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FACILE OXIDATIVE CONVERSION OF HYDRAZIDES OF CARBOXYLIC ACIDS TO CORRESPONDING ACIDS, ESTERS AND AMIDES USING COPPER COMPOUNDS

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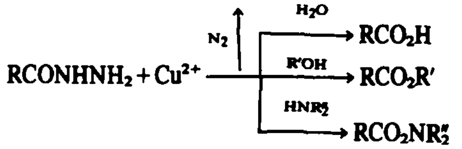
Abstract—Oxidative conversion of hydrazides of carboxylic acids to acids, esters and amides using Cu salts was studied. Acids were obtained in high yields by using a catalytic amount of $Cu(OAc)_2$ at room temperature by bubbling oxygen. Hydrazides were converted to esters by the treatment with Cu(OR)Cl or $Cu(OR)_2$ formed *in situ* from $CuCl_2$ and sodium alkoxide. Amides were obtained in high yields by the oxidation of hydrazides with $CuCl_2$ in the presence of amines.

In our continuous effort to oxidise organic compounds, especially various nitrogen compounds, with oxygen under mild conditions using Cu salts as a catalyst, we found smooth oxidative conversion of *o*-phenylenediamine to *cis,cis*-muconitrile,[1,2] and dihydrazones of α-diketones to acetylenic compounds.[3,4] These oxidation reactions proceed at room temperature with a catalytic amount of CuCl in pyridine pretreated with oxygen.

Also we found that hydrazide of carboxylic acids can be converted oxidatively to acids by using Cu salts under mild conditions. Acid hydrazides are usually crystalline compounds and used for identification and purification of carboxylic acids. In addition, acid hydrazides could be used as a protecting group of carboxylic acids, if there would be a suitable method to regenerate acids or esters from them under mild conditions without affecting sensitive functional groups present in the acid molecules. A common method of hydrolysis of hydrazides using acid or base as a catalyst is achieved usually by heating for a long period of time, and the method can not be applied to sensitive molecules. Another method is oxidative cleavage reaction. For this purpose, lead tetraacetate,[5,6] ceric ammonium nitrate[7] and manganese dioxide[8] are used. But these oxidising agents are too powerful to tolerate certain labile functional groups. Also more than stoichiometric amounts of the reagents are consumed. In this sense, the method for converting acid hydrazides to carboxylic acids described in this paper is the most convenient one because it utilises Cu salts as a catalyst and oxygen as an oxidising agent. The reaction proceeds smoothly in organic solvents at room temperature without using a strong acid or base to give corresponding carboxylic acids in high yields. Mild conditions and high yields make the method very useful for a synthetic purpose. In addition, the usefulness of the method is further augumented by the fact that not only carboxylic acids, but also esters and amides can be prepared directly from hydrazides in high yields under mild conditions, although stoichiometric amounts of Cu compounds are used in the latter cases. These transformations are not possible by other means.



$$RCONHNH_2 + Cu^{2+} \xrightarrow{-N_2} \begin{cases} \xrightarrow{H_2O} RCO_2H \\ \xrightarrow{R'OH} RCO_2R' \\ \xrightarrow{HNR''_2} RCO_2NR''_2 \end{cases}$$

Preliminary accounts of these reactions have already been given,[4,9] and the details of the method are presented in this paper.

RESULTS AND DISCUSSION

Formation of carboxylic acids

(a) *Stoichiometric oxidation to carboxylic acids*. We found that acid hydrazides are converted to carboxylic acids using several Cu^{2+} salts as an oxidising agent. For this study, octanohydrazide and benzohydrazide were used as representative aliphatic and aromatic acid hydrazides. Among several Cu^{2+} salts tested, the highest activity was observed with $Cu(OH)_2$ and Cu(OH)Cl, which were prepared *in situ* by the reaction of $CuCl_2$ with KOH in THF. The oxidation was carried out in THF at room temperature in the absence of oxygen. The stoichiometric oxidation of octanohydrazide proceeded rapidly with four moles of $Cu(OH)_2$ in THF at room temperature under N_2. Octanoic acid was obtained in 90% yield with quantitative evolution of N_2. Similarly benzoic acid was obtained in 92% yield from benzohydrazide. It was confirmed that at least four moles of Cu^{2+} salt are necessary for the oxidation of one mole of hydrazides in the absence of oxygen.

