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MANUFACTURE OF ALDEHYDES AND KETONES

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The present invention relates to a process for the preparation of aldehydes and ketones.

Various procedures have been proposed in the past for forming aldehydes and ketones from alkylating agents such as alkyl halides, alkyl chlorosulfonic acid esters, alkyl p-toluene sulfonic acid esters (tosylates), alkyl sulfuric acid esters and alkyl sulfites. However, none of these methods permitted the alkylating agent to be directly converted to the corresponding aldehyde or ketone.

Instead the previous procedures required at least two steps. In addition the yields by such prior art procedures in many cases gave poor yields of the desired products.

Accordingly it is an object of the present invention to devise a new procedure for preparing aldehydes and ketones.

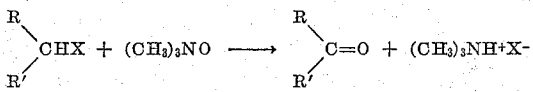
Another object is to develop a one step procedure for preparing aldehydes and ketones from alkylating agents.

A further object is to prepare aldehydes and ketones in improved yields.

Yet another object is to prepare aldehydes and ketones from readily available materials such as alkyl halides and other esters.

Still further objects and the entire scope of applicability of the present invention will become apparent from the detailed description given hereinafter; it should be understood, however, that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

It has now been found that these objects can be attained by reacting trimethylamine oxide with alkylating agents such as alkyl halides, alkyl esters of chlorosulfonic acid, alkyl esters of p-toluene sulfonic acid, alkyl esters of benzene sulfonic acid, alkyl esters of sulfuric acid, alkyl esters of sulfuorous acid and also the corresponding cycloalkyl, alkenyl and aromatic esters of these acids. The reaction goes smoothly in a one step procedure according to the following equation.



In the formula R is H, alkyl or aryl R′ is alkyl, alkenyl, aryl, aralkenyl, nitroaryl or haloaryl or R and R′ are joined together with the C to form a cycloalkyl or cycloalkenyl group. X is halogen, R_1SO_2O— where R_1 is aryl or alkyl, —OSO_2Cl,

where R_2 is alkyl or

where R_3 is alkyl.

When X is halogen preferably it has an atomic weight between 35 and 127.

As examples of suitable alkylating agents there can be used ethyl iodide, ethyl bromide, propyl chloride, propyl bromide, propyl iodide, isopropyl bromide, n-butyl bromide, isobutyl bromide, sec butyl bromide, n-butyl chloride, n-butyl iodide, n-hexyl iodide, n-hexyl bromide, n-amyl chloride, neopentyl bromide, n-octyl iodide, n-octyl chloride, n-octyl bromide, isoamyl bromide, n-dodecyl bromide, cetyl bromide, cetyl iodide, stearyl chloride, stearyl bromide, stearyl iodide, benzyl chloride, benzyl bromide, benzyl iodide, p-methyl benzyl chloride, o-decylbenzyl chloride, allyl chloride, allyl bromide, allyl iodide, methallyl bromide, crotyl bromide, cinnamyl chloride, cinnamyl bromide, oleyl chloride, p-nitrobenzyl bromide, p-chlorobenzyl chloride, cyclopentyl bromide, cyclooctyl bromide, cyclooctyl iodide, cyclooctyl chloride, cyclohexyl bromide, cyclopentenyl bromide, ethyl p-toluenesulfonate (ethyl tosylate), n-butyl tosylate, sec butyl tosylate, isobutyl tosylate, n-dodecyl tosylate, n-octadecyl tosylate, benzyl tosylate, o-nitrobenzyl tosylate, cyclopentyl tosylate, cinnamyl tosylate, sec amyl tosylate, isooctyl tosylate, isopropyl tosylate, n-amyl benzenesulfonate, n-octyl chlorosulfonate (n-octyl ester of chlorosulfonic acid), n-butyl chlorosulfonate, cyclooctyl chlorosulfonate, sec amyl chlorosulfonate, cetyl chlorosulfonate, stearyl chlorosulfonate, n-butyl butanesulfonate, di n-amyl sulfate, di n-butyl sulfate, di sec butyl sulfate, dilauryl sulfate, di octadecyl sulfate, dioleyl sulfate, n-pentan-ol-3 ester with p-toluene sulfonic acid), di n-butyl sulfite, di sec butyl sulfite.

