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Copper/Ascorbic Acid Dyad as a Catalytic System for Selective Aerobic Oxidation of Amines

Jiri Srogl* and Svatava Voltrova

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Praha 6

jsrogl@uochb.cas.cz

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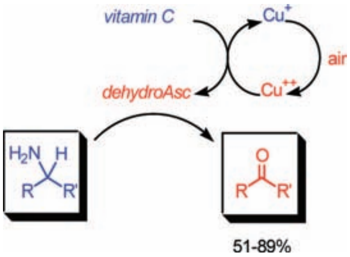
ABSTRACT



A new, environmentally benign system based on an ascorbic acid (vitamin C)/copper dyad is presented, which facilitates the oxidation of amines to carbonyl compounds. The oxidation utilizes aerobic oxygen as the ultimate electron scavenger, which accepts electrons in a cascade-like fashion via a Cu^+/Cu^{2+} and ascorbic/dehydroascorbic acid couple. Dehydroascorbic acid, the oxidation agent, finally oxidizes amine substrates in a selective fashion after forming a Schiff base intermediate. The selectivity as well as generality of the method is demonstrated on various substrates.

Oxidative reactions have always played an important role in organic synthesis. Because of the synthetic importance of carbonyl compounds—one of the prime targets of oxidative transformations—considerable attention from the chemical community has been focused on the development of convenient methods for obtaining these compounds from various substrates. The traditional ways used in the oxidative transformations of diverse functional groups have often been based on the utilization of high valent metallic reagents.[1] Inherent to these methods was the use of stoichiometric, highly reactive, and hence toxic reagents. To reach some chemical selectivity and "tame" these highly reactive species, extensive ligand modifications were often used with some success.[2] A different, milder approach has been used in the last couple of decades. It utilizes a stoichiometric nonmetallic oxidant and catalytic metal complex for an in situ transformation of the latter into a reactive species.[3]

Although numerous oxidative protocols for obtaining carbonyl compounds from alcohols have been successfully used in synthetic chemistry and in large scale industrial processes alike, the wide availability of amines prompted us to consider this group as a viable substrate for the oxidative preparation of desired aldehydes or ketones. Oxidations of amines are not unknown.[4] In most of the cases, however, they suffer from the typical maladies mentioned in the previous discussion—stoichiometric use of highly

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(1) Hudlicky, M. *Oxidation in Organic Chemistry*; ACS Monographs 186; Washington, D.C., 1990.

(2) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(3) (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. Marko, I. E.; Tsukazaki, M.; Giles, P. R.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2208. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329.

(4) (a) George, M. V.; Balachandran, K. S. *Chem. Rev.* **1975**, *75*, 491. (b) For metal-catalyzed oxidations of amines leading to various synthetic targets, see: Murahashi, S.-I.; Okano, Y.; Sato, H.; Nakae, T.; Komiya, N. *Synlett* **2007**, 1675. Suzuki, K.; Watanabe, T.; Murahashi, S.-I. *Angew. Chem., Int. Ed.* **2008**, *47*, 2079. Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490.

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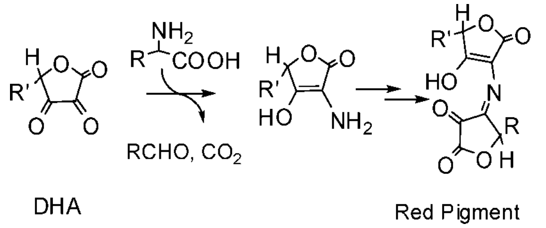
reactive metallic reagents with all the associated negative effects—toxicity, overoxidations of the substrate, and the lack of compatibility with other oxidizable functionalities. The ingenious take on this problematic process, enhancing the selectivity greatly and avoiding the detrimental stoichiometric metal salts, was introduced by Corey.[5] Its wider use, however, has been hampered by the limited availability of the quinone-based oxidation reagent. Very recently, the Backvall group has introduced a variation of the process, where amines underwent Ru-catalyzed aerobic oxidation in the presence of quinones.[5b]

Continuing the quest for a milder, environmentally benign oxidation protocol, we introduce a method based on the reported reactivity between dehydroascorbic acid (dehydroAsc) and various amines on one side and the copper-mediated aerobic oxidation of ascorbic acid (Asc) leading to dehydroAsc on the other.

