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Silane Reductions in Acidic Media. VII. Aluminum Chloride Catalyzed Hydrogen–Halogen Exchange between Organosilanes and Alkyl Halides. An Efficient Hydrocarbon Synthesis[1a]

Michael P. Doyle,*[1b] Charles C. McOsker,[1c] and Charles T. West

Department of Chemistry, Hope College, Holland, Michigan 49423

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Alkyl halides are conveniently reduced to hydrocarbons by organosilanes in good yields when a catalytic amount of aluminum chloride is used. Hydrogen–halogen exchange between organosilanes and tertiary, secondary, primary, or methyl halides is rapid, and no significant difference in reactivity between alkyl bromides and chlorides is observed. Reduction by triethylsilane is competitive with the rearrangement of bromocycloheptane to 1-bromo-1-methylcyclohexane and with Friedel–Crafts alkylation reactions. Deuterium transfer from triethyldeuteriosilane to the alkyl cation formed from 1-bromohexane or cyclohexylmethyl bromide and aluminum chloride gives 2-deuteriohexane or 1-deuterio-1-methylcyclohexane, demonstrating that rearrangement to a more stable carbenium ion precedes reduction in these cases. The scope and limitations in the use of organosilanes for aluminum chloride catalyzed alkyl halide reductions is discussed.

Alkanes have long been known to transfer hydrogen intermolecularly to carbenium ions formed from alkyl halides and catalytic amounts of aluminum chloride.[2] By comparison, Lewis acid catalyzed reductions of alkyl halides by organosilanes have received limited attention; and the synthetic potential of this process for hydrocarbon formation has not been examined. Whitmore, Pietrusza, and Sommer have shown that an aluminum chloride catalyzed hydrogen–halogen exchange of triethylsilane with primary alkyl chlorides can be used to trap carbenium ions but point out that the experimental method is beset by a relatively long "induction period" followed by an often violent exothermic reaction.[3] In a subsequent investigation Sommer, Citron, and Lyons described a palladium-catalyzed reaction between triorganosilicon hydrides and halocarbons that is reported to be superior to the Lewis acid catalyzed exchange reaction for silyl halide formation;[4] this method, however, is not satisfactory as a synthetic procedure for hydrocarbon formation owing to the often complex nature of the reduction products.[5]

We have found that alkyl halides are readily reduced to hydrocarbons by organosilanes in good yields when catalytic amounts of aluminum chloride are used, that there is no observable "induction period" when tertiary alkyl halides are involved, and that organosilanes are clearly superior to hydrocarbons in hydrogen transfer reactions with carbenium ions. In this paper we report the scope and limitations in the use of organosilanes for aluminum chloride catalyzed alkyl halide reductions.

Results and Discussion

Addition of anhydrous aluminum chloride (usually ≤5 mol %) to a solution of an alkyl halide and organosilane, cooled in an ice–water bath, produced a rapid exothermic reaction. A solvent, usually pentane, was required only when the alkyl halide and silane were not mutually soluble. Product analysis of the reaction mixture after heating at 40 °C for usually less than 1 h showed only alkane and silyl halide (eq 1).

$$RX + R'_3SiH \xrightarrow{AlCl_3} RH + R'_3SiX \qquad (1)$$

Results from organosilane reductions of representative alkyl halides are given in Table I. No major difference in product yields was observed when the alkyl halide was alternatively added to the cooled mixture of silane and aluminum chloride. The reaction temperature could, however, be more effectively controlled by the slow addition of the alkyl halides to the $AlCl_3$–silane mixture (method II) than by the addition of aluminum chloride to the alkyl halide–silane solution (method I).

Tertiary alkyl halides reacted smoothly with organosilanes in the presence of a catalytic amount of aluminum chloride and gave no evidence of an initial induction period. A short time period in which no apparent reaction occurred was usually observed with both secondary (≤1 min) and primary (2 min) alkyl halides when the aluminum chloride was added to the alkyl halide–organosilane solution or when the alkyl halide was added to the silane–aluminum chloride mixture. In no case, however, was a long induction period followed by a violent exothermic reaction, similar to that previously observed,[3] noted for the reactions reported in Table I. No significant difference in reactivity was observed in silane reductions of comparable alkyl chlorides and bromides.