It will be observed that all of the above compounds are esters.

The trimethylamine used in the reaction is not lost but can be recovered quite readily after the completion of the reaction. The process can be applied generally to prepare aliphatic, aromatic, branched chain, straight chain, cycloaliphatic, saturated and unsaturated aldehydes and ketones.

In carrying out the procedure, the alkylating agent, e.g. the alkyl halide or the chlorosulfonic or tosyl ester is reacted in equal molar amounts or with an excess of anhydrous trimethylamine oxide. The molar ratio of the alkylating agent to the trimethylamine oxide is preferably between 1:1 and 1:4. It is desirable to run the reaction in an organic solvent in which the trimethylamine oxide is soluble, e.g. in chloroform. The reaction can also be carried out in other solvent such as methylene chloride, dioxane, tetrahydrofuran, benzene, toluene, carbon tetrachloride xylene and dimethylformamide.

The reaction time is generally not longer than 20–30 minutes. In some cases it is even shorter. In many cases the resulting heat of reaction is sufficient; in other cases, particularly with long chain halides and tosylates, additional heating is necessary to complete the reaction.

The exact reaction conditions naturally vary from case to case. Too long a heating period is to be avoided since the aldehydes formed can react further occasionally according to the aldol condensation in basic medium. If the heating period is too long and the excess of trimethylamine oxide is much too large, further oxidation occurs.

However, both of these troublesome side reactions named above proceed considerably slower than the desired aldehyde or ketone formation so that an additional margin remains for the latter reaction and, if necessary, conditions of time and temperature, under which the carbonyl compound can be isolated without difficulty, can always be found by preliminary experiments.

To isolate the reaction product, the reaction solution, e.g. a chloroform solution, is shaken with a strong acid, e.g. a mineral acid after it is cooled. Such acids include hydrochloric acid, sulfuric acid and phosphoric acid. Then the aqueous layer is separated and the chloroform solution is washed with aqueous sodium bicarbonate or potassium bicarbonate solution. Then after separating

the aqueous layer and drying, the chloroform solution is distilled. Also, after first cooling the reaction solution, the ammonium salt formed in the reaction can be precipitated by the addition of ether. If the aldehyde or the ketone is stable, it can be recovered as the residue simply by distilling off the solvent after the removal of the ammonium salt.

Anhydrous trimethylamine oxide can be prepared from its hydrate in any convenient fashion, see Fieser et al. Organic Chemistry pages 239–240 but is preferably prepared by dehydration with dimethyl formamide, e.g. according to the following procedure:

40 g. trimethylamine oxide hydrate were dissolved with heating in 250 ml. of dry dimethyl formamide. It was heated further on an oil bath until the distillate had reached the boiling point of the dimethyl formamide. Then the bath was allowed to cool to about 65° C. and the residual solvent was distilled in the vacuum (water-jet) pump while the oil bath was reheated slowly to 120°. Anhydrous trimethylamine oxide remained behind, M.P. 210° C. Yield: 22 g.

Unless otherwise indicated all parts and percentages are by weight.

The yields given in the following examples are of the pure, distilled final products.

EXAMPLE 1

Preparation of Hexanal-1

0.2 mol of n-hexyl iodide was slowly added dropwise under agitation to a solution of 0.2 mol of anhydrous trimethylamine oxide in 55 ml. of chloroform. At the beginning it was heated on the water bath to 50–60° C. When about half of the hexyl iodide was added, the alkylation reaction started whereby the chloroform came to the boiling point. The water bath was removed and the remainder of the hexyl iodide was added dropwise. Subsequently the mixture boiled under reflux for 30 minutes. After cooling, 55 ml. of 2 N hydrochloric acid were added, mixed thoroughly, and the layers separated. The chloroform solution was washed with aqueous sodium bicarbonate solution, dried, and distilled.

