Oxidation of Pyridines with Copper Sulfate (1)

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Received December 19, 1978

Oxidation of pyridine, 3-picoline, 3,5-lutidine, quinoline, isoquinoline and acridine with hydrated copper sulfate at high temperatures gives the corresponding pyridones, possibly *via* the intramolecular reaction of a base - Cu(II) complex. Overall conversions are rather poor. 2- And 4-picolines and their methyl homologues undergo some demethylation under these conditions and some picolinic acid is isolated from 2-picoline. 2- And 4-ethylpyridines give both pyridine and 2- and 4-picoline, respectively.

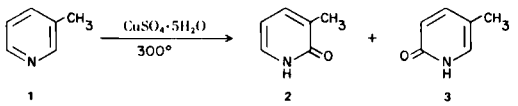
J. Heterocyclic Chem., **16**, 1283 (1979).

The reaction of 2-picoline with silver acetate in acetic acid under pressure was reported to give pyridine and metallic silver (2). This prompted us to study the possibility of effecting related redox reactions between pyridine and its derivatives and copper sulfate.

Indeed, fine grain metallic copper precipitates when pyridine and picolines are heated with hydrated copper sulfate. The yield of copper recovered depends, among other things, upon the nature and position of substituents in the heteroaromatic ring. For example, the yield of copper reached 91% with 2,4,6-collidine, 51% with 2-picoline and was only 6.5% with 3-picoline. This process has been considered suitable for the recovery of copper from aqueous solution of its salts (3,4), though the fate of the pyridines was not determined. We now describe some of the products (those that could be isolated) that are formed from pyridine, methylated pyridines, quinoline, isoquinoline and acridine.

When pyridine (0.1 mole) is heated with hydrated copper sulfate (0.06 mole) at 300°C, a high (95%) yield of 2-pyridone is formed, though the conversion is low (20%) and unreacted pyridine is recovered. Increasing the amount of copper sulfate used and/or the reaction time did not improve the percent conversion of pyridine. Cupric chloride did not effect any oxidation and a small amount of 5% sodium hydroxide solution inhibited the reaction completely. On the other hand, air had no influence on the reaction and neither did a small amount of hydrogen peroxide.

3-Picoline (**1**) underwent similar oxidation but in very much lower yield giving a 10% conversion to a mixture of 3-methyl-2-pyridone (**2**) (3.2%) and 5-methyl-2-pyridone (**3**) (6.8%) together with tars. Such a 2,3-/2,5- isomer ratio is rather typical of 3-picolines undergoing nucleophilic substitution by an intramolecular process (5), *e.g.* the Emmert reaction (6). On the other hand, intermolecular nucleophilic attack on 3-picoline usually leads to this ratio being greater than unity. 3,5-Lutidine gave a



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similarly low yield of 3,5-dimethyl-2-pyridone, together with copper and sulfur dioxide as usual. In all cases, the amount of copper formed is much higher than that of isolable identifiable pyridine derivatives and it appears that the tarry by-products also reduce copper sulfate efficiently.

On the other hand, no pyridones were isolated from the other methylpyridines studied. 2-Picoline (**4**) gave picolinic acid (**5**) (7.5%) and pyridine (7.7%). No acid could be isolated from the oxidation of 4-picoline, and only the dealkylation product, pyridine, was observed (4%). On the

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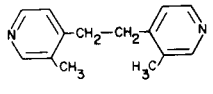
other hand, no dealkylation was observed with 3-picoline. The lutidines behaved similarly (see Table). Interestingly, with 2,4-lutidine only loss of the 4-methyl function was observed and the other dealkylated product and the di-dealkylated product were not detected by gas chromatography. In contrast, loss of a 2-methyl group and di-dealkylation was observed with 2,4,6-collidine (Table). 1,2-bis(3-Methyl-4-pyridyl)ethane (**6**) was also formed in very low yield from 3,4-lutidine. Again, much tar was formed with all the alkylated pyridines.



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2-Ethylpyridine (**7a**) gave both 2-picoline (**4**) (11.5%) and pyridine (1.9%), while 4-ethylpyridine (**7b**) behaved similarly, though the yields were still lower. As far as we are aware, this is the only example known of such an oxidation at the terminal atom of a side chain containing more than one carbon atom.