$$RCONHNH_2 + 4Cu(OH)_2 \rightarrow RCO_2H + N_2 + 3H_2O + 4[CuOH]$$

$CuCO_3$ is less active and the reaction proceeded slowly at room temperature, but rapidly at 70°. The reaction was very slow with $Cu(OAc)_2 \cdot H_2O$ at room temperature, but at 70° octanohydrazide was converted to octanoic acid in 90% yield by the reaction of four moles of $Cu(OAc)_2$ in THF. The oxidation with $Cu(OAc)_2$ carried out in methanol gave octanoic acid (57%) and methyl octanoate

(28%) at 70°. But the reaction with $Cu(OAc)_2$ proceeded at room temperature in THF under O_2. Other Cu^{2+} salts, such as $CuCl_2$, $Cu(NO_3)_2$, $CuSO_4$ and CuO, which have low solubility in THF or methanol were not active at room temperature and at 70°. CuCl in pyridine, pretreated with oxygen, was active.

(b) *Catalytic oxidation to carboxylic acids.* A catalytic reaction is most desirable for preparative purpose. It is well-known that Cu^{1+} salts are oxidised to Cu^{2+} very easily with oxygen. Therefore, the possibility of catalytic oxidation of hydrazides to acids under oxygen using a catalytic amount of Cu^{2+} salts was investigated and we found that actually the reaction proceeded catalytically. Easily available $Cu(OAc)_2$ in THF or methanol was found to be the most convenient reagent for the catalytic oxidation. The reaction was carried out by adding a THF solution of hydrazide slowly into a THF solution of $Cu(OAc)_2$ in a flask by bubbling oxygen at a room temperature. When the addition of hydrazide was too fast, N,N'-diacylhydrazine was formed in a considerable amount.

$$RCONHNH_2 + O_2 \xrightarrow{Cu(OAc)_2} RCO_2H + N_2 + H_2O + [RCONHNHCOR].$$

As shown in Table 1, the catalytic oxidation was carried out with different amounts of $Cu(OAc)_2$ in THF. As was confirmed in the stoichiometric reaction, four moles of $Cu(OAc)_2$ are equivalent amount for one mole of hydrazide. The reaction proceeded equally well when the amount of $Cu(OAc)_2$ was decreased to 1/16 equivalent. But the yield somewhat decreased with 1/32 equivalent. The method is applicable to both aromatic and aliphatic acid hydrazides. When the reaction was carried out in methanol as a solvent without addition of water, free carboxylic acid was formed as a predominant product and methyl ester was obtained as a minor product. The effect of some substituents on aromatic ring of benzohydrazide was tested in methanol. As shown in Table 2, various substituted benzohydrazides were oxidized smoothly to give corresponding acids as main products. However, the oxidation of *p*-nitrobenzohydrazide was abnormal. Although the oxidation took place, the main product was methyl *p*-nitrobenzoate and the minor product was free acid.

Formation of esters from hydrazides

As described above, the catalytic oxidation with $Cu(OAc)_2 \cdot H_2O$ in methanol produced mainly free carboxylic acids, and methyl esters were formed only as the minor product. This result suggests that water formed by the oxidation attacks preferentially the acyl cation formed as an intermediate even though a large excess of methanol is present. In order to prepare esters directly from hydrazides, the reaction was carried out using CuCl in a mixture of pyridine and methanol under oxygen atmosphere. In this system, the formation of $Cu(OCH_3)Cl$ is assumed.[10]

$$4CuCl + 4CH_3OH + O_2 + 4Py \rightarrow 2[PyCuCl(OCH_3)]_2 + 2H_2O.$$

Table 1. Yields of benzoic and octanoic acids by the catalytic oxidation of corresponding hydrazides with $Cu(OAc)_2 \cdot H_2O$ in THF

$Cu(OAc)_2 \cdot H_2O$/4×Hydrazide	1	1/2	1/4	1/8	1/16	1/32
Octanoic acid(%)	98	96	96	97	95	82
Benzoic acid(%)				96	95	

a. concentration of the hydrazide = 2.5/20 (mmol/ml of solvent)

b. The reaction was carried out at room temperature.