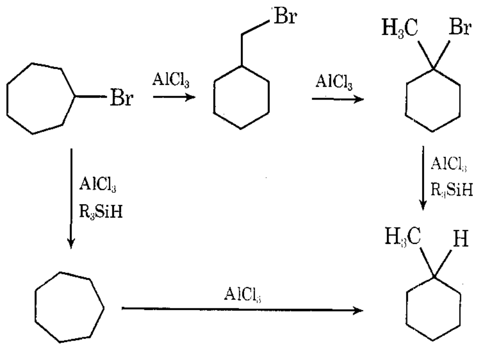
The aluminum chloride catalyzed reaction of organosilanes with alkyl halides provides an alternative and potentially useful synthetic route to hydrocarbons. Compared to the organotin hydrides,[6] organosilicon hydrides are stable to air and to acids and bases. Reductions of alkyl chlorides and bromides by organosilanes occur under the same reaction conditions; toward organotin hydrides alkyl chlorides are much less reactive than are the corresponding alkyl bromides and require reaction temperatures in excess of 100 °C for reasonable reaction times.[6] In addition, the organosilane reduction method favors tertiary alkyl halides over primary or secondary substrates; reactions with primary or secondary alkyl halides are usually preferred in procedures employing nucleophilic reducing agents.[7,8] Hy-

Table I. Aluminum Chloride Catalyzed Organosilane Reductions of Alkyl Halides

Registry no.	Alkyl halide	Organosilane	Method[a]	Hydrocarbon	% yield
768-90-1	1-Bromoadamantane[b]	Et_3SiH[h]	I	Adamantane	79[c]
7314-85-4	2-Bromoadamantane[b]	Et_3SiH	II	Adamantane	84[c]
13187-99-0	2-Bromododecane	*n*-$BuSiH_3$[i]	I	Dodecane	82[d,e]
	2-Bromododecane	*n*-Bu_3SiH	I	Dodecane	87[d]
90-99-3	Benzhydryl chloride	Et_3SiH	II	Diphenylmethane	100[f]
2114-39-8	2-Bromo-1-phenylpropane	Et_3SiH	I	*n*-Propylbenzene	43[f]
2404-35-5	Bromocycloheptane	Et_3SiH	II	Cycloheptane	39[d]
				Methylcyclohexane	26[d]
	Bromocycloheptane	*n*-$BuSiH_3$	II	Cycloheptane	<1[d]
				Methylcyclohexane	65[d]
2550-36-9	Cyclohexylmethyl bromide	Et_3SiH	II	Methylcyclohexane	52[d]
108-85-0	Bromocyclohexane	Et_3SiH	I	Cyclohexane	90[f]
542-18-7	Chlorocyclohexane	Et_3SiH	II	Cyclohexane	71[d]
137-43-9	Bromocyclopentane	Et_3SiH	II	Cyclopentane	71[d]
2534-77-2	*exo*-2-Bromonorbornane	Et_3SiH	II	Norbornane	96[d]
111-25-1	1-Bromohexane	Et_3SiH	I	Hexane	64[d,g]
629-06-1	1-Chloroheptane	Et_3SiH	II	Heptane	73[d]

[a] Method I, anhydrous aluminum chloride added to cooled solution of alkyl halide and organosilane; method II, alkyl halide added to cooled mixture of aluminum chloride and organosilane. [b] Pentane was used to dissolve the alkyl halide, 3 ml/10 mmol of halide. [c] Isolated recrystallized product yield. [d] Yield of product after quenching based on GLC analysis using an internal standard. [e] Dodecane isolated by distillation in 59% yield. [f] Yield based on ^1H NMR analysis. [g] Hexane isolated by distillation in 46% yield. [h] Registry no., 617-86-7. [i] Registry no., 1600-29-9.

