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METHOD OF REDUCTION WITH HYDROCARBONTIN HYDRIDES

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This invention relates to reduction processes utilizing novel reducing agents.

Reduction processes of many kinds are known. The various processes utilize a large variety of reducing agents to obtain desired products. We have now discovered a new class of reducing agents which are generally specific in nature and enable the obtention of many products by reduction processes which could not heretofore be prepared, or which could not heretofore be obtained in the excellent yields with which we can obtain them.

It is an object of this invention to provide reduction processes utilizing specific reducing agents.

It is another object of this invention to provide reduction processes by which it is possible to obtain desired reduction products in high yields by a facile process.

Still another object of the invention is to provide reduction processes capable of yielding desired specific stereoisomers.

The invention also contemplates providing specific reducing agents.

Generally speaking, the invention contemplates a wide variety of reduction processes in which hydrocarbontin hydrides are utilized as reducing agents. The hydrocarbontin hydrides are generally those in which the hydrocarbon radical is aliphatic or aromatic. These include the saturated and unsaturated chain hydrocarbon radicals and such aromatic radicals as the aryls. Preferred hydrocarbontin hydrides are those in which the hydrocarbon radical(s) is a saturated or unsaturated chain hydrocarbon having up to about 12 carbon atoms in the chain, e.g. butyl, vinyl, etc., or a monocyclic aryl hydrocarbon radical, e.g. phenyl.

Of the various hydrocarbontin hydrides tested, diphenyltin dihydride is the preferred reducing agent. It is far faster in reducing action than dibutyltin dihydride (in the order of 100 times faster) for the conditions tested.

Reducing agents generally vary in their effectiveness and their specificity. The hydrocarbontin hydrides are generally highly specific in their reducing action. When compounds having a carbonyl functional group with an ethylenically unsaturated group in the α, β position are reduced in the presence of diphenyltin dihydride, the reduction is almost 100% effective for the carbonyl group, leaving the unsaturated bonding unreacted. When a similar reduction takes place in the presence of dibutyltin dihydride, the addition reaction across the double bond is more competitive with the reduction of the carbonyl function (which is far slower than when diphenyltin dihydride is utilized) to yield different products and/or a much smaller yield of the product having only the reduced carbonyl function.

It is possible to obtain very high yields of stereospecific compounds when utilizing the hydrocarbontin hydrides in certain reduction processes. So far as we know, such unusual yields of stereoisomer cannot be obtained by other organic syntheses. This, of course, excepts those processes utilizing natural organisms. In the presence of diphenyltin dihydride, benzil was reduced to yield 84% of pure mesohydrobenzoin; d-carvone was reduced to yield 83% of carveols containing 97% di-cis-carveol; 4-t-butylcyclohexanone was reduced to yield 85% of 4-t-butylcyclohexanols containing about 90% trans isomer; 2-methylcyclohexanone was reduced to yield 83% of 2-methylcyclohexanols containg 78% trans isomer. The yields specified are of purified product; the overall yield is believed to be close to quantitative. This unusual ability to reduce compounds to specific stereoisomers has applicability in the pharmaceutical field, e.g., in the preparation of desired stereospecific steroid derivatives.

The theoretical reasons for the action of the hydrocarbontin hydrides as reducing agents are not understood. In some of the results, processes of the present invention are generally analogous to known reduction processes. For this reason these reagents are designated herein as "reducing agents." In certain respects their behavior as reducing agents in these systems is anomalous. In the usual reduction process, the reducing agent is itself oxidized during the course of the process. This does not appear to be the mechanism whereby the hydrocarbontin hydrides act. When methyl vinyl ketone was reduced by diphenyltin dihydride in wet diethyl ether at room temperature, the reaction products were diphenyltin and methyl vinyl carbinol. This is different from the usual reduction of carbonyl compounds by metal hydrides in which a metal salt of the alcohol is formed by the addition $M\text{-}H + R_2C{=}O \rightarrow R_2CHOM$ followed by hydrolysis to obtain the alcohol. As is apparent in the reduction utilizing diphenyltin dihydride, such a step is unnecessary. In this reaction of diphenyltin dihydride with methyl vinyl ketone, the diphenyltin product was a yellow solid insoluble in ether, probably polymeric in nature. Apparently the tin atom was also reduced. No explanation is offered as to the mechanism by which this material acts, apparently as a reducing agent, and at the same time appears itself to be reduced, without any apparent concomitant oxidation in the system. It is thought that the "reducing" action of these reagents is effected by the action at the tin to hydrogen bonds.