Table 2. Yields of substituted benzoic acids by the catalytic oxidation of their hydrazides in methanol

Substituents \ $Cu(OAc)_2 \cdot H_2O$/4×Hydrazide (mol/mol)	1/2	1/8	1/16
H	95 (0)%	82 (trace)%	70 (trace)%
o-CH_3	89 (7)	73 (20)	61 (14)
m-CH_3	82 (14)	74 (20)	63 (17)
p-CH_3	85 (14)	86 (14)	75 (13)
p-OCH_3	90 (8)	94 (5)	68 (16)
p-Cl	92 (7)	80 (16)	80 (16)
p-NO_2	40 (40)	20 (68)	18 (76)

The numbers in parentheses indicate the yield of methyl esters.

A considerable amount of methyl ester (up to 50%) was formed, but simultaneous formation of free carboxylic acid could not be minimized due to the formation of water during the oxidation, and this is not a satisfactory system for selective formation of the ester. Then we found that Cu(OR)Cl formed *in situ* from $CuCl_2$ by the reaction of one equivalent of sodium alkoxide in THF for 30 min is a good oxidizing reagent for the formation of ester. By using at least four moles of Cu(OMe)Cl formed *in situ* by the reaction of $CuCl_2$ with sodium methoxide in THF for one mole of octanohydrazide, methyl octanoate was obtained in 86% yield with 10% of octanoic acid at room temperature with rapid evolution of nitrogen.

$$RCONHNH_2 + 4Cu(OCH_3)Cl \rightarrow RCO_2CH_3 + 4CuCl + N_2 + 3CH_3OH.$$

As shown in Table 3, the reaction was carried out at room temperature with various Cu(OR)Cl and corresponding methyl (86%), n-butyl (80%), cyclohexyl (77%) and t-butyl esters (77%) were obtained. At the same time free octanoic acid was formed as minor products. When a large amount of alcohols is available, a satisfactory yield of the esters can be obtained from hydrazides by carrying out the oxidation using alcohol as the solvent instead of THF and alkoxide as the oxidising agent. It should be noted that the sterically hindered t-butyl ester was obtained in 77% yield. Then the different amounts of Cu(t-BuO)Cl were used to oxidise octanohydrazide and the results are shown in Table 4. It is apparent that four moles of the oxidant are necessary for one mole of hydrazide to give esters in a high yield. Also the oxidation was carried out in DMF and pyridine, instead of THF, but the yields of methyl octanoate were 54% and 46% respectively.

In addition to Cu(OR)Cl, satisfactory results were obtained with $Cu(OR)_2$ formed from $CuCl_2$ with two equivalents of sodium alkoxide. When benzohydrazide was oxidised with an equivalent amount of Cu(OR)Cl, the yield of the ester was low. Satisfactory yields of t-butyl benzoate (83%) was obtained by using $Cu(t\text{-}BuO)_2$ instead of Cu(t-BuO)Cl.

Formation of amides from hydrazides

Then the transformation of hydrazides to amides was attempted. $Cu(OAc)_2$ was found to be active in amines, but the best results were obtained by using $CuCl_2$. The reaction of octanohydrazide was carried out in THF containing $CuCl_2$ and pyrrolidine (1:5:5) under nitrogen atmosphere at room temperature and the corresponding octanamide was obtained in nearly quantitative yield without forming free octanoic acid. The oxidation was carried out with different amounts of amines in order to determine the minimum amounts of amine required. As shown in Table 5, about five moles of amine were necessary for one mole of hydrazide. Presumably, four moles of amine are consumed to neutralise the liberated hydrogen chloride. Not only pyrrolidine, but less basic