Boiling Point: 38° C. at 15 mm. Yield: 9.7 g.

Similar yields of hexanal-1 were obtained by replacing the hexyl iodide by 0.2 mol of n-hexyl bromide in this example.

EXAMPLE 2

Preparation of Octanal-1

0.2 mol of n-octyl iodide was added slowly under agitation to a solution of 0.2 mol of trimethylamine oxide in 55 ml. of chloroform. The solution was heated slightly at the beginning until the reaction began. After all of the octyl iodide was added dropwise, the mixture was boiled under reflux for 30 minutes. It was cooled and 55 ml. of 2N hydrochloric acid were added. The solution was mixed thoroughly, then the layers were separated. The chloroform solution was washed with aqueous potassium bicarbonate solution and dried. Then it was distilled.

Boiling Point: 77° C. at 25 mm. Yield: 12.5 g.

EXAMPLE 3

Reaction of Octyl Tosylate With Trimethylamine Oxide

Using the same procedure as in Example 2, 0.2 mol of n-octyl tosylate was reacted with 0.4 mol of trimethylamine oxide. The heating period was 20 minutes. n-Octanal-1 was obtained in a 55% theory yield.

EXAMPLE 4

Reaction of the Octyl Ester of Chlorosulfonic Acid With Trimethylamine Oxide

Under cooling and good agitation 0.15 mol of the octyl ester of chlorosulfonic acid was added dropwise to a solution of 0.53 mol of trimethylamine oxide in 150 ml. of chloroform. The reaction began immediately.

After the addition was completed, the chloroform solution was washed thoroughly with 2 N hydrochloric acid and then with sodium bicarbonate solution. It was dried and distilled.

Boiling Point of obtained octanol: $B.P._{11}$ 65° C. Yield: 10 g.

EXAMPLE 5

Preparation of Isovaleraldehyde

Using the same procedure as in Example 2.

0.027 mol of isoamyl bromide and 0.53 mol trimethylamine oxide were reacted to give isovaleraldehyde. $B.P._{760}$ 92°. Yield: 18 g.

EXAMPLE 6

Reaction of Di-n-Amyl Sulfate With Timethylamine Oxide

With cooling 0.15 mol of di-n-amyl sulfate was added dropwise to a solution of 0.4 mol of trimethylamine oxide in 200 ml. of methylene chloride. A perceptible reaction took place. After the addition was completed, the mixture was heated 10 minutes up to boiling. The ammonium salt formed was removed by washing with 2 N sulfuric acid and the organic solution was distilled to remove solvents. There was recovered as a residue n-valeraldehyde in a yield of 7.4 g.

EXAMPLE 7

Preparation of Dodecanal-1

0.2 mol of n-dodecyl bromide was added dropwise with slight heating and agitation to a solution of 0.4 mol of trimethylamine oxide in 150 ml. of chloroform. After the addition the solution was boiled under reflux for 20 minutes. The solution was cooled and treated with double its volume of ether. Thereby the ammonium salt formed precipitated and was separated. The ether-chloroform solution was washed thoroughly with 2 N hydrochloric acid and then aqueous sodium bicarbonate solution and dried. After removal of the solvents, the residue was fractionated to obtain dodecanal-1.

Boiling Point: $B.P._{22}$ 144–145°. Yield 21 g.

EXAMPLE 8

Preparation of Palmiticaldehyde

0.2 mol of cetyl iodide was slowly added dropwise to a solution of 0.5 mol of trimethylamine oxide in 150 ml. of chloroform. During the dropwise addition, the chloroform solution was heated slightly. The solution was boiled under reflux for 30 minutes. After cooling, the chloroform solution was treated with 400 ml. ether, whereby all of the ammonium salt formed was precipitated. The precipitate was separated, the ether-chloroform solution washed with 2 N hydrochloric acid and aqueous sodium bicarbonate solution and dried.

The solvent was distilled under nitrogen. The residue crystallized on standing to give palmitic aldehyde, melting point 35° C. Yield 24 g.

