

Ascorbic Acid-Mediated Reactions

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Contributor: Aparna Das, Bimal Banik, RAM YADAV

Ascorbic acid is a vitamin found in different types of food. It has tremendous medical applications in several different fields such as in pharmaceuticals, cosmetics, and in organic synthesis.

Keywords: Ascorbic acid ; Organic synthesis ; Catalyst

1. Introduction

Ascorbic acid, also known as Vitamin C, ascorbate, is the most well-known vitamin found in various foods ^[1]. However, humans and apes cannot synthesize ascorbic acid because of the lack of an enzyme gulonolactone oxidase ^[2]. In 1932, Haworth and King independently have established the molecular structure of hexuronic acid and renamed it as ascorbic acid ^[3]. Ascorbic acid molecule is structurally related to glucose ^[4]. There are many derivatives of ascorbic acid known ^[5].

The oxidation-reduction potential and the stability of its oxidation products add values to the application of ascorbic acid as an antioxidant ^[6]. Because of the low one-electron transfer potential, the two-way reactions among three forms occur very easily. As a result, ascorbic acid has been known to be chemically unstable ^[7].

It is evident that ascorbic acid readily undergoes pH-dependent autooxidation and produces hydrogen peroxide ^[8]. Besides, in the presence of catalytic metals, this oxidation is accelerated ^[9]. The combination of metal (mainly iron) and ascorbic acid is a very effective oxidizing system. This is mainly used for the hydroxylation of alkenes, aromatics, and other oxidations ^[10]. Ascorbic acid can also exert pro-oxidant effects in the presence of catalytic metal ions ^[11].

In this review, we mainly focus on the ascorbic acid-catalyzed mechanistically important reactions.

2. Ascorbic acid-mediated reactions

Catalysts such as organocatalysts, enzymes, and ionic liquids have shown very promising results in synthesis by diminishing the number of hazardous effects of chemical reactions. Among them, the catalytic activities of ascorbic acid are assuring due to its extraordinary abilities.

2.1 Oxidation of amines to carbonyl compounds

Ascorbic Acid/copper dyad can be used as a catalytic system for selective aerobic oxidation of amines ^[12]. On dyad, the reactive organic mediator in its oxidized state and the easily oxidizable metal built an oxidation process. The oxidation process starts with atmospheric oxygen ^[13] and continues in a cascade-like fashion.

All three reactions are pointed out that dehydroascorbic acid is the reaction intermediate and it acts as the oxidation mediator ^[12]. But in turn, a very slow reaction is observed when the same reaction is performed with ascorbic acid and without the copper catalyst.

2.2 Cross-coupling of disulfides with aryl iodides

Srogl *et al.* reported the Cu (I)-catalyzed, ascorbic acid-mediated cross-coupling reaction of aryl iodides with disulfides ^[14]. It describes that the formation of organocopper species has occurred in the first step which is then reduced by ascorbate in the next step. In the final step, the species interact with disulfide moiety and forms the thioether.

2.3 ATRA of polyhalogenated compounds to alkenes

Atom-transfer radical addition (ATRA) reactions take place through a radical chain propagation mechanism. ATRA reactions are effective methods for the functionalization of olefins ^[15].

Pintauer *et al.* reported the use of ascorbic acid as an environmentally benign reducing agent for copper-catalyzed atom transfer radical addition (ATRA) and cyclization (ATRC) reactions utilizing a variety of alkenes and alkyl halides [16]. It is also reported that the reactions conducted in the absence of catalyst demonstrated negligible conversions [17]. Ascorbic acid can also be used as a reducing agent for atom transfer radical polymerization (ATRP) reactions, where the reactions were conducted in aqueous media, mini-emulsion, or heterogeneously [18].

