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## COPPER-AMMONIA MEDIATED OXIDATION OF CARBONYL COMPOUNDS

Pramod K. Arora and Lawrence M. Sayre\* Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106

<u>SUMMARY</u>: Copper(II) in aqueous NH<sub>4</sub>OH, in most cases in conjunction with  $0_2$  or  $K_2S_2O_8$  as auxiliary oxidant, induces oxidative cleavage of ketones to nitriles when there is a good carbon electrofuge; for unactivated ketones, the main reaction observed is oxidative coupling of ketimines to give azines.

It has been reported that o-quinones are converted to semi-nitriles of muconic acid in the presence of NH<sub>3</sub> and a copper oxidant (e.g.,  $Cu^{II} \cdot O_2$ )<sup>1</sup> via the monoimine (eq 1).<sup>2</sup> In addition, PhCHO is converted to PhCN under the influence of  $O_2$  and a Cu(II) catalyst in methanolic ammonia containing NaOMe (eq 2).<sup>3,4</sup> Both reactions occur most readily under strongly basic conditions, suggesting that oxidation occurs via coordination of Cu(II) to the *deprotonated* imine.<sup>5</sup> The overall transformations correspond to a 2e oxidation (depicted below as 2e processes;  $Cu_{II}^{OX}$  represents Cu(III) or a binuclear Cu(II) species), though the actual mechanisms are unknown, and stepwise le oxidations via radical intermediates could also be involved.



Based on these observations, we figured that cleavage of carbonyl compounds to nitriles by Cu(II)-NH<sub>3</sub>-based oxidants might be a general reaction when one of the groups attached to the carbonyl carbon is a good electrofuge (e.g., H<sup>+</sup>, CO<sub>2</sub>, or stabilized carbocation). Our efforts to explore this possibility are described here. By itself, Cu(II) was usually found to be ineffective, in which case O<sub>2</sub> bubbling or more often the use of K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as auxiliary oxidant was needed to ensure good yields. A key feature of the NH<sub>4</sub>OH medium is the ability to achieve basic but homogeneous aqueous solutions of Cu(II) (ligation of NH<sub>3</sub> prevents precipitation of copper hydroxide species). For water-insoluble reactants, an organic cosolvent (CH<sub>3</sub>CN or pyridine) was employed. All reactions were conducted for 15 h at  $25^{\circ}$ C, and no attempts were made to optimize yields (low % conversions may merely represent slow reactions). In each case discussed below, we have not determined the oxidation mechanisms (le vs. 2e); the reactions are depicted as 2e processes for purposes of illustration only.

Besides confirming the Cu(II)-dependent conversion of substituted benzaldehydes to the corresponding benzonitriles (Table 1), we found that PhCOCOOH underwent facile

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Reactant	Conditions		Isolated product	yields (%)	)	
PhCHO	A	PhCN (82.2	) PhCOOH (10.8)	Unchanged	reactant	(7.0)
PhCHO	С	PhCN (35.0	) PhCOOH (11.9)	Unchanged	reactant	(36.5)
p-CH3C6H4CHO	Α	ArCN (72.5	) ArCOOH (2.2)	Unchanged	reactant	(4.0)
p-CH3C6H4CHO	E		ArCOOH (2.3)	Unchanged	reactant	(60.5)
o-CH3OC6H4CHO	В	ArCN (88.0	)			
PhCOCOOH	Α	PhCN (51.1	) PhCOOH (5.5)			
PhCOCOOH	D	PhCN (30.0	) PhCOOH (29.5)			
PhCOCOOH	E	PhCN (10.8	) PhCOOH (63.0)			
(CH <sub>3</sub> ) <sub>2</sub> C(OH)COCH <sub>3</sub>	А	1:1 CH3CN -	+ снзсоснз (70)	Unchanged	reactant	(15)
(CH <sub>3</sub> ) <sub>2</sub> C(OH)COCH <sub>3</sub>	D	1:1 CH3CN -	+ CH3COCH3 (40)	Unchanged	reactant	(50)
Ph(CH3)C(OH)COPh	В	1:1 PhCN +	PhCOCH <sub>3</sub> (13)	Unchanged	reactant	(75)

Table 1. Representative product yields as a function of reaction conditions

Conditions (all at 25°C using con. NH<sub>4</sub>OH as solvent): A: 2 equiv Cu(NO<sub>3</sub>)<sub>2</sub>, 2.5 equiv K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, N<sub>2</sub>. B: same as A but using CH<sub>3</sub>CN as cosolvent (1:1). C: 2 equiv Cu(NO<sub>3</sub>)<sub>2</sub>, O<sub>2</sub>. D: same as A but no K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>. E: same as A but no Cu(NO<sub>3</sub>)<sub>2</sub>.

oxidative decarboxylation to PhCN (with varying amounts of PhCOOH being formed, depending on the oxidation conditions; Table 1). $^6$  The addition of NH<sub>3</sub> to the ketone carbonyl evidently provides a low energy pathway for oxidation (eq 3), because

