Ascorbic Acid-Induced Reactions

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Ascorbic acid is the most well-known 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. Ascorbic acid can be used as a substrate or mediator in organic synthesis. In this review, we report ascorbic acid-catalyzed reactions in organic synthesis. Several examples are included in this review to demonstrate that ascorbic acid is a versatile catalyst for the synthesis of diverse organic compounds. Reactions catalyzed by ascorbic acid are performed in organic or aqueous media. The readily available and easy handling features of ascorbic acid make these procedures highly fascinating.

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] and it has been used as a component of various dermatologic drugs and cosmetics for many years. Thermodynamically, ascorbic acid is an antioxidant. Its oxidation-reduction potential and the stability of its oxidation products add values to the application of ascorbic acid as an antioxidant [2]. In organic synthesis, ascorbic acid can be used as a reactant in accessing chiral synthons, and also it can be used as a catalyst to accelerate the reaction.

2. Ascorbic acid-mediated reactions

One of the important objectives of green chemistry is the utilization of eco-friendly solvents and catalysts instead of poisonous and toxic materials. To fulfill this, bio-based solvents and catalysts, which are usually non-toxic, biodegradable, and biocompatible, are one of the choices. 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.

3. Oxidation of amines to carbonyl compounds

Ascorbic Acid/copper dyad can be used as a catalytic system for selective aerobic oxidation of amines [3]. The oxidation process starts with atmospheric oxygen [4] and continues in a cascade-like fashion bypassing its oxidation potential to metallic salt, then to the organic mediator, which finally reacts with the substrate with high selectivity.All three reactions are pointed out that dehydroascorbic acid is the reaction intermediate and it acts as the oxidation mediator [3].

4. Cross-coupling of disulfides

Srogl*et al.* reported the Cu (I)-catalyzed, ascorbic acid-mediated cross-coupling reaction of aryl iodides with disulfides [5]. Ascorbic acid is a very good reducing agent, particularly when coupled with the Cu catalyst [6].

5. 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 [7]. The studies showed that metal complexes of ruthenium, nickel, iron, or copper can act as better halogen atom transfer agents than alkyl halides to improve the selectivity of addition to highly reactive alkenes. [8]. 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 [9]. It is also reported that the reactions conducted in the absence of catalyst demonstrated negligible conversions [10].

6. ATRP of polyhalogenated compounds to alkenes

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. [11].

7. 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, where ARGET-ATRC represent activators regenerated by electron transfer atom transfer radical addition. 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 [12].

8. Amination of aryl halides to primary aromatic amines

Aromatic amines are very important intermediates in the chemical industry, they are widely used in the manufacture of pharmaceuticals, agrochemicals, dyes, and polymers [13]. Transition-metal-catalyzed C−N bond formation has become a powerful and reliable method [14]. Even though this method has a lot of disadvantages, as ammonia is one of the cheapest chemicals [15], extensive investigations of the metal-catalyzed direct amination of aryl halides have been undertaken [16] using ammonia itself rather than ammonia surrogates [17]. 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 [18].

It was also found that the copper(I)- catalyzed amination of iodobenzene in liquid ammonia at room temperature requires only 1 mol % copper catalyst, which is lower than that reported generally [19] and 1 mol % of ascorbic acid.

9. Oxidation of sulfides

An inexpensive, convenient, and environmentally benign method for the selective oxidative transformation of sulfides into sulfoxides has been studied in detail [20].In this method synthetic flavin, 5-ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate acts as an efficient catalyst [21] for the oxidation of sulfides [22] in water under an oxygen atmosphere (1 atm) with the assistance of ascorbic acid as a reductant [23]. Imada et *al.*performed oxidation of a variety of aliphatic and aromatic sulfides.