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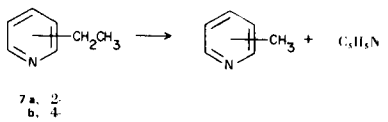
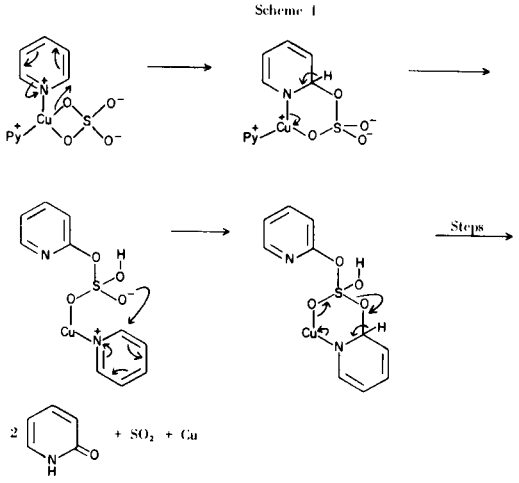


7a, 2
b, 4

Quinoline, isoquinoline, and acridine gave modest to low yields of carbostyril, 1-(2*H*)isoquinolone, and 9-(10*H*)-acridone, respectively. On the other hand, the three nitrotoluenes, the methylnaphthalenes and carbazole were not oxidized under the same reaction conditions.

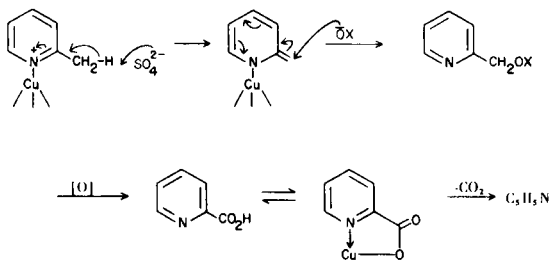
Cu(II) ions form a square plannar complex with four molecules of pyridine, but with two molecules of base in the case of 2-picoline and 2,6-lutidine (7). The formation of 2-pyridones from pyridine may be envisaged as taking place as sketched in Scheme 1 which takes into account the proposed intramolecularity of the process (*vide supra*). Here it is assumed that only two moles of base are initially involved in the square planar complex in the absence of solvent and at the high temperature used. Free radical processes (copper catalyzed) could also be involved in this and the other reactions described below but the absence of any effect by air or peroxide suggests this is not the case. It is not clear why the overall conversion is low but we suspect that solubility problems may be partly responsible.

Scheme 1



With the 2- and 4-picolines, hydrogen-abstraction may be taking place from the side-chain (which is energetically much less favored in the 3-methyl case):

Scheme 2



Formation of some 2-picolinic acid in the oxidation of 2-picoline may be owing to the formation of a relatively stable copper chelate (8). Such a chelate cannot be formed with isonicotinic acid which, therefore, undergoes decarboxylation under the reaction conditions. Since the stability constant of the corresponding 6-methylpyridine-2-carboxylic acid copper chelate is much lower (*ca.* 200 fold) than that of **8** (8) decarboxylation occurs much more readily and no acid is isolated. While one α-methyl group has only a small effect on the stability of complexes at the pyridine nitrogen atom, 2,6-dimethyl substitution leads to marked decreases in the stability constants (7,9). The unusual oxidation of not only the α- but also the β-carbon atom in 2- and 4-ethylpyridine remains to be explained, but a free radical process seems likely to be involved. We have not studied the effect of air or peroxides on this reaction.

While oxidation of quinoline and isoquinoline can be explained by involving Scheme 1, formation of acridone from acirdine probably requires an intermolecular pathway. Nucleophilic attack at C-9 of a complexed acridine would account for the small amount of acridone produced.

EXPERIMENTAL

All the pyridine bases were purified as described earlier (10). Their purity was checked by glc on a 3 x 0.0003 m column packed with 10% polyethylene glycol adipate on Chromosorb WNAN(60-80 mesh) with a column temperature of 92° for the picolines and 115° for the ethylpyridines. The nitrogen carrier gas flow rate was 100 ml./minute.

General Procedures in the Oxidations.

The pyridine base (0.1 mole) and cupric sulfate pentahydrate (0.06 mole) was heated at 300° for 8-10 hours in a steel autoclave (50 ml.) with a glass insert. When anhydrous cupric sulfate was used the yields were 50% lower.

Separation of the Pyridones.