2.4 ATRC of polychloroamides to cyclic amides

Ghelfi *et al.* reported a greenway for the cycloisomerization of N-allyl- α -polychloroamides to γ -lactams through a copper-catalyzed ARGET-ATRC in ethanol and in the presence of ascorbic acid [19]. The recognized mechanism for the transition metal catalyzed ATRA (TMC-ATRA) consists of three elementary steps. First the metal complex M^nL_m , in its reduced state, abstracts (reversibly) a halogen atom from the halo-precursor, generating a radical species and thereby increasing the oxidation state of the metal by one ($M^{n+1}L_mX$). The radical intermediate, in the next step, adds to the olefinic substrate yielding a new radical. Finally, the adduct radical is quenched by halogen transfer from $M^{n+1}L_mX$ (the metal complex in its oxidized state), regenerating the active form of the catalyst (M^nL_m) and affording the reaction product. The atom transfers to and from the metal complex follow a concerted mechanism, via an inner-sphere electron transfer process. Copper-catalyzed ARGET-ATRC, using ascorbic acid as reducing agent, in ethanol was used for the synthesis of α , β -unsaturated 4-chloromethyl- γ -lactams from N-(2-chloroallyl)- α -polichloroamides [19].

2.5 Amination of aryl halides to primary aromatic amines

Page *et al.* reported the amination of a variety of aryl halides with copper(I) iodide and ascorbic acid in liquid/ ammonia at room temperature for aryl iodides and 100°C for aryl bromide and aryl chloride [20]. In principle, Cu^+ can act as either an electron donor or acceptor, but on the basis of the small rate enhancement by the reductant ascorbic acid, it seems likely that in liquid ammonia, Cu^+ is acting as a reducing agent. The Cu(I) catalyst is present at only 1 mol % and any adventitious oxidation to Cu(II) will terminate the reaction, so the function of the ascorbic acid is probably to reduce any such Cu(II) to its catalytically active form. Theoretical studies on the cation- π interactions of Cu^+ and benzene indicate that, in the gas phase, Cu^+ forms a η^2 complex with benzene, especially if a counterion is present. Other theoretical studies on the copper(I)-catalyzed amidation of aryl halides have suggested a mechanism involving rate-limiting oxidative addition through a penta-coordinated copper(III) intermediate and a single electron transfer (SET) mechanism depending on the electron-donating abilities of the ligand and the nucleophile. The small rate enhancement brought about by ascorbic acid given its ability to act as a radical trap, does not suggest that a SET mechanism is operative in liquid ammonia.

2.6 Oxidation of sulfides

An inexpensive, convenient, and environmentally benign method for the selective oxidative transformation of sulfides into sulfoxides has been studied in detail by Imada *et al.* [21].

The present reaction can be rationalized by assuming the redox process of the flavin species. The oxidized form of flavin (Fl_{ox}) undergoes a single electron transfer from the ascorbate anion (AH^-) to form a flavin radical anion intermediate, which is then converted into reduced flavin (Fl_{red}) by repeated single electron transfer from a second ascorbate anion. Two equivalents of ascorbic acid are required in this catalytic system, probably due to the low reducing ability of the resulting ascorbate radical species. In addition, the reaction does not proceed via a photooxidation process involving resulting ascorbate radical species, because the reaction proceeded efficiently under light-shielding conditions. Incorporation of molecular oxygen into the reduced flavin affords 4a-hydroperoxyflavin ($FIOOH$), which effects oxygen transfer to the sulfides to afford the corresponding sulfoxides. Dehydration of the resulting $FIOH$ regenerates Fl_{ox} to complete the catalytic cycle.

2.7 Arylation of arenes with anilines

Carrillo *et al.* used ascorbic acid as a radical initiator in a metal-free direct C-H arylation of (hetero)arenes [22]. On the basis of the above observations and previous reports, a tentative mechanism is proposed for the arylation of furan. First, the aniline reacts with tertbutyl nitrite to yield the diazonium salt I. In the initiation step, ascorbic acid protonates a small part of I, which results in a change of the anion to ascorbate and leads to diazonium salt II. Ascorbate then reduces the arenediazonium ion by a single-electron transfer through an inner-sphere mechanism. This reduction consists of a nucleophilic addition of ascorbate to the diazonium moiety to afford a diazoether, followed by a hemolytic rupture to generate nitrogen, ascorbyl radical, and the aryl radical III. Ascorbyl radical tends to dismutate into dehydroascorbic acid and ascorbic acid, which can reduce another arenediazonium ion. On the other hand, the aryl radical III undergoes a

homolytic aromatic substitution to yield initially radical IV, which propagates the reaction by losing one electron to reduce another molecule of diazonium salt I with the formation of the carbocation V, whose counterion, tert-butoxide, immediately abstracts a proton to yield the final product by rearomatization of the furan ring.