10. Arylation of arenes with anilines

In organic synthesis, synthesis of biaryl compounds has become one of the most important reaction types due to the high impact of the biaryl structural motif in biologically active molecules, natural products, and materials chemistry [24]. Numerous metal-based and metal-free synthetic methods are available for the arylation of arenes [25]. Ascorbic acid as a radical initiator in a metal-free direct C-H arylation of (hetero)arenesis described [26]. The study showed that L-threo-ascorbic acid can act as a reductant towards arene diazonium ions [27] to generate aryl radicals in the absence of metals. [28].

11. Cyclization of aryl radicals with arenes

Radical cyclization reactions are important organic chemical transformations. That produces cyclic compounds through radical intermediates. The three basic steps during this process are selective radical generation, radical cyclization, and conversion of the cyclized radical to product [29]. Ascorbic acid can be used as an initiator for tandem radical cyclization of N-arylacrylamides to give 3,3-disubstituted oxindoles [30].

12. Metal-Free Synthesis of Aryl Sulfides

Carbon–sulfur (C-S) bonds can be found in a great number of pharmaceuticals, natural products, functional materials [31], ligands, and chiral auxiliaries in synthetic chemistry [32]. Thus the development of new, efficient, and stable approaches for the construction of the C-S bond has become a prominent area of research and been investigated by several research groups over the past few decades [33]. For example, Aryl sulfides are valuable building blocks for the syntheses of fine chemicals and medicinal agents [34] and the traditional approach to generate aryl sulfides is the Stadler–Ziegler reaction [35]. Stadler–Ziegler reaction has been studied and modified by several groups over the last century [36] and now it is extensively applied in the synthetic industry. Later, a new version of the Stadler–Ziegler reaction has been reported by researchers with reduced reaction steps. [37]. Transition-metal-catalyzed cross-coupling reactions of aryl halides with thiols or disulfides is another powerful and reliable method for the synthesis of aryl sulfides [38]. Later, an efficient new method for C-S bond formation has been reported by several groups that rely on the reaction of carbon-centered radicals and disulfides under relatively mild conditions [39]. Ascorbic acid-promoted synthesis of aryl sulfides with anilines nitrosated*in situ* by *tert*-Butyl Nitriteis reported [40].

13. Oxidative arylation of vinyl arenes to 2-Aryl acetophenones

2-Aryl acetophenones are versatile synthons. It is mainly used as a common precursor for the synthesis of a large variety of organic molecules. For example, it is used for the synthesis for heterocycles (quinoxaline [41], furan [42],imidazole [43], terminal alkenes [44], α-hydroxy ketones [45], 1,2-diketones [46], ketones [47], and aryl-substituted 2-aryl acetophenones [48]. Along with that, they are also found as structural motifs in different biologically important molecules and pharmaceuticals such as oxcarbazepine and ketotifen [49].

A convenient and general method for oxidative arylation of vinyl arenes by aryl radicals generated *in situ* from arenediazonium fluoroborates promoted by ascorbic acid in the air at room temperature was developed in absence of any additive and visible light irradiation [50].

14. Photoreductive removal of *O*-benzyl groups

There are different methods are available for the deprotection of the benzyl O-protective group [51]. A photoreductive method to remove benzyl O-protective groups from oxyarene N-heterocycles at positions capable for 2-/4-Opyridine−2-/4-pyridone tautomerismwas developed [52]. Ascorbic acid was chosen for the reduction and protonation. But protonation was also responsible for a decrease in reduction potential. The reduction potentials [53] were reduced to appropriate values for the commonly used photocatalysts.

15. Photocatalytic Reductive Fluoroalkylation of Nitrones

Novel methods for the introduction of a fluorinated fragment into a specific position of organic molecules are important [54] due to the wide range of applications of organofluorine compounds in medicinal chemistry and related fields [55]. A methodology of nucleophilic fluoroalkylation has dominated in this area for a long time [56]. Nitrones are mostly behaving as efficient radical traps [57]. They have sometimes been used to intercept fluorinated radicals leading to observable nitroxyl species [58]. A method for the addition of fluorinated groups to nitrones using an iridium photocatalyst and ascorbic acid as a stoichiometric reducing agent was described [59]. Ascorbic acid was used as a stoichiometric reductant [60]. It is reported that ascorbate anion can also serve as a source of hydrogen atom toward nitroxyl radical, besides its reducing activity [61]. For optimization studies, the group considered difluorinated iodide [62] and trifluoromethyl iodide [63] as model substrates.