Table 3. Yields of esters of octanoic acid by the oxidation with Cu(OR)Cl

R	Nitrogen evolved (%)	Yield (%)	
		Ester	Acid
CH_3	100	86	12
n-Bu	98	80	19
Cyclohexyl	99	77	16
t-Bu	98	77	18

Cu(OR)Cl/4×Hydrazide = 1.25

Rate of addition of the hydrazide = 1 (mmol/hr)

Table 4. Yields of t-butyl octanoate formed with different amounts of Cu(O-t-Bu)Cl

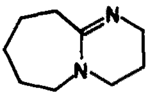
Cu(O-t-Bu)Cl/4×Hydrazide	Nitrogen evolved (%)	Yield (%)	
		t-Butyl octanoate	Octanoic acid
0.75	76	60	17
1.00	100	78	22
1.25	98	77	20
2.00	96	76	18

Rate of addition of the hydrazide = about 1 (mmol/hr)

The concentration of the hydrazide = 2.5 mmol/20 ml of THF morpholine and ammonia were used to give similar results as shown in Table 6.

It was found that only one equivalent of amine is enough when diazabicycloundecene (DBU) was used as a ligand of $CuCl_2$. As shown in Table 7, high yields of amides were obtained by using one equivalent of amine in the presence of $CuCl_2$ and DBU (1:1 molar).

As a related reaction, oxidative conversion of N-tosylhydrazides with lead tetraacetate in amines to give amides has recently been reported.[11] But the present method using $CuCl_2$ is simpler and gives better yields.



DBU

Table 5. Yields of amides of pyrrolidine from octanohydrazide using $CuCl_2$

Pyrolidine/Hydrazide (mol/mol)	Nitrogen evolved(%)	Yield(%)	
		Amide(%)	Acid(%)
72.0	100	99	0
5.0	100	99	0
4.0	96	94	0
3.0	90	79	trace
2.5	85	70	trace
1.25	77	22	44
1.0	70	16	62

$CuCl_2$/Hydrazide = 5 (mol/mol) = 1.25 equiv.

Rate of addition of the hydrazide = about 1.5 (mmol/hr)

The concentration of the hydrazide = 2.5 mmol/20 ml of THF

Table 6. Yields of various amides by using $CuCl_2$

Amine	Yield(%)	
	Octamide	Benzamide
Pyrrolidine	99	94
Morpholine	96	94
Ammonia[b]	93	89

a. $CuCl_2$/Hydrazide = 5 (mol/mol)

Amine/Hydrazide = 5 (mol/mol)

Rate of addition of the hydrazide = about 1.5 (mmol/hr)

b. Ammonia was saturated in THF.

Table 7. Yields of amides by using $CuCl_2$-DBU complex

Amine	Yield(%)	
	Octanamide	Benzamide
Pyrrolidine	96	95
Morpholine	93	95
i-ButylAmine	92	93

$CuCl_2$/Hydrazide = 5 (mol/mol)

DBU/Hydrazide = 5 (mol/mol)

Amine/Hydrazide = 1 (mol/mol)

Rate of addition = 1.5 (mmol/hr)

Reaction mechanism

The formation of acids, esters, and amides by the reactions of water, alcohols and amines suggests the intermediacy of acyl cation. Nucleophilic attack of water, alcohols and amines to the acyl cation gives acids, esters and amides respectively. The formation of the acyl cation as the intermediate is explained by the stepwise four-electron oxidation of hydrazide. Cu^{2+} ion is one electron donor and hence four moles of Cu^{2+} are required to form the acyl cation. Thus it is reasonable that four moles of Cu reagents were used in the stoichiometric oxidation. On the other hand, it is known that Cu^{1+} can be oxidised to Cu^{2+} state easily with oxygen. Therefore, it is possible to carry out the oxidation with a catalytic amount of Cu^{2+} ion by bubbling oxygen. In this case, the reoxidation of the reduced Cu^{1+} to Cu^{2+} with oxygen takes place to form a catalytic cycle.

$$RCONHNH_2 + 3CuXY \rightarrow R\dot{C}O + 3CuX + 3HY + N_2$$

$$R\dot{C}O + CuXY \rightarrow RCO^+ + CuX + Y^-$$

$$RCO^+ + Y^- \rightarrow RCOY$$

$$Y = OH, OR, NR_2$$

EXPERIMENTAL

Materials. All Cu salts used in the experiments were commercial products and used without purification.