Using the same procedure as Example 8 but replacing the cetyl iodide with 0.2 mol of the cetyl alcohol ester of chlorosulfonic acid an equally good yield of palinitic aldehyde was obtained. Similarly using 0.2 mol of cetyl bromide in place of cetyl iodide gave a good field of palmitic aldehyde.

EXAMPLE 9

Preparation of Stearic Aldehyde

Using the method of Example 8, 0.2 mol of stearyl chlorosulfonate was reacted with 0.5 mol of trimethylamine oxide in 150 ml. of chloroform to give stearicaldehyde, melting point 38° C. in a yield of 22 g.

EXAMPLE 10

Preparation of Benzaldehyde

0.2 mol of anhydrous trimethylamine oxide was dis-

solved in 55 ml. of chloroform and charged into a three-neck flask equipped with an agitator, dropping funnel, and reflux condenser. With cooling, 0.1 mol of benzyl chloride was added dropwise. Then the mixture was heated slowly to boiling and boiled under reflux for 50 minutes. After cooling, the solution was treated with an equal volume of 2 N hydrochloric acid, the layers are separated, and the chloroform solution was washed with aqueous sodium bicarbonate solution. The chloroform solution was dried and distilled.

Yield of benzaldehyde: 46% of theory. Similar yields of benzaldehyde were obtained by replacing the benzyl chloride by 0.1 mol of benzyl bromide in Example 10.

EXAMPLE 11

Preparation of Benzaldehyde

The procedure of Example 10 was modified by replacing the benzyl chloride with 0.2 mol benzyl tosylate and by utilizing 0.4 mol of trimethylamine oxide in 110 ml. of chloroform. The benzaldehyde was obtained in a yield of 45% of theory.

EXAMPLE 12

Preparation of p-Nitrobenzaldehyde

0.2 mol of anhydrous trimethylamine oxide was dissolved in 60 ml. of chloroform and charged into a three-neck flask equipped with agitator, reflux condenser, and dropping funnel. With cooling, 0.15 mol p-nitrobenzyl chloride dissolved in 50 ml. of chloroform was added dropwise. The reaction solution became warm. After the addition was completed, the mixture was allowed to stand another 10 minutes at room temperature, then shaken thoroughly with 2 N sulfuric acid, the aqueous layer separated, and the chloroform layer dried and evaporated under vacuum. The p-nitrobenzaldehyde remained behind, as a residue having a melting point of 107° C. The yield was 12.1 g.

EXAMPLE 13

Preparation of p-Tolylaldehyde

0.2 mol of anhydrous trimethylamine oxide was dissolved in 60 ml. of chloroform and with agitation was treated with 0.15 mol of p-methylbenzyl chloride. The halide was slowly added dropwise. Subsequently the mixture was boiled under reflux for 20 minutes. The chloroform solution was washed thoroughly with 2 N sulfuric acid and dried. After removing the solvents, the p-tolylaldehyde remained behind.

Boiling Point 204° C. Yield 9.2 grams.

EXAMPLE 14

Preparation of Cinnamaldehyde

0.2 mol of anhydrous trimethylamine oxide was dissolved in 60 ml. of chloroform. With agitation and cooling, a solution of 0.1 mol of cinnamyl chloride in 50 ml. of chloroform was added dropwise. The reaction solution became warm. After the addition was completed, the mixture was allowed to stand at room temperature for 20 minutes. Then the chloroform solution was washed with 2 N sulfuric acid and dried. After the removal of the solvent, the cinnamaldehyde remained behind, $B.P._{12}$ 158° C. Yield 6.4 g.

EXAMPLE 15

Preparation of Cyclopentanone

0.2 mol of cyclopentyl bromide was added dropwise to a solution of 0.4 mol of trimethylamine oxide in 110 ml. of chloroform. At the beginning the mixture was heated slightly. After the addition of the cyclopentyl bromide was completed the mixture was heated under reflux for 1½ hours. The ammonium salt formed was removed by washing with 2 N hydrochloric acid. After drying, the chloroform was distilled off. The cyclopentanone residue had a $B.P._{760}$ 130° C. and was obtained in a yield of 10 g.