16. Reductions of N-Heterocyclic Nitroaryls to Anilines

Arylamineshas a lot of applications. They are common substructures in pharmaceuticals, agrochemicals, dyes, and pigments, and a variety of other fine and specialty chemicals [64]. A variety of conventional stoichiometric reagents are appropriate for specific lab-scale conversion [65], while transition-metal-catalyzed hydrogenations dominate industrial applications [66].

A photoreductive method utilizing Ru- $(bpy)_3{}^{2+}$photocatalyst, blue light LEDs, and ascorbic acid to reduce nitro N-heteroaryl to the corresponding anilines was developed by Helaja et al. [67]. The optimization of the reaction conditions was checked with the photoreduction of 2-methoxy-6-nitroquinoline in the presence of ascorbic acid as the reductant and $Ru(bpy)_3Cl_2$ as the photosensitizer [68].

17. Dehalogenation of Vicinal Dibromo-, α-Halo-, and α,α-Dibromocarbonyl Compounds

Dehalogenation of *vic*-Dibromo-, α -halo-, or α, α -dibromocarbonyl compounds using catalytic tris(2,2'-bipyridyl)ruthenium dichloride ($Ru(bpy)_3Cl_2$) in combination with 1,5-dimethoxynaphthalene (DMN) and ascorbate as sacrificial electron donor was reported by Reiser and co-workers [69].

18. Synthesis of cyclic carbonates from CO_2

Cyclic organic carbonates represent a relevant class of chemicals and have a wide range of applications [70] and there are different methods available for its synthesis. Ascorbic acid/TBAI was an efficient organocatalytic pair for the synthesis of cyclic carbonates under ambient or very mild conditions [71].

19. Synthesis of 3-Aminoquinolinones, 3-Aminocoumarins and Anilines

3-Substituted quinolin-2(1H)-ones are heteroaromatic compounds, having a wide range of pharmacological properties [72]. Among the quinolin-2(1H)-ones family, 3-aminoquinolin-2(1H)-one and its derivatives are more important because of their promising biological activities [73], and their potential application in organic synthesis. A variety of multi-step methods are available for the synthesis of 3-aminoquinolinones, including the sequential nitration/reduction of 4-hydroxyquinolinones into 3-amino-4-hydroxyquinolinones [74], the Hofmann rearrangement of quinolinone-3-carboxylic acid derivatives,and cyclization of a suitable N-chloroacetyl-ortho-aminobenzophenone precursor to form a pyridiniumsalt followed by hydrazinolysis [75].A method to provide a range of 3-aminoquinolin-2(1H)-ones and 3-aminocoumarins from 3-bromoquinolinones and 3-bromocoumarins, respectively was introduced. The same method was also used for the synthesis of various anilines [76].

20. Synthesis of polyhydroquinoline and 1,8 dioxodecahydroacridine derivatives

The 1,4-dihydropyridine derivatives have a wide range of biological activities [77].For example, polyhydroacridine-1,8-diones, the poly-functionalized derivatives of dihydropyridine, containing acridine moiety possesses a wide range of pharmacological properties such as antifungal, [78] anticancer, [79] antitumor, [80] calcium β-blockers, [81] and antileukemic [82]. It has been reported that polyhydroquinoline derivatives, which having a 1,4-dihydropyridine moiety, also have biological properties such as antimalarial, antibacterial, antiasthmatic, anti-inflammatory, and anticancer [83]. 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 [84]. A catalytic role of ascorbic acid in the synthesis of 1,8-dioxodecahydroacridine and polyhydroquinoline derivatives through a multicomponent condensation reaction was described [85].