2.8 Cyclization of aryl radicals with arenes

Cheng and co-workers reported that ascorbic acid can be used as an initiator for tandem radical cyclization of N-arylacrylamides to give 3,3-disubstituted oxindoles [23]. On the basis of previous reports and the above experimental results, a tentative mechanism is proposed. First, tert-butyl nitrite reacts with 4-nitroaniline to yield diazonium salt, which is partly protonated by ascorbic acid (H_2Asc) to afford the ascorbate diazonium salt. The nucleophilic addition of ascorbate to the diazonium moiety provides diazoether. At this step, the strong electron-withdrawing ability and conjugative effect of the nitro group can facilitate the addition of nitrogen-nitrogen triple bonds and successive diazoether homolytic rupture. Thus, the nucleophilic addition and homolytic rupture steps are more difficult when 4-nitroaniline was replaced by other aniline derivatives under our reaction conditions, which finally resulted in a complex reaction mixture. Next, diazonium salt is reduced by ascorbate to generate nitrogen, ascorbyl radical and the aryl radical. Ascorbyl radical tends to dismutate into dehydroascorbic acid and ascorbic acid, which can reduce another arene diazonium ion. On the other hand, aryl radical undergoes an addition to the carbon-carbon double bond of N-arylacrylamide to generate the alkyl radical. The intermolecular cyclization of radical gives another radical intermediate, which loses one electron to reduce the diazonium salt molecule to generate carbocation and another aryl radical. The final step is deprotonation of carbocation by the tert-butoxide anion that generated in the reaction system to yield the desired cyclization compound.

2.9 Metal-Free Synthesis of Aryl Sulfides

Bu *et al.* reported the ascorbic acid-promoted synthesis of aryl sulfides with anilines nitrosated *in situ* by tert-Butyl Nitrite [24]. The synthesis was metal-free and one-pot.

According to this observation and previous literature reports, a suggested mechanism was proposed. The aniline undergoes a nitrosation by tert-butyl nitrite to give the aryl diazonium salt, which is protonated by ascorbic acid, and the diazonium salt is formed upon the change of anion. Then, an electron transfers from ascorbate to aryl diazonium ion to generate the aryl radical. The resulting ascorbyl radical dismutates into dehydroascorbic acid and ascorbic acid which can react with another diazonium salt. Finally, the radical intermediate reacts with disulfide to generate the product.

2.10 Oxidative arylation of vinyl arenes to 2-Aryl acetophenones

A convenient and general method for oxidative arylation of vinyl arenes by aryl radicals generated *in situ* from arene diazonium fluoroborates promoted by ascorbic acid in the air at room temperature was developed in absence of any additive and visible light irradiation by Ranu *et al.* [25].

In the first step the aryl diazonium salt interacts with ascorbic acid to generate an intermediate diazoether via nucleophilic attack of ascorbate anion to diazonium ion. Subsequently this diazoether undergoes a homolytic cleavage to produce an aryl radical. In the next step the aryl radical attacks at β -position of vinyl arene to form a relatively stable benzyl radical which captures O_2 from air to produce the peroxy radical. This peroxy radical then reacts with another molecule to provide an oxyl radical which leads to 2-phenyl acetophenone by abstraction of a hydrogen radical.

2.11 Photoreductive removal of O-benzyl groups

A photoreductive method to remove benzyl O-protective groups from oxyarene N-heterocycles at positions capable for 2-/4-Opyridine–2-/4-pyridone tautomerism was developed by Helaja and co-workers [26].

The cycle begins by ascorbic acid protonating the N-heterocycle and continues by reduction of the excited state of the photocatalyst with ascorbic acid. Thereafter, the reduced state catalyst donates electron for the substrate, which is fragmented into benzyl radical and neutral pyridone. This scenario is firmly supported by correlation of various substrate reduction potentials vs several catalyst RSRPs. Additionally, Stern–Volmer plot indicates that ascorbic acid acts as a primary fluorescence quencher of [Ru] catalyst.

2.12 Photocatalytic Reductive Fluoroalkylation of Nitrones

A method for the addition of fluorinated groups to nitrones using an iridium photocatalyst and ascorbic acid as a stoichiometric reducing agent was described by Dilman *et al.* [27].

