Effect of Metal Ions in Organic Synthesis; VII. Conversion of Acylhydrazines and *N*-Acyl-*N'*-tosylhydrazines to Carboxylic Acids and Esters in the Presence of Copper(II) Chloride

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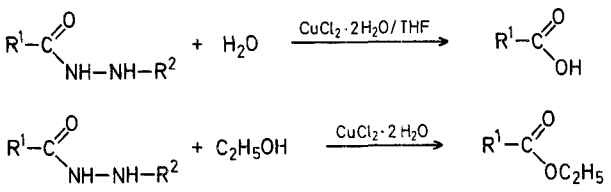
The role of transition and non-transition metals in organic chemistry and biochemistry has in recent years received increasing attention due to the ability of some metal ions to form complexes with various organic and in particular bioorganic ligands[1,2,3]. We have previously investigated the effects of copper and iron ions in certain organic reactions[1,2] and have now studied the hydrolysis and alcoholysis of some carboxylic acid hydrazides in the presence of copper(II) chloride hydrate.

Hydrazide derivatives of carboxylic acids are not only useful educts, intermediates, and products in organic and bioorganic chemistry and derivatives for identification of carboxylic acids[4,5], the carboxylic hydrazide moiety may also be used as a protective group, e.g., in peptide synthesis. Unfortunately, acylhydrazines may be highly resistent to hydrolysis so that their conversion into the carboxylic acids often requires strongly basic or acidic media or even the use of strong oxidizing agents (oxidative cleavage). These conditions may be incompatible with sensitive substrates or with insufficiently stable groups present in the molecule[6].

It has been shown[7] that hexanoylhydrazine and benzoylhydrazine can be cleaved to give the parent carboxylic acid by bubbling oxygen or air through a solution of the hydrazide in methanol in the presence of copper(II) acetate or copper(II) acetylacetonate at room temperature [copper(I) chloride was found to be less active and copper(II) nitrate, copper(II) chloride, or copper(I) oxide showed no activity], and that benzoylhydrazine can be converted into methyl benzoate by bubbling oxygen through a solution of benzoylhydrazine in methanol containing copper(I) methoxide [*in situ* from copper(I) chloride and sodium methoxide].

We report here that the cleavage of carboxylic acid hydrazides (acylhydrazines) and carboxylic *N'*-tosylhydrazides (*N*-acyl-*N'*-tosylhydrazines) can be achieved without the use of oxygen. Treatment of the acylhydrazines or *N*-acyl-*N'*-tosylhydrazines with copper(II) chloride dihydrate in tetrahydrofuran/water affords the parent carboxylic acids in 75–95% yields and treatment with the same reagent in ethanol affords the ethyl carboxylates in 80–95% yield.



R^1 = Alkyl, Aryl
R^2 = H, Tos

The reaction appears to be a hydrolytic or alcoholytic process rather than an oxidative cleavage. Two observations support this assumption: the hydrolytic cleavage proceeds with good yields also under a nitrogen atmosphere, and the ethanolytic cleavage proceeds with good yields and with formation of less by-products when it is carried out under exclusion of moisture and air [under nitrogen, use of anhydrous copper(II) chloride and anhydrous ethanol]; only traces of carboxylic acid could be detected when an acylhydrazine was treated with anhydrous copper(II) chloride. It is known that some reactions of the type discussed here can be catalyzed by copper[1,2,3]. The cleavage reactions described in this communication probably proceed via organometallic complexes which activate the —CO—NH— group. This assumption is an accordance with previous investigations of similar reactions[1,2] and with the well known role of metal ion-ligand and chelate complexes [in particular, copper(II) complexes having multidentate organic ligands] in organic and bioorganic chemistry (e.g., amino acids, proteins, enzymes).

The mild conditions used may make our cleavage method advantageous over other similar methods.

Carboxylic Acids from the Hydrolysis of Acylhydrazines; General Procedure:

A solution of copper(II) chloride dihydrate (0.47 g, ~2.75 mmol) in water (10 ml) is added to a stirred solution of the acylhydrazine (1.10 mmol) in tetrahydrofuran (50 ml), and stirring is continued for 18–20 h at room temperature. The mixture is then concentrated to a small volume under reduced pressure. The residue is extracted with ether (20 ml) and 10% aqueous sodium carbonate or sodium hydrogen carbonate (3 × 15 ml). The aqueous layer is separated, acidified with 10% aqueous sulfuric acid, and extracted with ether

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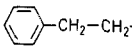
Table. Hydrolysis and Ethanolysis of Acylhydrazines in the Presence of Copper(II) Chloride Dihydrate

R^1	R^2	Carboxylic Acid			Ethyl Carboxylate		
		Yield[a] [%]	m.p. [°C]		Yield[a] [%]	b.p. [°C]/torr	
			found	reported[b]		found	reported[b]
	H	75	119–121	122.4	95	212–214	213
	H	85	74–76	77	95	226–228	227
n-$C_{15}H_{31}$–	H	95	60–62	63	80	189–192/10	191/10
	Tos	95	119–121		95	212–214	
	Tos	85	45–47	48.6	95	247–249	247.2
n-$C_{15}H_{31}$–	Tos	80	60–62		95	189–192/10	

[a] Isolated product, identified by comparison with authentic specimens.
[b] From *Handbook of Chemistry and Physics*, The Chemical Rubber Co., 51st Ed., 1970–1971.

(3 × 15 ml). The organic extract is washed with water (3 × 20 ml), dried with sodium sulfate, and concentrated under reduced pressure to afford the carboxylic acid in satisfactory purity. The product can be further purified by recrystallization from water.

Ethyl Carboxylates from the Ethanolysis of Acylhydrazines; General Procedure:

A solution of copper(II) chloride dihydrate (0.47 g, ~ 2.75 mmol) in ethanol (40 ml) is added to a stirred solution of the acylhydrazine (1.10 mmol) in ethanol (30 ml), and stirring is continued for 20–22 h at room temperature. The mixture is then concentrated to a small volume under reduced pressure. The residue is extracted with ether (20 ml) and 10% aqueous sodium hydroxide (3 × 15 ml). The organic phase is separated, washed with water (3 × 20 ml), dried with sodium sulfate, and evaporated under reduced pressure to afford the ethyl carboxylate in satisfactory purity. The product can be further purified by distillation.

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