The formation of colorful Schiff bases between dehydroAsc and amines with consequent degradation reactions has been well-known to food industry scientists for years.[6] It is the likely culprit in fruit and vegetable darkening (version of Maillard reaction) (Scheme 1).

Scheme 1. Naturally Occurring Aerobic Reaction of Ascorbic Acid and Amino Acids

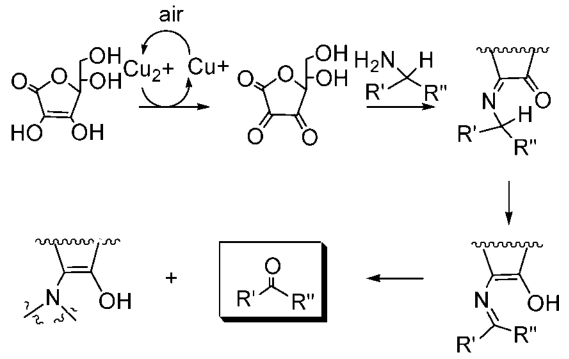


The second part of the proposed plan is based on cupric complexes and ascorbic acid (Asc) connected intimately in the redox couple—the interaction well documented in chemical and biochemical literature.[7] Thus, using the link between the easily oxidizable metal and the reactive organic mediator that reacts in its oxidized state, with amines, we envisioned an oxidation process built on the chemistry of the copper/ascorbic acid (Asc) dyad (Scheme 2).

This synthetically interesting oxidation process starts with atmospheric oxygen as the cheapest and most abundant ultimate “electron scavenger”.[3b] It continues in a cascade-like fashion by passing its oxidation potential through metallic salt to the organic mediator, which finally reacts with the substrate with high selectivity.

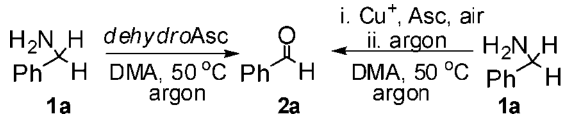
With respect to the ideas outlined above, we examined the validity of the concept. In the cursory experiment, the amine substrate **1a** was treated by the commercial dehydroAsc under an inert atmosphere. The corresponding aldehyde **2a** was easily formed. The same was true (and it pointed again to the dehydroAsc as the likely reaction intermediate) when dehydroAsc was preformed in situ by the copper-catalyzed aerobic oxidation of Asc (Scheme 3).

Scheme 2. Copper/Ascorbic Acid Catalyzed Oxidative Deamination



Although Asc or its derivative could be, in theory, reoxidized a number of times, thus rendering Asc catalytic, in our hands 2 equiv was needed to obtain the full conversion of amine into the desired carbonyl product. The likely culprit of this stoichiometry requirement can be identified by the observation of ammonia containing stable oligomers formed in the naturally occurring (Maillard) reaction. These species, which involve at least two Asc or dehydroAsc subunits (See the Scheme 3), are detrimentally unreactive toward a fresh molecule of amine substrate, preventing the required formation of the Schiff base-centered intermediate. Hence, more than 1 equiv of Asc was needed for the efficient oxidation of amines in our case.

Scheme 3. DehydroAsc as the Oxidation Mediator



In a separate control experiment, the Asc was fully omitted from the reaction mixture. This test did not lead to the formation of any signifficant amount of the product. When, in turn, the copper catalyst was left out, the reaction proceeded very slowly, and the conversion of the substrate reached 10−20% in several days as compared to hours needed for the high conversions in the copper-catalyzed process. Our reasoning of the observation is supported by the well-documented slow spontaneous aerobic oxidation of Asc. The reaction was carried out in various solvents (THF, dioxane, ether, AcOH). On the basis of the best isolated yields, however, amidic solvents DMF and DMA were the

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(5) (a) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429. (b) Samec, S. M.; Ell, A. H.; Backvall, J.-E. *Chem.−Eur. J.* **2005**, *11*, 2327.

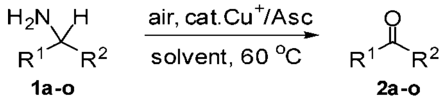
(6) Hayashi, T.; Namiki, M.; Tsuji, K. *Agric. Biol. Chem.* **1983**, *47*, 1955. Larisch, B.; Pischetsrieder, M.; Severin, T. *J. Agric. Food Chem.* **1996**, *44*, 1630.