EXAMPLE 16

Preparation of Cyclooctanone

0.2 mol of anhydrous trimethylamine oxide was dissolved in 60 ml. of chloroform. With agitation 0.1 mol of cyclooctyl bromide was added dropwise. Then the mixture was boiled under reflux for 30 minutes. The ammonium salt formed was removed by washing with 2N sulfuric acid. The solvent was removed by distillation. The cyclooctanone remained behind.

Boiling point 197° C. Yield 8.1 g.

EXAMPLE 17

Preparation of Cyclooctanone

0.2 mol of anhydrous trimethylamine oxide was dissolved in 100 ml. of methylene chloride. With agitation 0.1 mol of the cyclooctyl ester of chlorosulfonic acid was added dropwise then the mixture was boiled under reflux for 30 minutes. The mixture was allowed to cool and the ammonium salt formed was then precipitated by the addition of ether and removed. The solvent was then distilled off to leave a residue of the desired cyclooctanone, B.P. 197.

EXAMPLE 18

Preparation of Diethyl Ketone

Utilizing the procedure of Example 16 0.15 mol of the n-pentan-ol-3 ester of p-toluene sulfonic acid was reacted with 0.2 mol of trimethylamine oxide to produce 7.2 grams of pentanone-3 (diethyl ketone).

I claim:

1. A process of preparing a carbonyl compound of the group consisting of aldehydes and ketones comprising reacting trimethylamine oxide with an alkylating agent having a formula selected from the group consisting of

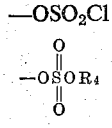
and R_2CHX

where R is selected from the group consisting of hydrogen, alkyl and aryl;

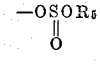
R_1 is selected from the group consisting of alkyl, alkenyl, aryl, aralkenyl, nitroaryl and haloaryl;

R_2CH is selected from the group consisting of cycloalkyl and cycloalkenyl;

and X is selected from the group consisting of halogen, R_3SO_2O —where R_3 is selected from the group consisting of alkyl and aryl,



where R_4 is alkyl, and



where R_5 is alkyl.

2. A process according to claim 1 wherein the molar ratio of trimethylamine to the alkylating agent lies between the limits 1:1 and 4:1.

3. A process according to claim 1 wherein the reaction is carried out in an organic solvent selected from the group consisting of polychlorinated aliphatic hydrocarbons, dioxane, aromatic hydrocarbons, tetrahydrofurane and dimethyl formamide.

4. A process according to claim 3 wherein the reaction is carried out with heating at a temperature up to the boiling point of the solvent.

5. A process according to claim 1 wherein the reaction is carried out in an organic solvent, and the reaction

solution is acidified with aqueous mineral acid, separated from the acid, washed with alkaline bicarbonate solution and then the carbonyl compound is recovered by removing the solvent by distillation.

6. A process according to claim 1 wherein the reaction is carried out in an organic solvent, the ammonium salt formed is precipitated from the reaction solution by the addition of ether and the precipitate is separated from the solution.

7. A process of preparing an aldehyde comprising reacting anhydrous trimethylamine oxide with a primary alkyl halide having at least two carbon atoms, the halogen of said halide having an atomic weight of between 35 and 127.

8. A process of preparing an aldehyde comprising reacting anhydrous trimethylamine oxide with a primary dialkyl sulfate, said alkyl groups having at least two carbon atoms.

9. A process of preparing an aldehyde comprising reacting anhydrous trimethylamine oxide with an aralkenyl halide having a single aromatic ring, the halogen of said halide having an atomic weight between 35 and 127.

10. A process of preparing a cyclic ketone comprising reacting anhydrous trimethylamine oxide with a cycloalkyl halide, the halogen of said halide having an atomic weight between 35 and 127.

11. A process of preparing a dialkyl ketone comprising reacting anhydrous trimethylamine oxide with a secondary alkyl halide having at least three carbon atoms, the halogen of said halide having an atomic weight between 35 and 127.

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