21. Aerobic benzylic C-H oxidation

Selective aerobic benzylic C–H oxidation of alcohols and hydrocarbons by TiO_2/AA/Co nanohybrid in ethyl acetate was reported [86].

22. Synthesis of Benzimidazoles

Benzimidazoles are building blocks for the construction of various important compounds such as pharmaceuticals, natural products, functional materials, and agrochemical compounds [87].A one-pot environmentally benign synthesis of benzimidazoles by cobalt ascorbic acid complex coated on TiO_2 nanoparticles *via* aerobic photooxidative cyclization reactions was realized [88].

23. Synthesis of 1,5-disubstituted 1,2,3-triazoles

1,5-Disubstituted 1,2,3-triazoles has many applications in chemistry, biology, and drug discovery. For instance, it contains two adjacent aryl substituents which are a privilege arrangement in many drugs and bioactive molecules [89]. Several methods are available for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles [90]. A copper-catalyzed decarboxylativeregioselective 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 was reported [91].

24. Synthesis of α-acyloxycarboxamides

Synthesis of carboxamide scaffolds, from the reaction of aldehyde, benzoic acid, and isocyanide derivatives catalyzed by ascorbic acid was performed [92].

25. Synthesis of 2-(alkylamino)- 2-oxo-1-arylethyl 4-(alkylamino)-4-oxo-3-arylbutanoates

The reaction of various aldehydes. Meldrum’s acid**,** and cyclohexylisocyanidewere investigated in the presence of ascorbic acid as a catalyst in the water at room temperature [92].

26. Synthesis of benzodiazepines derivatives

Benzodiazepines are important molecules in organic and medicinal chemistry [93]. Several synthetic routes have been reported for the synthesis of benzodiazepine derivatives [94]. Synthesis of benzodiazepines by the pseudo-five-component reaction in water catalyzed by ascorbic acid was reported [92].

27. Synthesis of benzoxazepine derivatives

The catalytic performance of ascorbic acid for the direct synthesis of benzoxazepine rings was evaluated [93].

28. Synthesis of dihydropyrimidinones derivatives

3,4-Dihydropyrimidin-2(1H)-ones exhibit a wide range of pharmacological applications, such as antiviral, antitumor, antibacterial, antiinflammatory activities, hepatitis B virus replication inhibitors [95], calcium channel modulators [96] and α_{1a}-adrenergic receptor antagonists [97].Synthesis of 3,4-dihydropyrimidin-2(1H)-ones was first reported by Biginelli in 1893 [98] Later, a lot of studies were carried out in the Biginelli reaction using different types of catalysts and conditions to enhance productivity [99]. 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 was developed [100].

29. Synthesis of octahydroxanthenes

Mohamadpour reported a green, convenient, and highly versatile method for the facile synthesis of 12-aryl-tetrahydrobenzo α xanthene-11-ones, 1,8-dioxo-octahydroxanthenes, and 14-aryl-14H-dibenzo α,j xanthenes under solvent-free conditions [101]. This method was based on the use of ascorbic acid as a natural green and highly effective catalyst. The study exhibited synthesis of a series of aromatic aldehydes afforded the various xanthene derivatives in high to excellent yields within a short reaction time

30. Conclusions

This review has illustrated the application of ascorbic acid as a catalyst/mediator in organic synthesis. Ascorbic acid-based catalytic system is non-toxic, economical, and readily available. In view of the current trend of conducting organic reactions under environmentally benign conditions, ascorbic acid-catalyzed transformations are extremely valuable. Notably, a diverse range of reactions is successfully conducted with ascorbic acid-catalyzed reactions. In many instances, the pertinent mechanism of the processes is advanced to explain the formation of the products. Based on this review, it is our expectation that many more reactions will appear using ascorbic acid as a catalyst.

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