Experimental procedure. All oxidations were performed in a similar way and only typical examples are shown below.

Stoichiometric oxidation of benzohydrazide to benzoic acid in THF. The reaction was carried out in a 3-necked flask connected to a gas burrett. A soln of $Cu(OH)_2$ was prepared *in situ* by the treatment of $CuCl_2$ (1.35 g, 10 mmol) with powdered KOH (1.12 g, 20 mmol) in THF (25 ml) at room temp for 30 min. Then a soln of benzohydrazide (0.34 g, 2.5 mmol) in THF (20 ml) was added dropwise in 1 hr. During the addition, rapid evolution of N_2 was observed. The mixture was neutralised with 6N-HCl and the soln was concentrated. Then CH_2Cl_2 was added. The acidic component was extracted with a sat $NaHCO_3$ aq, from which the acid was extracted again with CH_2Cl_2 after acidification. Benzoic acid was obtained as crystals after evaporation of CH_2Cl_2 (0.28 g, 92%, m.p. 122.5°).

Catalytic oxidation of octanohydrazide to octanoic acid with $Cu(OAc)_2 \cdot H_2O$ *in THF.* A soln of octanohydrazide (0.396 g, 2.5 mmol) in THF (20 ml) was added dropwise to a soln of $Cu(OAc)_2 \cdot H_2O$ (0.25 g, 1.25 mmol) in THF (25 ml) at room temp in 2 hr. During the addition, O_2 was bubbled continuously. After evaporation of the solvent, the mixture was dissolved in ether. The ethereal soln was extracted with $NaHCO_3$ aq. The extract was acidified again and reextracted with CH_2Cl_2. The organic layer was dried and the solvent was evaporated. AcOH was removed by distillation and chromatographic purification of the residue afforded octanoic acid (0.35 g, 97%).

Oxidation of octanohydrazide to methyl octanoate. $CuCl_2$ (3.36 g, 25 mmol) was added slowly to a soln of NaOMe (1.35 g, 25 mmol) in THF (50 ml) under N_2 and the soln was stirred for 30 min to prepare $Cu(OCH_3)Cl$. Then a soln of octanohydrazide (0.79 g, 5 mmol) in THF (40 ml) was added slowly over a period of 5 hr. The dark brown color of the soln changed to pale brown during the reaction. After neutralisation, most of the solvent was evaporated and the residue was extracted with CH_2Cl_2. The extract was dried with Na_2SO_4 and evaporated. Chromatographic purification of the residue afforded methyl octanoate (0.68 g, 86%) and octanoic acid (0.09 g, 12%). The structure was confirmed by comparing IR and NMR spectra with those of an authentic sample.

Oxidation of benzohydrazide to amide of morpholine by DBU complex of $CuCl_2$. In a 50 ml 3-necked flask, equipped with a magnetic stirrer, and a dropping funnel, DBU (0.96 g, 6.25 mmol), morpholine (0.11 g, 1.25 mmol) and THF (12 ml) were placed. To the mixture, $CuCl_2$ (0.84 g, 6.25 mmol) was added in several portions to form a green soln. Then, a soln of benzohydrazide (0.17 g, 1.25 mmol) in THF (10 ml) was added dropwise in 1 hr under N_2. Most of the solvent was evaporated, and the residue was treated with 40 ml of 6N HCl at 0°. Then the mixture was extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ aq and dried. Evaporation of the solvent gave the amide of morpholine (0.227 g, 95%). The structure was determined by its IR and NMR spectra.

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