First, fluorinated alkyl iodide is reduced by a catalyst to generate the corresponding free radical, which adds at the nitron double bond. Subsequent single-electron reduction of nitroxyl radical and protonation of nitroxide species affords hydroxylamine. As a stoichiometric reductant we used readily available ascorbic acid. Two distinct pathways can work with the use of the same photocatalyst. In mode A, the light-activated catalyst serves as a source of electrons (oxidative quenching), and its reduced state is regenerated with the aid of ascorbate. In mode B, the catalyst is first reduced by ascorbate (reductive quenching) leading to a strongly reductive species, which activates the alkyl iodide. Besides reducing the catalyst, ascorbate anion can also serve as a source of hydrogen atom toward nitroxyl radical.

2.13 Reductions of N-Heterocyclic Nitroaryls to Anilines

A photoreductive method utilizing $[\text{Ru}(\text{bpy})_3]^{2+}$ photocatalyst, blue light LEDs, and ascorbic acid to reduce nitro N-heteroaryl to the corresponding anilines was developed by Helaja et al. [28]. The mechanism seems to involve numerous steps: the reaction is initiated by a multisite proton-coupled electron transfer (MS-PCET) between the nitro quinoline, AscH_2 , and $[\text{Ru}^{2+}]$, i.e., proton and electron are transferred from one donor to two separate acceptors. This is supported by Stern–Volmer titrations, in which concentrations of substrates were fixed and the amount of AscH_2 was varied. The protonation energies of reactive nitro substrates by AscH_2 were calculated to vary between thermoneutral (0.7 kcal/mol) and endergonic (15.4 kcal/mol), where the endergonicity of protonation does not exclude hydrogen-bonding interactions between acid and base, which in turn can facilitate MS-PCET reactions. The protonation of hydroxylamine and the subsequent reduction of $[\text{Ru}^{2+}]$ to $[\text{Ru}^+]$ by AscH^- are required for the reduction of the substrate by $[\text{Ru}^+]$, as the reduction of electron-rich hydroxylamine quinolines.

2.14 Dehalogenation of Halo Compounds

Dehalogenation of *vic*-Dibromo-, α -halo-, or α, α -dibromocarbonyl compounds using catalytic tris(2,2'-bipyridyl)ruthenium dichloride ($\text{Ru}(\text{bpy})_3\text{Cl}_2$) in combination with 1,5-dimethoxynaphthalene (DMN) and ascorbate as sacrificial electron donor was reported by Reiser and co-workers [29]. The combination of 1,5-dimethoxynaphthalene as a primary and ascorbic acid as a sacrificial electron donor worked effectively as a photocatalytic system.

2.15 Synthesis of cyclic carbonates from CO_2

Elia et al. found that ascorbic acid/TBAI was an efficient organocatalytic pair for the synthesis of cyclic carbonates under ambient or very mild conditions [30]. Overall, for the reaction mechanism of ascorbic acid, the calculated barriers range from 12.0 kcal/mol to 16.0 kcal/mol, which are consistent with the observed activity at room temperature. The cycloaddition reaction mechanism for the acetal protected ascorbic acid derivative (APAA) is calculated. The main results can be summarized in the following points: The calculated ring opening barrier (TS-AB') for APAA is 3.2 kcal/mol higher in energy than the corresponding barrier for ascorbic acid (16.2 kcal/mol vs 13.0 kcal/mol, respectively); The calculated CO_2 insertion barrier (TS-BC') for APAA is significantly higher in energy (by 5.5 kcal/mol) when compared to the corresponding barrier for ascorbic acid. These observations can be partly attributed to the acetal protecting group acting as an electron donor and influencing the hydrogen bonding ability of APAA; Similar to ascorbic acid, the ring closure step is predicted to be the rate-determining step. However, the calculated barrier (TS-CD') for APAA is 3.4 kcal/mol higher than the corresponding barrier for ascorbic acid.

2.16 Synthesis of 3-Aminoquinolinones, 3-Aminocoumarins and Anilines

Alami and co-workers introduced a method to provide a range of 3-aminoquinolin-2(1H)-ones and 3-aminocoumarins from 3-bromoquinolinones and 3-bromocoumarins, respectively [31]. This method was based on the efficient copper-catalyzed *in situ* C(sp²)-NH₂ bond formation. This reaction used copper powder as the catalyst, ascorbic acid as the additive, and eco-friendly ethanol as the solvent in the presence of pipecolic acid as the ligand [31].

