that the α-propyl, α-butyl, α-pentyl, and α-hexyl isomers had eluted together. Thus it appears that during the isomerization reaction all possible dialkylacetic acid isomers are formed; however, the data in Table II do suggest that branching at the 2 and 3 positions of the chain is preferred. Comparing the isomer distribution obtained for pelargonoyl chloride with that of α-methyloctanoyl chloride

does not seem to indicate that the isomerization reaction is an equilibrium controlled distribution, since the isomer ratios obtained for the two starting acid chlorides are different but reproducible. During the course of the isomerization reaction, any one of the isomeric acid chlorides may undergo decarbonylation to alkene and, therefore, prevent the establishment of a true equilibrium. The major difference observed is that when starting with the branched acid chloride a larger amount of the α -ethyl and α -propyl isomers are formed.

A mechanistic rationale which readily accounts for the observed skeletal isomerization of saturated acid chlorides is shown in Scheme I. In formulating this reaction pathway the



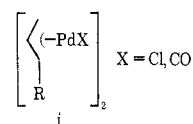
following two assumptions were made: (a) the mechanism of decarbonylation is the reverse of carbonylation,³ and (b) the organometallic reactions shown proceed by the 16 and 18 electron rule as proposed by Tolman.⁹ The initial step of this mechanism requires the oxidative addition of the acyl chloride to the four-coordinate palladium bromide catalyst to give the six-coordinate acyl-palladium complex 1. The latter intermediate then undergoes loss of ligand to the five-coordinate species 2 which then rearranges to the six-coordinate alkyl-palladium complex 3. The σ -bonded carbon-metal complex 3 can then readily undergo rearrangement via a hydride transfer mechanism¹⁰ to the internally σ -bonded carbon-metal complex 4. This step could also provide a pathway for alkene formation. The next step in this cycle is the reverse of decarbonylation, namely carbonylation to the five-coordinate complex 5 which can add a ligand to give the six-coordinate acyl-palladium complex 6 which is analogous to complex 1. Reductive elimination of the α -branched acyl halide from complex 6 then regenerates the palladium catalyst for recycle. Since both normal and α -branched chain acid chlorides can be isomerized, all of the steps in this catalytic cycle must be reversible.

Included in Scheme I is a mechanism which accounts for the formation of alkene from either σ -bonded carbon-metal complexes 3 or 4. As shown with complex 4, reductive elimination of the elements of hydrogen halide leads to formation of the π -bonded alkene-palladium complex 7 which on dissociation produces the alkene and the four-coordinate palladium complex 8 which can reenter into the catalytic cycle. This latter cycle is the reverse mechanism of the carbonylation of alkenes. Accordingly, it may serve as an alternative pathway for the isomerization of acid chlorides.

The inhibition of acid chloride isomerization by phosphines can be attributed to the greater stability of transition metal complexes which contain a phosphine ligand. Whereas phosphine-metal complexes readily undergo oxidative addition with acyl chlorides to acyl metal complexes analogous to 3 (Scheme I), the latter complexes are apparently stabilized by the phosphine ligand and cannot rearrange to the branched

acyl chloride. While no such acyl-palladium complexes have been isolated, the analogous acylrhodium complexes have.¹¹

The reluctance of unsaturated acid chlorides to undergo acyl migration in the presence of palladium salts cannot be ascribed solely to the presence of the π bond contained within the molecule, since as noted previously, the addition of alkenes or dienes did not inhibit the isomerization of saturated acid chlorides. Since unsaturated acid chlorides can be decarbonylated to dienes,⁷ oxidative addition of the unsaturated acid chloride to the metal complex must occur to give an intermediate σ complex analogous to 3 (Scheme I). The latter σ -bonded intermediate probably then rearranges rapidly via a hydride transfer mechanism to a more stable π -allylic intermediate comparable to i. It has been reported that π -allylic palladium complexes such as i undergo preferential carbonylation at C₁.¹² Such a pathway in the present study would lead to the re-formation of the normal chain acid chloride. Alternatively, it has been shown that π -allylic complexes analogous to i generally coordinate carbon monoxide weakly¹³ and therefore would favor decarbonylation rather than acyl migration of the unsaturated acid chloride as is observed.



Experimental Section

Material and Equipment. Palmitoyl chloride (bp 138 °C, 0.5 mm), pelargonyl chloride (bp 58 °C, 0.4 mm), α -methyloctanoyl chloride (bp 53 °C, 0.2 mm), 11-undecenoyl chloride (bp 80 °C, 0.4 mm), and oleoyl chloride (bp 153 °C, 0.45 mm) were prepared by reaction of the free carboxylic acids with oxaloyl chloride employing the procedure of Bosshard et al.¹⁴ PdCl₂ and PdBr₂ were obtained from Engelhard Industries, Inc., Carteret, N.J.,¹⁵ and were used as received. Palladium acetylacetonate [Pd(AcAc)₂] was prepared by literature procedure.¹⁶ Infrared spectra (ir) were obtained on a Perkin-Elmer Model 237 spectrometer using sodium chloride disks. Mass spectra were obtained on a Du Pont 21-492 double focusing instrument operating at an ionization potential of 70 eV. The gas chromatograph was a Hewlett-Packard Model 7620A instrument equipped with dual flame and thermal conductivity detectors. Separations were obtained on stainless steel columns (0.125 in. \times 10 ft) containing 10% DEGS on Gas-Chrom S. Integration of peak areas was carried out with an Infotronics Model CRS-11HSB digital integrator.