Scheme I



drocarbon syntheses by organosilane reductions are limited to alkyl halides that do not undergo extensive structural rearrangement with aluminum chloride, to phenyl-substituted alkyl halides for which the Friedel–Crafts alkylation process does not predominate, and to functionalized alkyl halides possessing neither a nitro nor a cyano substituent.

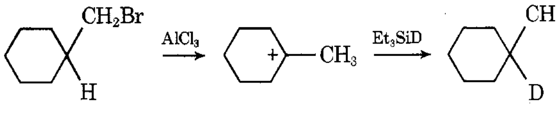
Reduction of bromocycloheptane by triethylsilane using 5 mol % aluminum chloride gave after 30 min reaction time a mixture of 26% methylcyclohexane and 39% cycloheptane (Table I); after 3 h 31% methylcyclohexane and 31% cycloheptane were observed. Without the organosilane present, cycloheptyl bromide isomerized under the same reaction conditions to a mixture composed of 1-bromo-1-methylcyclohexane, cyclohexylmethyl bromide, and bromocycloheptane in a 3.5:2:1 ratio after 2 h. Similarly, cycloheptane slowly isomerized to methylcyclohexane in the presence of aluminum chloride: after 1 h the ratio of methylcyclohexane to cycloheptane was 1:2, while after 2 h this hydrocarbon ratio was 1:1. As expected, rearrangement of cycloheptyl bromide occurred at a faster rate than did rearrangement of cycloheptane. These results show that the rate of reduction by triethylsilane is competitive with the rate of the aluminum chloride catalyzed isomerization of cycloheptyl bromide (Scheme I). In contrast, only methylcyclohexane was produced from the reaction of *n*-butylsilane with bromocycloheptane, indicating that hydrogen transfer from trialkylsilanes is appreciably faster than from monoalkylsilanes. A similar rearrangement process in silane reductions of cyclohexyl halides leading to methylcyclopentane was not observed.

2-Bromo-1-phenylpropane gave in addition to *n*-propylbenzene (43% yield) Friedel–Crafts alkylation products. However, only diphenylmethane was obtained from the reaction of triethylsilane with benzhydryl chloride. Thus, the stability of the carbenium ion produced by the interaction of an alkyl halide and aluminum chloride is a major determinant of the extent of reactions competing with organosilane reductions.

Attempts to reduce *p*-nitrobenzyl bromide to *p*-nitrotoluene with triethylsilane were unsuccessful. In pentane, methylene chloride, or nitromethane, using as much as 50 mol % of aluminum chloride and reaction times as long as 95 h, only unreacted starting material was recovered. Similarly, neither 3-bromopropanonitrile nor 5-bromopentanonitrile were reduced by organosilanes to the corresponding nitriles, even when a 10 mol % excess of aluminum chloride was used. However, both methyl iodide and ethyl bromide reacted vigorously with triethylsilane in the presence of aluminum chloride,[10] which suggests that relatively basic functional groups of functionalized alkyl halides modify the catalytic activity of the aluminum chloride. Such a catalyst modification might decrease the degree of ionization of the carbon–halogen bond from that required in reactions with organosilanes.[11]

In order to determine the extent of intramolecular hydrogen transfer in organosilane reductions of primary alkyl halides, 1-bromohexane and cyclohexylmethyl bromide were separately reacted with triethyldeuteriosilane according to the procedure outlined in Table I. 1-Bromohexane gave 2-deuteriohexane which was isolated and identified by ^1H NMR and mass spectroscopy. Cyclohexylmethyl bromide yielded 1-deuterio-1-methylcyclohexane which was isolated and likewise identified by spectrometric methods. In neither case was evidence obtained for deuterium transfer to the primary position. Thus rearrangement to the more stable secondary or tertiary carbenium ion (eq 2, 3) precedes reduction in these cases, although, as is evident from the observed reductions of methyl iodide and ethyl

$$CH_3(CH_2)_4CH_2Br \xrightarrow{AlCl_3} CH_3(CH_2)_3\overset{+}{C}HCH_3 \xrightarrow{Et_3SiD} CH_3(CH_2)_3CHDCH_3 \quad (2)$$



(3)

bromide by triethylsilane, formation of a secondary or tertiary alkyl cation is not a necessary prerequisite for hydrogen–halogen exchange. These reactions also suggest that specific labeling at a fixed position of a hydrocarbon is possible through deuterium transfer from an organosilicon deuteride to the most stable carbenium ion formed from an alkyl halide and aluminum chloride.