(7) Silverblatt, E.; Robinson, A. L.; King, C. G. *J. Am. Chem. Soc.* **1943**, *65*, 137.

solvents of choice. Different Cu sources (CuI, $Cu(OAc)_2$, Cu_2O, CuMeSal) were also examined. Although all the copper salts (except for Cu_2O) catalyzed the reaction, CuMeSal was used for its superior solubility.

The reaction optimization, emerging from our investigations, was successfully applied on a variety of amines. The results are reported in Table 1.

Table 1. Amine Oxidation*

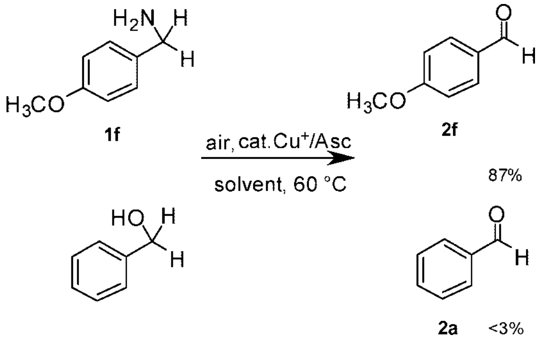


entry	starting material	R^1	R^2	isolated yield of **2a−o** (%)
1	**1a**	Ph	H	82[a]
2	**1b**	3-MePh	H	85[a]
3	**1c**	4-MePh	H	73[a]
4	**1d**	4-*t*Bu-Ph	H	70[a]
5	**1e**	3-MeOPh	H	78[a]
6	**1f**	4-MeOPh	H	87[a]
7	**1g**	4-MeOOC-Ph	H	89[a]
8	**1h**	4-HOOC-Ph	H	67[a]
9	**1i**	Ph	Ph	81[b]
10	**1j**	Ph	Me	53[b]
11	**1k**	$-(CH_2)_5-$	58[b]	
12	**1l**	$-(CH_2)_{11}-$	51[b]	
13	**1m**	$PhCH_2$	COOEt	63[b]
14	**1n**	Ph	COOH	49[b,c]
15	**1o**	$C_{12}H_{25}$	H	60[b,d]

* Typical procedure: [a] Ascorbic acid (0.704 g, 4 mmol), copper(I) 3-methylsalicylate (8.6 mg, 0.04 mmol), and primary amine (2 mmol) were dissolved in DMA (4 mL) and heated with stirring at 50 °C (bath temperature) in an air-open flask for 2 h. [b] Ascorbic acid (0.704 g, 4 mmol) and copper(I) 3-methylsalicylate (8.6 mg, 0.04 mmol) were dissolved in DMA (2 mL) and heated with vigorous stirring at 50 °C (bath temperature) in an air-open flask under a drying tube for 30 min. This solution (1 mL) was then added to the stirred primary amine (2 mmol) dissolved in DMA (2 mL) and heated to 55 °C for 8−20 h. After 8 h, the addition of ascorbic acid solution prepared as above (1 mL) was repeated. [c] Benzaldehyde was formed as the product of decarbonylation of the resulting α-ketoester. [d] GC-MS yield.

The issue of selectivity was addressed by the following experiment. Structurally similar benzyl alcohol and amine **1f** were treated side by side in one reaction mixture under the reaction condition (Scheme 4).

Scheme 4. Chemoselectivity of the Oxidation



The reaction resulted in an almost quantitative formation of **2f**, while the alcohol remained under those conditions practically intact and less than 3% of **2a** was detected. While foreseeable and consistent with our mechanistic considerations, the example offers an interesting example of highly selective oxidation. *N*-Secondary amines were also examined as potential substrates. They did not, however, undergo the desired oxidative transformation in our hands.

In conclusion, we present here an efficient oxidation process which will, due to the ambience of the oxidation reagents, chemical selectivity, and environmental benigness of the reaction condition, hopefully find a position in the synthetic toolbox of the organic chemist. Further investigations into the scope and synthetic application of the reaction are now in progress.

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Supporting Information Available: Brief experimental details and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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