Isomerization Procedures. A. Open System. Into a 25-ml round-bottom flask equipped with a magnetic stirring bar, condenser, and N₂ gas inlet tube was placed the pelargonyl chloride (3.0 g, 17 mmol) and catalyst PdBr₂ (45.7 mg, 0.17 mmol). The stirred mixture was then heated in a constant temperature bath at a given temperature for a specified time period (Table I). The reaction mixture was cooled to ambient temperature, and methanol (10 ml) was added. The mixture was heated to reflux for 0.5 h to ensure complete esterification. The ester mixture was transferred to a separatory funnel, diluted with water, and extracted with hexane. The combined hexane extracts were washed with H₂O until neutral, dried over MgSO₄, and the hexane solvent removed in vacuo to give the crude methyl ester (2.92 g). The ester mixture was then analyzed for product distribution and isomer distribution by GLC and mass spectrometry (Tables I and II).

B. Sealed System. Into a 125-ml Hastelloy-C autoclave was placed the acid chloride and metal catalyst (mole ratio of 100:1). The reactor was purged with N₂ gas, sealed, and heated by means of an electric furnace to the specified internal temperature as determined by means of a thermocouple inserted into the outside wall of the reactor. After the specified reaction time period, the autoclave was cooled to ambient temperature, vented, and the liquid contents transferred to a flask. The crude reaction mixture was esterified and analyzed in the same manner as the product from the open flask procedure.

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Monoterpene Syntheses via a Palladium Catalyzed Isoprene Dimerization

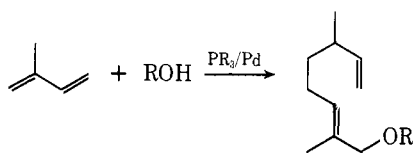
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Isoprene has been reductively dimerized with formic acid and triethylamine at room temperature using 1% palladium-organophosphine catalysts, to head-to-tail dimers in up to 79% yields. The two head-to-tail dimers obtained are easily separated in high yield from the other dimers present by conversion into 7-chloro-3,7-dimethyl-1-octene with aqueous hydrochloric acid at room temperature. This chloro derivative is a convenient and practical starting material for the preparation of various terpene products. Hydroboration and pyrolysis, for example, produced a 1:3 mixture of α - and β -citronellol. *tert*-Butyl peracetate, hydrolysis, and pyrolysis gave linalool. 2,3-Dimethyl-1,3-butadiene and *cis*- and *trans*-1,3-pentadiene were also dimerized by these catalysts. Possible reaction mechanisms for the dimerization are discussed.

Several reports of transition metal catalyzed dimerizations of isoprene have appeared but yields of the dimer with the desired "head to tail" structure have generally been low and/or conversion of the dimer into useful terpene derivatives required several steps. For example, Uchida et al.¹ have reported a tetraallylzirconium-ethylaluminum sesquichloride catalyzed dimerization to 2,6-dimethyl-1,3,6-octatriene in 50% yield. The conversion of this isomer into useful terpenes probably would require several steps. Similarly, Takahashi et al.² have reported a dimerization catalyzed by dibromobis(diphenylphosphinoethane)palladium(II) and sodium phenoxide which produced the more desirable isomer, 2,6-dimethyl-1,3,7-octatriene, but only in 49% yield. Perhaps the most successful dimerizations were achieved in alcohol solution with triorganophosphine-palladium catalysts where ca.



75% yields of 8-alkoxy-3,7-dimethyl-1,6-octadienes were obtained.^{3,4} More recently, the 8-ethoxy-3,7-dimethyl-1,6-octadiene has been converted into citronellol in three steps in 43% yield.⁵ Promising dimerizations employing main group organometallics have also been reported recently.^{6,7}

The isomeric dimers produced by palladium catalysis are clearly very dependent upon the ligands, solvent, and reaction conditions employed. Note, for example, that Josey⁸ reports that in acetone solution with maleic anhydride-bis(triphenylphosphine)palladium(0) as catalyst at 105 °C isoprene gave mainly 2,7-dimethyl-1,3,7-octatriene as a product. The problem of the head to tail dimerization of isoprene with palladium catalysts seemed attractive to us because it appeared that with the proper choice of reaction conditions and ligands a practical monoterpene synthesis might be achievable.

Several of the reported palladium catalyzed dimerizations

were investigated initially and eventually it was decided to concentrate on the triorganophosphine palladium salt dimerization carried out in the presence of formic acid and triethylamine which had previously been tried only with butadiene.^{9,10} This reaction produced dimer dienes and carbon dioxide rather than trienes or formate esters. Preliminary experiments with isoprene indicated that good yields of head to tail dimers could be obtained under some conditions. After considerable effort, catalysts were developed which produce desirable dimers in better than 75% yields based upon the isoprene used. Experiments have determined that these dimers may be easily separated and converted into known, natural monoterpenes.

Results and Discussion

Several variables occur in the reductive diene dimerization reaction. These were investigated empirically and the results were combined in various ways to produce the most favorable yields of the desired head to tail isoprene dimers. Representative experiments of the large number carried out are shown in Table I. Very small amounts of dimers (and reduced dimers) other than those listed in Table I were observed in some experiments but these were not identified with certainty. Spectral data for the isoprene dimers and other products prepared in this investigation are listed in Table II, which will appear only in the microfilm edition of this journal. (See paragraph at end of paper regarding supplementary material.) The investigation began with the use of dichlorobis(triarylphosphine)palladium(II) complexes as catalysts. The first five entries in Table I show clear trends with changes in the para substituents in the arylphosphine ligands. The total yields of dimers decrease as the electron-donating capacity of the para substituent increases. The *p*-CF₃ complex gives 91% while the *p*-OCH₃ derivative produced only 27% dimer; the remainder of the isoprene is converted to isomeric methylbutenes. The percentage of head to tail dimers in the mixture does not vary much with these changes but, of course, the total yields based upon isoprene consumed decrease significantly, from 41 to 12% in the series. The reaction rates, on the other hand, in-