The aluminum chloride catalyzed organosilane reductions of primary and secondary alkyl halides represent the only procedure by which hydride transfer from silicon occurs to a primary or secondary carbon position. In previous studies, which have employed trifluoroacetic acid and alkenes,[12] alcohols,[13] or alcohol derivatives,[9,14] hydrocarbon formation has been limited to substrates that could form carbenium ions at least as stable as a tertiary alkyl cation.[15] No such limitation is found when aluminum chloride is employed as the catalyst. Indeed, since numerous procedures using aluminum chloride are known to efficiently catalyze Friedel–Crafts reactions of benzene with a wide variety of organic substrates, similar procedures may expand the scope of aluminum chloride catalyzed organosilane reductions. Since aluminum chloride can be easily removed from the reaction mixture, its use simplifies the procedures required for product isolation.

Halogenation of organosilanes by *tert*-butyl halides is effectively promoted by aluminum chloride. Only a catalytic quantity of aluminum chloride is required, hydrogen–halogen transfer is spontaneous and occurs smoothly, and the hydrocarbon product is a gas. No solvent is required and no hydrogen chloride is evolved in this halogenation process. We have previously shown that di-*tert*-butylchlorosilanes are conveniently produced through this process.[16] In this study, tri-*n*-hexylchlorosilane was produced in the same manner. With other alkyl halide substrates (Table I), triethylsilane and tri-*n*-butylsilane formed their respective chloride or bromide derivative which was identified as the only organosilicon reaction product. Two of the three available hydrogens of *n*-butylsilane were readily transferred in reactions with alkyl halides. Polymethyl hydrogen siloxane (PMHS) did not undergo hydrogen–halogen exchange with alkyl halides.

Intermolecular hydrogen transfer from tertiary carbon centers of hydrocarbons to the *tert*-butyl cation, generated from *tert*-butyl chloride and a catalytic amount of aluminum chloride, has proven to be a rapid and efficient procedure for hydrogen-halogen exchange.[17,18] However, secondary reactions, including elimination–carbenium ion addition reactions, can be predominant, particularly if reaction times are not carefully controlled.[17] Hydrogen transfer from secondary carbon positions to the *tert*-butyl cation has also been observed, but the extent of this process is usually low.[19] We have found that when adamantane is employed as the hydrogen donor with a fivefold molar excess of cyclohexyl bromide and a catalytic amount of aluminum chloride in carbon tetrachloride, 49% 1-bromoadamantane, 9% 1-chloroadamantane, and 58% cyclohexane (based on adamantane) were formed after 16 h at 40 °C.[20] Likewise, hydrogen–halogen transfer between adamantane and cyclohexyl chloride under the same reaction conditions was far from complete (18% 1-chloroadamantane formed) even after 21 h at 40 °C. Thus, although hydrogen–halogen exchange between tertiary carbon centers is rapid and usually occurs in high yield, this method is not generally suitable for hydrocarbon synthesis.

Experimental Section

General. Instrumentation has been previously described.[21] Use was made of 5 ft columns of 10% SE-30 and 15% SF-96, each on Chromosorb P. A Varian Model 485 digital integrator was used to determine peak areas in GLC analyses; reported yields were determined with the use of experimentally determined thermal conductivity ratios. With the exception of *n*-butylsilane,[22] organosilanes were obtained commercially. Alkyl halides and alkanes employed as standards were commercial samples that were used without prior purification. Finely powdered aluminum chloride was stored in a desiccator over phosphorus pentoxide. All glassware was oven dried and assembled in a dry atmosphere.