The reaction mixture was evaporated to dryness (in the case of pyridine and its homologues) followed by extraction with hot benzene of the solid residue mixed with silica gel or with sand, or directly by continous extraction with benzene (in the cases of quinoline, isoquinoline, and acridine). The products separated on concentration of the extracts. The isomeric 3- and 5-methyl-2-pyridones were resolved by column chromatography on silica gel (0.063-0.02 mesh) using ethanol-benzene (3:17 v/v) as eluent. Products were compared with authentic samples prepared by the diazotization of the corresponding amine or from quinoline or isoquinoline using potassium hydroxide and potassium oxide (11).

Attempted Isolation of Carboxylic Acids.

The reaction mixtures resulting from heating methylpyridines with cupric sulfate pentahydrate were acidified with 4*N* sulfuric acid to *p*H 3, metallic copper was filtered off and the filtrate was saturated with hydrogen sulfide until precipitation of cupric sulfide was complete. This was filtered and the *p*H of the filtrate was adjusted to that corresponding to the isoelectric point of the expected pyridinecarboxylic acid. The solution was evaporated to

Table

Products of Oxidation at 300°

Base	Hydroxylation Product (a)	Recovered Base (%)	Dealkylation Product (a)	Copper (%)	Other Products (b)
Pyridine	2-pyridone, m.p. 107° (95%)	80			
2-Picoline (b,c)		83.7	Pyridine (7.7%)	51	Picolinic Acid m.p. 137° (7.5%)
3-Picoline	3-methyl-2-pyridone m.p. 140° (3.2%) 5-methyl-2-pyridone, m.p. 184° (6.8%)	80		6.5	
4-Picoline (c)		38.6	Pyridine (4.1%)	17	
2,3-Lutidine (c)		56	3-Picoline (0.5%)	22	
2,4-Lutidine (c)		45	2-Picoline (1.4%)	52	
2,6-Lutidine (c)		55	2-Picoline (2.8%)	64	
3,4-Lutidine (c)		20	3-Picoline (4.6%)	85	1,2-bis(3,3'-dimethyl-4,4'-dipyridyl)ethane m.p. 156-159° (0.16%)
3,5-Lutidine (c)	3,5-dimethyl-2-pyridone, m.p. 117° (10%)	80		12	
2,4,6-Collidine (c)		15	2-Picoline (1.0%) 2,6-Lutidine (1.48%) 2,4-Lutidine (2.0%)	91	
2-Ethylpyridine (c)		9.8	Pyridine (1.9%) 2-Picoline (11.5%)	88	
4-Ethylpyridine (c)		53	Pyridine (2.6%) 4-Picoline (1.6%)	60	
Quinoline	Carboxtyril m.p. 200° (25%)	70		13	
Isoquinoline	1-(2*H*)isoquinolone, m.p. 209° (17%)	80		10	
Acridine	9-(1*H*)acridone, m.p. 350° (1.2%)	95		0.65	

(a) Yields are calculated on the amount of base consumed. (b) The reaction can be carried out at 180° and gives the same yields as when carried out at 300°. (c) Tars are also formed.

dryness and the residue was extracted with hot benzene. Only picolinic acid, identical with an authentic sample, could be isolated.

1,2-bis(3,3'-Dimethyl-4,4'dipyridyl)ethane.

The mixture resulting from the oxidation of 3,5-lutidine (0.1 mole) was treated with anhydrous sodium carbonate (10 g.) and evaporated to dryness under reduced pressure. The residue was extracted with hot benzene, the extract concentrated and chromatographed on a column of silica gel (230-400 mesh). Elution with acetone gave the ethane (0.25 g., 0.16%): m.p. 156-159°; nmr (carbon tetrachloride): δ 8.55 (br s, 4, α-H), 7.18 (d, 2, $J_{\alpha,\beta}$ = 4 Hz, β-H), 3.15 (s, 2, CH_2), 2.6 (s, 6, CH_3).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.61; N, 13.19. Found: C, 79.24; H, 7.60; N, 13.69.

Dealkylation Products.

The reaction mixtures resulting from the oxidation of the methyl- and ethylpyridines were treated with concentrated aqueous potassium hydroxide and distilled under reduced pressure and the distillates dried over solid potassium hydroxide. The products were analyzed by glc as described above.

Acknowledgement.

The authors would like to thank the NSF Excess Foreign Currency Program for a grant #OIP75-02094 in support of this work.

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