The hydrocarbontin hydrides have shown themselves to be reducing agents for a wide variety of functional groups. Carbonyl functional groups have been reduced, e.g. aldehydes and ketones to alcohols; nitrogen-containing functional groups, e.g., the nitro and the azo groups to amines; and halogen-containing functional groups have been reduced with replacement of the halogen atom by hydrogen. The foregoing listing of functional groups is illustrative of the wide applicability of reduction processes utilizing hydrocarbontin hydrides.

The reductions are carried out by reacting (usually mixing to cause reaction) the hydrocarbontin hydride and the material to be reduced. Room temperatures are often conveniently used but in specific cases different temperatures are desirable and/or necessary. In all cases, the process temperature would be below the decomposition temperature of the desired reaction product under the specified conditions. The reaction is generally carried out in the presence of an inert solvent, preferably a hydrocarbon solvent such as an aliphatic, cycloaliphatic, or aromatic hydrocarbon, or in the presence of an ether. The inert solvents are those which will not re-

act and/or decompose any of the reactants or reaction products. Atmospheric pressure is generally used, but pressure systems might advantageously be used for specific systems. The hydrocarbontin hydrides are generally reactive with oxygen of the atmosphere, requiring that the process be carried out in a system from which such oxygen is excluded. An inert atmosphere, such as nitrogen, which is most economical, is preferred.

The actual reduction process steps utilized may be varied widely. The criticality of the various process steps and conditions is dependent upon the particular process being carried out and reactants utilized. Dependent upon the process and reactants, a change in conditions may result in a marked change in yield and/or product. The hydrocarbontin dihydrides are generally soluble in the usual organic solvents. The system is homogeneous permitting wide applicability of these processes in common solvent systems.

The hydrocarbontin hydrides may be prepared by a number of syntheses. Such materials as diphenyltin dihydride, tributyltin hydride, and dibutyltin dihydride may be prepared by reacting the respective chlorides with lithium aluminum hydride in an inert solvent, such as diethyl ether, to yield the desired hydride. Diphenyltin dihydride may be more economically prepared by reacting diphenyltin dichloride with sodium in liquid ammonia to yield diphenyltin disodium, which is then reacted with ammonium chloride in liquid ammonia to yield the desired diphenyltin dihydride, as is shown in the literature.

For the purpose of giving those skilled in the art a better understanding of the invention, the following illustrative examples are given.

The reductions were usually carried out in a standardized manner as exemplified by the reduction of methyl vinyl ketone, described below.

Methyl vinyl ketone, 13.5 g. (15 ml.) was placed in a 500 ml. flask and flushed with nitrogen. A wet diethyl ether solution of diphenyltin dihydride (0.150 mole) (10% excess) was added to the flask, at room temperature. The flask was shaken to mix thoroughly. The flask was flushed with nitrogen and allowed to stand (overnight). No gas was evolved. A yellow precipitate of diphenyltin was formed after several hours of standing. Diethyl amine was then added to destroy excess diphenyltin dihydride. The reaction product was extracted with diethyl ether. The yield was 59% of pure methyl vinyl carbinol. The diphenyltin dihydride utilized was prepared by reduction of diphenyltin dichloride with lithium aluminum hydride in ethyl ether. Excess lithium aluminum hydride was removed by hydrolysis.

The other reductions utilizing diphenyltin dihydride were prepared generally following the procedure illustrated. Reduction processes utilizing dibutyltin dihydride were also generally similar to that illustrated, with the exception that diethyl amine was not added to the reaction product as it does not destroy dibutyltin dihydride under these conditions. Room temperature was used, except that a reduction was carried out using diisopropyl ether at the boiling point of the system. The reductions with tributyltin hydride also generally followed the procedure illustrated with the exception that the tributyltin hydride was not added in diethyl ether. It (tributyltin hydride) had been prepared earlier and purified to the liquid product. In the reduction of triphenylchloromethane, the tributyltin hydride was added in benzene. The reduction of phenylethylbromide was carried out in the absence of solvent, at 100° C.

In Table I are noted the results of reductions utilizing diphenyltin dihydride. The reductions which were separately carried out with dibutyltin dihydride, as well as with diphenyltin dihydride, are marked with an asterisk (*). Similarly, the marked (*) yields are those obtained using dibutyltin dihydride. Table II lists two reductions carried out utilizing tributyltin hydride. Standard conditions were utilized except as noted. The yields specified are of purified material. The actual overall yield of reduction product was undoubtedly higher.