Triethyldeuteriosilane. To a stirred mixture of lithium aluminum deuteride (96% D, 1.0 g, 23 mmol) in 60 ml of anhydrous ether contained in a three-necked flask, equipped with a water condenser, addition funnel, and drying tube, was added triethylchlorosilane (12.3 g, 82 mmol) dropwise over a 30-min period. After the addition was complete the mixture was refluxed for 2 h. Ether and 5 g of ice were slowly added to the reaction mixture followed by 50 ml of a cold 25% aqueous sulfuric acid solution. The ether layer was separated, and the aqueous solution was washed with two 20-ml portions of ether. The combined ether solution was washed with 20-ml portions of 25% aqueous sulfuric acid, 10% aqueous sodium hydroxide, and water, and then dried with anhydrous magnesium sulfate. Fractional distillation through a 10-cm Vigreux column gave 5.52 g (47 mmol, 57% yield) of triethyldeuteriosilane: bp 105–106.5 °C; ir (film) 1550 cm^{-1} (Si–D), no Si–H adsorption observed at 2100 cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (m, 6 H) and 0.62 (m, 9 H).

Organosilane Reductions of Alkyl Halides. In a typical experiment the silane (12 mmol) and anhydrous aluminum chloride (0.05 g, 0.4 mmol) were weighed into a dry three-necked flask equipped with a reflux condenser, drying tube, and addition funnel. The alkyl halide was added dropwise to the stirred mixture cooled in an ice–water bath. In an alternate procedure the aluminum chloride was added to a stirred organosilane–alkyl halide solution cooled in an ice–water bath. A solvent, pentane, was employed to dissolve the bromoadamantanes. After the addition of the alkyl halide or aluminum chloride, the reaction mixture was heated at 40 °C until GLC analysis indicated complete reduction. Reaction times were generally less than 1 h. For reactions requiring longer times, an additional 0.05-g portion of aluminum chloride was added to hasten reduction. Solid sodium carbonate (0.2 g) was used to destroy the aluminum chloride catalyst and had little effect on the halosilane product. Adamantane was isolated by removal of the pentane solvent and recrystallized from acetone. Dodecane and hexane were fractionally distilled from excess silane and silyl halide. Hydrocarbon and silyl halide products were identified by ^1H NMR and/or GLC methods. Cycloheptane, methylcyclohexane, and triethylsilane were separable on 15% SF-96 columns.

Reductions with Triethyldeuteriosilane. Reactions were run as previously described through the addition of the alkyl halide to the silane–aluminum chloride mixture. Hexane-d_1 was fractionally distilled, bp 66–67 °C. Spectral analysis by comparison with undeuterated hexane showed the most probable position of deuterium incorporation to be position 2: ^1H NMR (CCl_4) δ 1.55–1.05 (m, 7 H) and 1.05–0.80 (m, 6 H); mass spectrum *m/e* (rel intensity) 87 (8, parent ion), 72 (4), 71 (2.5), 58 (78), 57 (73), 43 (100), 42 (94), 41 (88).

Methylcyclohexane-d_1 was collected by GLC methods. Spectral analysis by comparison with undeuterated methylcyclohexane showed the most probable position of deuterium incorporation to be position 1 of the cyclohexane ring: ^1H NMR (CCl_4) δ 1.80–1.30 (m, 6 H), 1.30–1.00 (m, 4 H), and 0.93 (distorted s, 3 H); mass spectrum *m/e* (rel intensity) 99 (8, parent ion), 85 (27), 84 (47), 71 (20), 70 (20), 57 (63), 56 (100), 16 (1.5), 15 (12).