The reaction proceeds by a nitrene thermolysis mechanism. Initially, the azide intermediate is probably formed followed by the nitrene species, produced by the thermo-initiated N₂ liberation, was presumably converted to the product by hydrogen abstraction.

2.17 Synthesis of polyhydroquinoline and 1,8-dioxodecahydroacridines

Chemists developed several methods for the synthesis of polyhydroquinoline and 1,8-dioxodecahydroacridine derivatives, which involves three-component reaction methods and four-component reaction methods, in the presence of a variety of catalysts [32]. Debache et al. reported the catalytic role of ascorbic acid in the synthesis of 1,8-dioxodecahydroacridine and polyhydroquinoline derivatives through a multicomponent condensation reaction [33].

Ascorbic acid facilitates the enolization of a molecule of the 1,3-diketone and changes the aldehyde into convenient electrophile by protonation, obtained and reacted together to give the intermediate by a Knoevenagel-type reaction. Furthermore, a second diketone molecule or an ethyl acetoacetate molecule undergoes enolization under the influence of ascorbic acid to yield intermediate. Then a Michael-type reaction takes place. The resulting intermediate reacts with ammonium acetate to yield imine which undergoes an intramolecular cyclization and dehydration to yield the expected product.

2.18 Aerobic benzylic C-H oxidation

Rezaeifard and co-workers reported the selective aerobic benzylic C–H oxidation of alcohols and hydrocarbons by TiO₂/AA/Co nanohybrid in ethyl acetate [34].

2.19 Synthesis of Benzimidazoles

Rezaeifard *et al.* reported the one-pot environmentally benign synthesis of benzimidazoles by cobalt ascorbic acid complex coated on TiO₂ nanoparticles via aerobic photooxidative cyclization reactions [35]. The results revealed that the reaction rate affected by the electronic demands of the substrates. For example, benzyl alcohol bearing electron-donating groups were efficiently converted to the pertinent benzimidazole derivatives with a high yield of 94%. However, the strong electron-withdrawing nitro group on the phenyl ring of both alcohol and amine molecules significantly retarded the reaction.

2.20 Synthesis of 1,5-disubstituted 1,2,3-triazoles

Kumar *et al.* reported a copper-catalyzed decarboxylative regioselective protocol for the synthesis of 1,5-disubstituted 1,2,3-triazoles through direct annulation of cinnamic acids with aryl azides in the presence of ascorbic acid [36]. The first step of the reaction is the regioselective 1,3-dipolarcycloaddition of azides with cinnamic acid to form the cation intermediate. Subsequently, a decarboxylation to copper triazoline occurs, followed by the loss of a proton to afford a copper complex 1,4,5-trisubstituted 1,2,3-triazole. In acidic media, the copper complex readily undergoes protonolysis, providing free 1,5-disubstituted 1,2,3-triazoles and allowing the Cu(II) species to participate again in the catalytic cycle. The Cu(II) can be regenerated from the Cu(I) species with oxygen under acidic conditions.

2.21 Synthesis of α -acyloxy carboxamides

Shaabani *et al.* reported the synthesis of carboxamide scaffolds, from the reaction of aldehyde, benzoic acid, and isocyanide derivatives catalyzed by ascorbic acid [37]. The formation of a strong hydrogen bond between an aldehyde and diol group in ascorbic acid activates molecule. Subsequently, nucleophilic addition of an isocyanide leads to an intermediate, which is subsequently attacked by carboxylate to produce desired compound.

2.22 Synthesis of arylbutanoates

The reaction of various aldehydes, Meldrum's acid, and cyclohexyl isocyanide were investigated in the presence of ascorbic acid as a catalyst in the water at room temperature by Shaabani *et al.* [37]. The formation of a hydrogen bond between ascorbic acid and ketone led to intermediate, which subsequently reacted with 1,2-phenylenediamines. An intramolecular imine-enamine cyclization formed seven-membered ring heterocycle, which was then attacked by isocyanide and water and subsequent tautomerization led to the desired product.

2.23 Synthesis of benzodiazepines

Shaabani *et al.* reported the synthesis of benzodiazepines by the pseudo-five-component reaction of 4-nitro-1,2-phenylenediamine, acetone, and cyclohexyl isocyanide in water catalyzed by ascorbic acid [37]. The best yield of product (90%) was obtained in the presence of 10 mol% of ascorbic acid in water at room temperature.