Table I

Reactant		Product	Yield, percent
methyl vinyl ketone*	←	methylvinylcarbinol	59
mesityl oxide	←	methylisobutenylcarbinol.	60
chalcone	←	phenylstyrylcarbinol	75
cyclohexanone	←	cyclohexanol	82
benzophenone*	←	diphenylcarbinol	59 *85
benzil*	←	meso-hydrobenzoin	84 *93
d-carvone*	←	carveol: 97% d-cis form 95% d-cis form*	83 *71
4-t-butyl-cyclohexanone*	←	4-t-butylcyclohexanols (90% trans).	85
2-methylcyclohexanone	←	2-methylcyclohexanols (78% trans).	83
benzoquinone	←	1,4-dihydroxybenzene	
cinnamaldehyde	←	cinnamyl alcohol	75
crotonaldehyde*	←	propenylcarbinol	59
p-bromoazobenzene	←	p-bromoaniline	
p-bromonitro-benzene	←	p-bromoaniline	55
azobenzene	←	aniline	
m-nitrobenzaldehyde	←	m-aminobenzaldehyde	65

Table II

Reactant		Product	Yield, Percent
triphenylchloromethane	→	triphenylmethane	75
ϕCH_2CH_2Br	[1] →	ethylbenzene	85

[1] 100° C.—4 hrs.

The foregoing examples illustrate the wide applicability of the processes utilizing the hydrocarbontin hydrides. Their startling ability to reduce compounds to largely specific stereoisomers is especiallyapparent. It is possible to reduce functional groups in the presence of either a single ethylenic bonding in the molecule or in the presence of conjugated unsaturated systems. It is believed that reduction of functional groups, such as the carbonyl group, etc., in materials which also contain more than two double bonds and/or triple bonds is within the invention. The reduction of complex materials such as steroid compounds is also believed to be within the invention. Although the disclosure herein is largely limited to concrete examples utilizing the hydrocarbontin hydrides tested, i.e., diphenyltin dihydride, dibutyltin dihydride, and tributyltin hydride, it is believed that other hydrocarbontin hydrides also have the unusual reducing action described herein and are within the invention.

It is also believed that the unusual reducing ability of the hydrocarbontin hydrides, and especially diphenyltin dihydride, extends beyond the field of purely hydrocarbon compounds with substituted functional groups, generally illustrated hereinbefore. This broad class of reduction processes, which are believed to be within the invention, include the reduction of halides of metal and metalloid elements, e.g., halosilanes, to the hydride, as well as the organometallic compounds, having the general formula R_nMX_{m-n}, to the respective hydride; wherein R is an organic radical, M is a metal or metalloid element, X is a replaceable group, e.g., halogen, *n* and *m* are integers of one or more, and m plus n equal the valence of the metal (M). The utility of our process is based on the ability to obtain reduction products more efficiently and economically than heretofore, where such products could be obtained heretofore. It is also possible to obtain many reduction products, especially stereospecific isomers in good yields which could not heretofore be obtained by reduction processes.

As many embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that the invention includes all such modifications and variations as come within the scope of the appended claims.

We claim:

1. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a functional group selected from the group consisting of ketone, aldehyde, nitro, azo, and aralkyl halide groups by subjecting the organic compound containing said functional group to the action of a hydrocarbontine hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

2. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a functional group selected from the group consisting of ketone, aldehyde, nitro, azo, and aralkyl halide groups by subjecting the organic compound containing said functional group to the action of a hydrocarbontin hydride selected from the group consisting of diphenyltin dihydride, dibutyltin dihydride and tributyl hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

3. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a functional group selected from the group consisting of ketone, aldehyde, nitro, azo, and aralkyl halide groups by subjecting the organic compound containing said functional group to the action of diphenyltin dihydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

4. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a functional group selected from the group consisting of ketone, aldehyde, nitro, azo, and aralkyl halide groups by subjecting the organic compound containing said functional group to the action of dibutyltin dihydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

5. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a functional group selected from the group consisting of ketone, aldehyde, nitro, azo, and aralkyl halide groups by subjecting the organic compound containing said functional group to the action of tributyltin hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

6. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a ketone group by subjecting the organic compound containing said ketone group to the action of a hydrocarbontin hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

7. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of an aldehyde group by subjecting the organic compound containing said aldehyde group to the action of a hydrocarbontin hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

8. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of a nitro group by subjecting the organic compound containing said nitro group to the action of a hydrocarbontin hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

9. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of an azo group by subjecting the organic compound containing said azo group to the action of a hydrocarbontin hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

10. In organic reduction processes wherein an organic compound containing a reducible functional group is treated with a reducing agent to reduce said functional group and thereby produce an organic compound containing a reduced functional group, the improvement which comprises the reduction of an alkylaryl halide group by subjecting the organic compound containing said alkylaryl halide group to the action of a hydrocarbontin hydride in an inert solvent and in the presence of a non-oxidizing atmosphere.

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