Reactions of Alkyl Halides with Adamantane. The cyclohexyl halide (25 mmol) was added dropwise to an ice–water bath cooled mixture of adamantane (10 mmol) and anhydrous aluminum chloride (0.057 g, 0.3 mmol) in 5 ml of carbon tetrachloride. After the addition was complete, the stirred reaction mixture was heated at 40 °C. The progress of the reaction was monitored by GLC analysis. In pentane 2-bromoadamantane is completely isomerized by aluminum chloride to 1-bromoadamantane within 1 h; adamantane is formed in low yield under these reaction conditions.

Acknowledgment. We gratefully acknowledge the support of the Research Corporation for this work.

Registry No.—$AlCl_3$, 7446-70-0; triethyldeuteriosilane, 1631-33-0; lithium aluminum deuteride, 14128-54-2; triethylchlorosilane, 994-30-9; hexane-*2*-d_1, 32740-26-4; methylcyclohexane-*1*-d_1, 34097-86-4; adamantane, 281-23-2.

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Synthesis of a Cytotoxic Vernolepin Prototype. Ozonization of Silyloxyalkenes[1]

Robin D. Clark and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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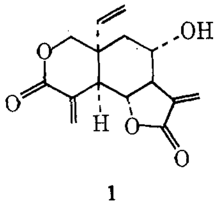
Regiospecific silyloxyalkene formation, followed by ozonization, has been used in two syntheses of α-methylene-δ-lactone **2**, a prototype of vernolepin, a sesquiterpene lactone possessing antitumor and cytotoxic properties. Compound **2** has been found to have moderate in vitro toxicity toward cells derived from human carcinoma of the nasopharynx (KB) in cell culture. Silyloxyalkenes react rapidly with ozone in methanol at −78 °C to give carboxylic acids. The silyloxyalkene double bond is sufficiently reactive that it may be selectively ozonized in the presence of certain normal double bonds. Since silyloxyalkenes may often be generated regiospecifically, the reaction constitutes an effective method for the regiospecific cleavage of ketones. Silyloxyalkenes derived from esters (alkyl silyl ketene acetals) give mixtures of the cleavage product (one-carbon degradation of the ester) and the corresponding α-silyloxy ester. This "abnormal" mode of oxidation is also observed for the hindered silyloxyalkene derived from camphor.

Vernolepin (**1**) is a sesquiterpene bislactone of the elemane class,[2] which has been found to show in vitro cytotoxicity toward cells derived from human carcinoma of the nasopharynx (KB) in cell culture, and in vivo antitumor activity against the Walker intramuscular carcinosarcoma 256.[3,4]



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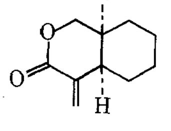

2, R = CH═CH$_2$
3, R = CH$_3$
4, R = CH$_2$CH$_3$

As a part of a general project aimed at the total synthesis of sesquiterpene antitumor lactones, we have developed two efficient synthetic routes to **2**, a prototype of vernolepin which contains only one of the two α-methylene lactone functions. One of the routes has also been utilized to synthesize vernolepin analogues **3** and **4**.

A key step in both synthetic routes involves ozonization of a silyloxyalkene. We have carried out a brief study of the scope of this new reaction. In this paper we report the results of these studies. Since we embarked upon this project, several other syntheses of lactone **2** have been reported.[5–8]

Lithium divinylcuprate is added to enone **5**[9] at −75 °C in dimethyl sulfide–THF, and the resulting reaction mixture is worked up by the addition of trimethylsilyl chloride, HMPT, and triethylamine.[10] Silyloxydiene **6** is obtained in 75% yield. Selective ozonization of the silyloxyalkene linkage in **6** proceeds at −75 °C without incident. After reduction of the intermediate methoxy hydroperoxide with sodium borohydride, the reaction mixture is acidified and worked up to obtain lactone **7** in 93% yield. Grieco's two-stage procedure was used to introduce the α-methylene group (**7** → **2**).[5,11] One advantage of this process for constructing the vernolepin A ring is that analogues may be prepared in which the angular vinyl group is replaced by other groups. Since Kupchan has shown that dihydrovernolepin retains the cytotoxic and antitumor properties of