2.24 Synthesis of benzoxazepines

Shaabani and co-workers reported the catalytic performance of ascorbic acid for the direct synthesis of benzoxazepine rings [37]. They performed the three-component reaction of 2-aminophenol, dimedone, and benzaldehyde in the presence of ascorbic acid under various reaction conditions to obtain 1,4-benzoxazepine derivatives. Initially, in the presence of the catalyst, 2-aminophenol and dimedone undergo enamine formation. Then, an intermediate is produced by nucleophilic attack of enamine to activate aldehyde followed by the intramolecular cyclization led to the product.

2.25 Synthesis of dihydropyrimidinones

Debache and co-workers described an efficient one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via a three-component Biginelli condensation of aldehyde, ethyl acetoacetate, and urea or thiourea [38]. This Biginelli reaction was carried out in the presence of a catalytic amount of ascorbic acid (5 mol %). The method describes an ascorbic acid-catalyzed one-pot condensation of aldehyde, 1,3-dicarbonyl compounds and urea, or thiourea to 3,4-Dihydropyrimidin-2(1H)-ones. The mechanism follows usual Biginelli condensation.

2.16 Synthesis of Xanthenes

Mohamadpour reported a green, convenient, and highly versatile method for the facile synthesis of 12-aryl-tetrahydrobenzo[*a*]xanthene-11-ones, 1,8-dioxo-octahydroxanthenes, and 14-aryl-14H-dibenzo[*α, j*]xanthenes under solvent-free conditions [39]. This method follows usual acid-induced cyclization process.

3. Conclusions

This review has explored the application of ascorbic acid as a catalyst in organic synthesis. In many instances, the pertinent mechanism of the processes is advanced to explain the formation of the products.

Contributors

Aparna Das^a, Ram Naresh Yadav^b and Bimal Krishna Banik^c

^a Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Prince Mohammad Bin Fahd University, Al Khobar 31952, KSA, Email: adas@pmu.edu; aparnadasam@gmail.com.

^b Department of Chemistry, Faculty of Engineering & Technology, Veer Bahadur Singh Purvanchal University, Jaunpur-222003(UP), India.

^c Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Deanship of Research, Prince Mohammad Bin Fahd University, Al Khobar 31952, KSA; Email: bimalbanik10@gmail.com; bbanik@pmu.edu.sa.

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References

1. Haytowitz, D. Information from USDA's nutrient data book. *Journal of Nutrition*, 1995, 125, 1952-1955.
2. Nishikimi, M.; Fukuyaman, R.; Minoshiman, I.; Shimizux, N.; Yag, K. Cloning and chromosomal mapping of the human non-functional gene for l-gulono-γ-lactone oxidase, the enzyme for l-ascorbic acid biosynthesis missing in man. *J. Biol. Chem.*, 1994, 269, 13685-13688.
3. Buettner, G.R.; Schafer, F.Q.; Albert, Szent-Györgyi. Vitamin C identification. *Biochemist.*, 2006, 28, 31-33.
4. Velisek, J.; Cejpek, K. Biosynthesis of food constituents: Vitamins. Water-soluble vitamins, part 2-A review. *Czech Journal of Food Science*, 2007, 25, 49-64.
5. Galesso, M.; Gatta, M.; Galiano, F. Comparative studies on the stability of ascorbic acid and its derivatives in various matrices and interaction with commonly used cosmetic preservatives. *Cosmet Toiletries Journal.*, 1993, 2, 58-74.
6. Uri, N. In *Autoxidation and Antioxidants*. Interscience Publishers Inc., New York. 1: 55-106, 1961.
7. Higdon, J.V.; Frei, B. Vitamin C: an introduction. In: Packer, L.; Traber, M.G.; Kraemer, K.; Frei, B. editors. *The antioxidants C and E*. 1st ed. California: AOCS Press, Santa Barbara; 2002.
8. Calcutt, G. The formation of hydrogen peroxide during the autoxidation of ascorbic acid. *Experientia.*, 1951, 7, 26.
9. Bielski, B.H.J. Chemistry of ascorbic acid radicals. In: Seib, P.A.; Tolbert, B.M., editors. *Ascorbic Acid: Chemistry, Metabolism, and Uses*. Vol. 200. American Chemical Society; Washington D.C: p.81-100, 1982.
10. Khan, M.M.; Martell, A.E. Metal ion and metal chelate catalyzed oxidation of ascorbic acid by molecular oxygen. II. Cupric and ferric chelate catalyzed oxidation. *J. Am. Chem. Soc.*, 1967, 89, 7104-7111.
11. Halliwell, B. Vitamin C: poison, prophylactic or panacea? *Trends Biochem. Sci.*, 1999, 24, 255-259.

