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ORGANIC SYNTHESIS BY MEANS OF METAL COMPLEXES. XV[1]
FACILE OXIDATIVE CONVERSION OF ACID HYDRAZIDES TO ACIDS, ESTERS AND AMIDES WITH OXYGEN ACTIVATED BY COPPER SALTS

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Acid hydrazides can be converted into acids, esters and amides by oxidation with molecular oxygen activated by copper salts in high yields.

The formation of highly crystalline acid hydrazides is a common method for purification, identification and characterization of carboxylic acids. Also acid hydrazides have a potential use as a protecting group of a carboxylic acid group. But the potential utility and applicability as the protecting group are diminished considerably owing to their high hydrolytic stability. Thus a mild procedure for regenerating acids from hydrazides is desirable which is rapid and does not affect other sensitive groups present in the molecule. Acid hydrazides can be cleaved oxidatively by using oxidizing agents such as lead tetraacetate,[2] ceric ammonium nitrate[3] and manganese dioxide.[4] However, these reagents are powerful and can not tolerate certain labile groups. We now wish to report oxidative cleavage of hydrazides to form not only original acids, but also esters and amides with oxygen activated by copper salts at room temperature. The reaction conditions are mild and a high yield is obtained. We found that acid hydrazides are converted to acids most conveniently by oxidation in the presence of cupric acetate in methanol.

$$RCONHNH_2 + O_2 \longrightarrow RCOOH + N_2 + H_2O$$

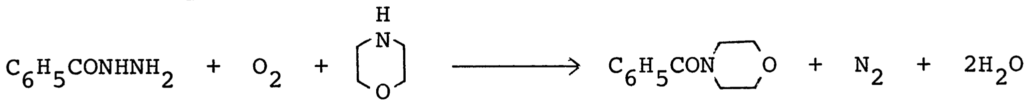
In a typical example, cupric acetate(2.0 g) was dissolved in methanol(25 ml), and the benzoylhydrazine(0.68 g) in methanol(10 ml) was added dropwise in 20 min at room temperature. The solution was stirred for 30 min. Oxygen or air was bubbled throughout the reaction. Methanol was evaporated and the residue was treated with dichloromethane and aqueous hydrochloric acid. From the organic layer, benzoic acid was isolated in 95% yield. When the addition of the benzoylhydrazine solution was too fast, N,N'-dibenzoylhydrazine was formed as a byproduct. It should be pointed out that benzoic acid was obtained selectively and no methyl benzoate was formed even though the reaction was carried out in dry methanol. For this reaction, besides cupric acetate, copper acetylacetonate showed the similar activity. Cuprous chloride was less active, but it showed the high activity in pyridine instead of methanol. Cupric nitrate, cupric chloride, and cuprous oxide showed no activity. Similarly caproylhydrazine was converted into caproic acid in 78% yield.

In order to convert acid hydrazides into corresponding esters, the reaction was carried out with cuprous methoxide formed in situ by the treatment of cuprous chloride with sodium methoxide in excess methanol. By adding a methanolic solution of benzoylhydrazine(2.72 g) into the methanolic cuprous methoxide (from 3.26 g of CuCl) at room temperature with bubbling of oxygen, methyl benzoate was obtained in 83% yield.

$$C_6H_5CONHNH_2 + O_2 + Cu(OCH_3) \longrightarrow C_6H_5COOCH_3 + N_2 + H_2O + CuOH$$

When the oxidation was carried out in a mixture of pyridine and methanol in the presence of cuprous chloride, a mixture of the ester and free acid was formed. The ratio of these two products changed depending on the ratio of pyridine and methanol, but the selective formation of the ester was not possible. The conversion of hydrazides to esters by treatment with chloral in alcohol was reported[5], but the present method of oxidation seems to be more simple.

Finally, conversion of hydrazides to amides was achieved by carrying out the oxidation in an amine solution of cupric acetate. A solution of benzoylhydrazine (0.68 g) in morpholine(10 ml) was added slowly in 20 min to a solution of cupric acetate(2.0 g) in morpholine(25 ml) with bubbling of oxygen. After 30 min volatile material was removed by evaporation under reduced pressure and the residue was treated with dichloromethane and dilute hydrochloric acid. From the organic layer, N-benzoylmorpholine was obtained in 75% yield. Also benzoic acid was isolated as a byproduct in 20% yield.



The above mentioned oxidative cleavage reactions can be explained by the stepwise oxidation mechanism of the hydrazide group to form acyl cation with liberation of nitrogen and water. The acyl cation then reacts with nuclephiles such as water, alcohol and amine.

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