PhCOCOOH 
$$\frac{Cu^{II} \text{ (or } O_2 \text{ or persulfate)}}{aq. NH_4OH} PhC \xrightarrow{N-Cu_n ox} - CO_2 PhCN \qquad (3)$$

PhCOCOOH is inert to Cu(II)-O<sub>2</sub> under similarly basic conditions (CH<sub>3</sub>OH-pyridine-Et<sub>3</sub>N) in the absence of NH<sub>3</sub>.<sup>7</sup> In analogy to the  $\alpha$ -ketoacid, we found that the  $\alpha$ -ketoamide isatin underwent clean oxidative cleavage to 2-aminobenzonitrile (eq 4).<sup>8</sup>



We also examined the  $\alpha$ -hydroxyketones 1 and  $2^{10}$ . Our thinking was that overall 2e oxidative cleavage of the imines would proceed with concomitant oxidation of the alcohol group to the corresponding ketone, which might be aided by a chelation effect with the copper, as illustrated in eq 5. The results are listed in Table 1.



The observed oxidative cleavage of  $\alpha$ -hydroxyketones suggested that  $\alpha$ -aminoketones might react analogously. However, since  $\alpha$ -aminoketones exist substantially as easily autoxidizied enols, we were careful to exclude  $0_2$  in these particular reactions. We found that 2-aminoacetophenone was converted by 2 equiv each of  $Cu(NO_3)_2$  and  $K_2S_2O_8$  in aq NH<sub>4</sub>OH at 25°C under N<sub>2</sub> to the expected aminative cleavage product PhCN (~20% yield), but PhCOOH, PhCONH<sub>2</sub>, and other unidentified products were also formed. Under the same conditions, 1-benzyl-3-piperidone was converted mainly (~70%) to polymer, but the nitrile expected according to eq 6 was isolated in 10% yield.<sup>11</sup>



We also considered whether oxidation of benzylic ketones might result in C-C cleavage with expulsion of a benzyl cation, especially when stabilized (e.g., by a 2-methoxy group). However, the main product (65% yield) formed from 2-methoxyphenylace-tone when treated with 2 eq Cu(NO<sub>3</sub>)<sub>2</sub> in aq NH<sub>4</sub>OH was the imidazole  $5.1^2$  Our finding that O<sub>2</sub> rather than persulfate was crucial to ensure a good yield of  $5.1^3$  suggested the involvement of a Cu(II)-mediated oxygenation of the starting benzylic ketone to a mixture of 1,2-diketone 3 and aldehyde  $4, 1^6$  followed by an aminative coupling of these two materials (eq 7). Such reaction has precedent in the formation of imidazoles from



quinones, aldehydes, and ammonium acetate, proposed to arise via diimine intermediates.<sup>17</sup> Since we could obtain 5 from a 1:1 mixture of 4 and independently prepared<sup>18</sup> 3 in the presence of ammonium acetate, the role of Cu(II) in eq 7 is apparently crucial only in the initial generation of 3 and 4.

It was also of interest to examine the fate of ketones which would not be expected to undergo facile oxidative cleavage. In this regard, we found that both aceto-phenone and its o-hydroxy derivative were partly converted (~15%) to the corresponding azines under the influence of 2 eq of Cu(II) and 2.5 eq of K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in aq NH<sub>4</sub>OH (no reaction was observed using O<sub>2</sub> rather than persulfate). Azine formation from benzo-phenone has been previously noted in the Cu(II)-MeOH-NH<sub>3</sub>-NaOMe system, <sup>5</sup> in which case

a le radical coupling of the corresponding imines was proposed. Some other ketones, however (e.g, cyclopropyl phenyl ketone and 2,2-dimethylpropiophenone) failed to give any azine under these conditions, suggestive of a steric effect.

The 2e oxidation of a ketimine nitrogen considered in this study is electronically equivalent to the Beckmann rearrangement. In fact, the C-C cleavage reaction shown in eq 5 is formally equivalent to the "abnormal" Beckmann rearrangement that occurs when one of the R groups attached to the carbonyl carbon is a good electrofuge. In this regard, it is of interest to consider the possibility that an appropriate metal oxidant combined with NH3 might be capable of effecting a one-pot Beckmann rearrangement of ketones, via ketimines, to the corresponding amidines. Such reaction would require a strong 2e oxidant which had little tendency to act as a le oxidant, in order to circumvent oxidative coupling of the ketimine (giving azine).

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## References and Notes

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- (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 7.00-7.15 (m, 4H), 7.24-7.28 (m, 2H), 7.52 and 8.35 (2dd, 1H each, J = 1.6 & 7.8 Hz).
- 13. The yield of imidazole decreased when  $K_2S_20_8$  was used (40% for 1.25 eq), in which case other products isolated in minor amounts were aldehyde 4, 2-methoxybenzamide, a diastereomeric mixture (dl + meso) of 3,4-bis-(2-methoxyphenyl)-2,5-hexanedione arising from Cu(II)-mediated oxidative coupling<sup>14</sup> of the parent ketone, and 3,4-ic bis-(2-methoxyphenyl)-2,5-dimethylpyrrole, arising from Paal-Knorr condensation<sup>15</sup> of the latter diketone.
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