12. Srogl, J.; Voltrova, S. Copper/Ascorbic Acid Dyad as a Catalytic System for Selective Aerobic Oxidation of Amines. *Org. Lett.*, 2009, 11, 843-845.
13. Punniyamurthy, T.; Velusamy, S.; Iqbal. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen, *J. Chem. Rev.*, 2005, 105, 2329.
14. Martinek, M.; Korf, M.; Srogl, J. Ascorbate mediated copper catalyzed reductive cross-coupling of disulfides with aryl iodides, *Chem. Commun.*, 2010, 46, 4387-4389.
15. Eckenhoff, W. T.; Pintauer, T. Copper Catalyzed Atom Transfer Radical Addition (ATRA) and Cyclization (ATRC) Reactions in the Presence of Reducing Agents. *Catal. Rev. Sci. Eng.*, 2010, 52, 1-59.
16. Taylor, M.J.W.; Eckenhoff W.T.; Pintauer, T. Copper-catalyzed atom transfer radical addition (ATRA) and cyclization (ATRC) reactions in the presence of environmentally benign ascorbic acid as a reducing agent, *Dalton Trans.*, 2010, 39, 11475-11482.
17. Eckenhoff, W.T.; Pintauer, T. *Inorg. Chem.*, 2007, 46, 5844-5846.
18. Min, K.; Gao H.; Matyjaszewski, K. Use of Ascorbic Acid as Reducing Agent for Synthesis of Well-Defined Polymers by ARGET ATRP. *Macromolecules*, 2007, 40, 1789-1791.
19. Casolari, R.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U.M.; Parsons, A.F.; Spinelli, D. A green way to γ -lactams through a copper catalyzed ARGET-ATRC in ethanol and in the presence of ascorbic acid, *Tetrahedron*, 2011, 67, 408-416.
20. Ji, P.; Atherton, J.H.; Page, M. I. Copper(I)-Catalyzed Amination of Aryl Halides in Liquid Ammonia, *J. Org. Chem.*, 2012, 77, 7471-7478.
21. Imada, Y.; Kitagawa, T.; Wang, H.-K.; Komiya, N.; Naota, T. Flavin-catalyzed aerobic oxidation of sulfides in aqueous media, *Tetrahedron Lett.*, 2013, 54, 621-624.
22. Crisostomo, F.P.; Martin, T.; Carrillo, R. Ascorbic Acid as an Initiator for the Direct C-H Arylation of (Hetero)arenes with Anilines Nitrosated In Situ, *Angew. Chem. Int. Ed.*, 2014, 53, 2181-2185.
23. Liu, S.; Cheng, P.; Liu, W.; Zeng, J. Ascorbic Acid-Initiated Tandem Radical Cyclization of N-Arylacrylamides to Give 3,3-Disubstituted Oxindoles, *Molecules*, 2015, 20, 15631-15642.
24. Bu, M.j.; Lu, G.-p.; Cai, C. Ascorbic Acid Promoted Metal-Free Synthesis of Aryl Sulfides with Anilines Nitrosated In Situ by tert-Butyl Nitrite, *Synlett.*, 2015, 26, 1841-1846.
25. Majhi, B.; Kundu, D.; Ranu, B.C. Ascorbic Acid Promoted Oxidative Arylation of Vinyl Arenes to 2-Aryl Acetophenones without Irradiation at Room Temperature under Aerobic Conditions. *J. Org. Chem.*, 2015, 80, 15, 7739-7745.
26. Todorov, A.R.; Wirtanen, T.; Helaja, J. Photoreductive Removal of O-Benzyl Groups from Oxyarene N-Heterocycles Assisted by O-Pyridine-pyridone Tautomerism, *J. Org. Chem.*, 2017, 82, 13756-13767.
27. Supranovich, V.I.; Levin, V.V.; Struchkova, M.I.; Dilman, A. D. Photocatalytic Reductive Fluoroalkylation of Nitrones, *Org. Lett.*, 2018, 20, 840-843.
28. Todorov, A.R.; Aikonen, S.; Muuronen, M.; Helaja, J. Visible-Light-Photocatalyzed Reductions of N-Heterocyclic Nitroaromatics to Anilines Utilizing Ascorbic Acid Reductant, *Org. Lett.*, 2019, 21, 3764-3768.
29. Maji, T.; Karmakar, A.; Reiser, Visible-Light Photoredox Catalysis: Dehalogenation of Vicinal Dibromo-, α -Halo-, and α,α -Dibromocarbonyl Compounds, *J. Org. Chem.*, 2011, 76, 736-739.
30. Arayachukiat, S.; Kongtes, C.; Barthel, A.; Vummaleti, S.V.C.; Poater, A.; Wannakao, S.; Cavallo, L.; D'Elia, V. Ascorbic acid as a bifunctional hydrogen bond donor for the synthesis of cyclic carbonates from CO₂ under ambient conditions. *ACS Sustainable Chem. Eng.*, 2017, 5, 8, 6392-6397.
31. Messaoudi, S.; Brion, J.-D.; Alamia, M. An Expedient Copper-Catalyzed Access to 3-Aminoquinolinones, 3-Aminocoumarins and Anilines using Sodium Azide. *Adv. Synth. Catal.*, 2010, 352, 1677-1687.
32. (a) Maleki, B.; Tayeb, R.; Kermanian, M.; Ashrafi, S. S. J. One-Pot Synthesis of 1,8-Dioxodecahydroacridines and Polyhydroquinoline using 1,3-Di (bromo or chloro)-5,5-Dimethylhydantoin as a Novel and Green Catalyst under Solvent-Free Conditions. *Mex. Chem. Soc.*, 2013, 57, 290-297; (b) Shen, Y.-B.; Wang, G.-W. Solvent-free synthesis of xanthenediones and acridinediones. *Arkivoc.*, 2008, xvi, 1-8.
33. Sehout, I.; Boulcina, R.; Boumoud, B.; Boumoud, T.; Debache, A. Solvent-free synthesis of polyhydroquinoline and 1,8-dioxodecahydroacridine derivatives through the Hantzsch reaction catalyzed by a natural organic acid: A green method. *Synth. Commun.*, 2017, 47, 1185-1191.
34. Jafarpour, M.; Feizpour, F.; Rezaeifard, A. Aerobic benzylic C-H oxidation catalyzed by a titania-based organic-inorganic nanohybrid. *RSC Adv.*, 2016, 6, 54649-54660.

35. Feizpour, F.; Jafarpour, M.; Rezaeifard, A. A Tandem Aerobic Photocatalytic Synthesis of Benzimidazoles by Cobalt Ascorbic Acid Complex Coated on TiO₂ Nanoparticles Under Visible Light. *Catal. Lett.*, 2018, 148, 30-40.
36. Kumar, N.; Ansari, M.Y.; Kant, R.; Kumar, A. Copper-catalyzed decarboxylative regioselective synthesis of 1, 5-disubstituted 1, 2, 3-triazoles. *Chem. Commun.*, 2018, 54, 2627-2630.
37. Shaabani, A.; Khodkari, V.; Nazeri, M.T.; Ghasemi, S.; Mohammadian, R.; Shaabani, S. Vitamin C as a green and robust catalyst for the fast and efficient synthesis of valuable organic compounds via multi-component reactions in water. *J. IRAN. CHEM. SOC.*, 2019, 16, 1793-1800.
38. Sehout, I.; Boulcina, R.; Boumoud, B.; Berrée, F.; Carboni, F.; Debache, A. Ascorbic acid-catalyzed one-pot three-component Biginelli reaction: a practical and green approach towards synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones/thiones. *Lett. Org. Chem.*, 2013, 10, 463-467.
39. Mohamadpour, F. Ascorbic acid as a natural green, highly efficient and economical catalyst promoted one-pot facile synthesis of 12-aryl-tetrahydrobenzo[A]xanthene-11-ones, 1,8-dioxo-octahydroxanthenes and 14-aryl-14H-dibenzo[A,J]xanthenes under solvent-free conditions. *UPB Scientific Bulletin, Series B: Chemistry and Materials Science*, 2018, 80, 101-116.

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