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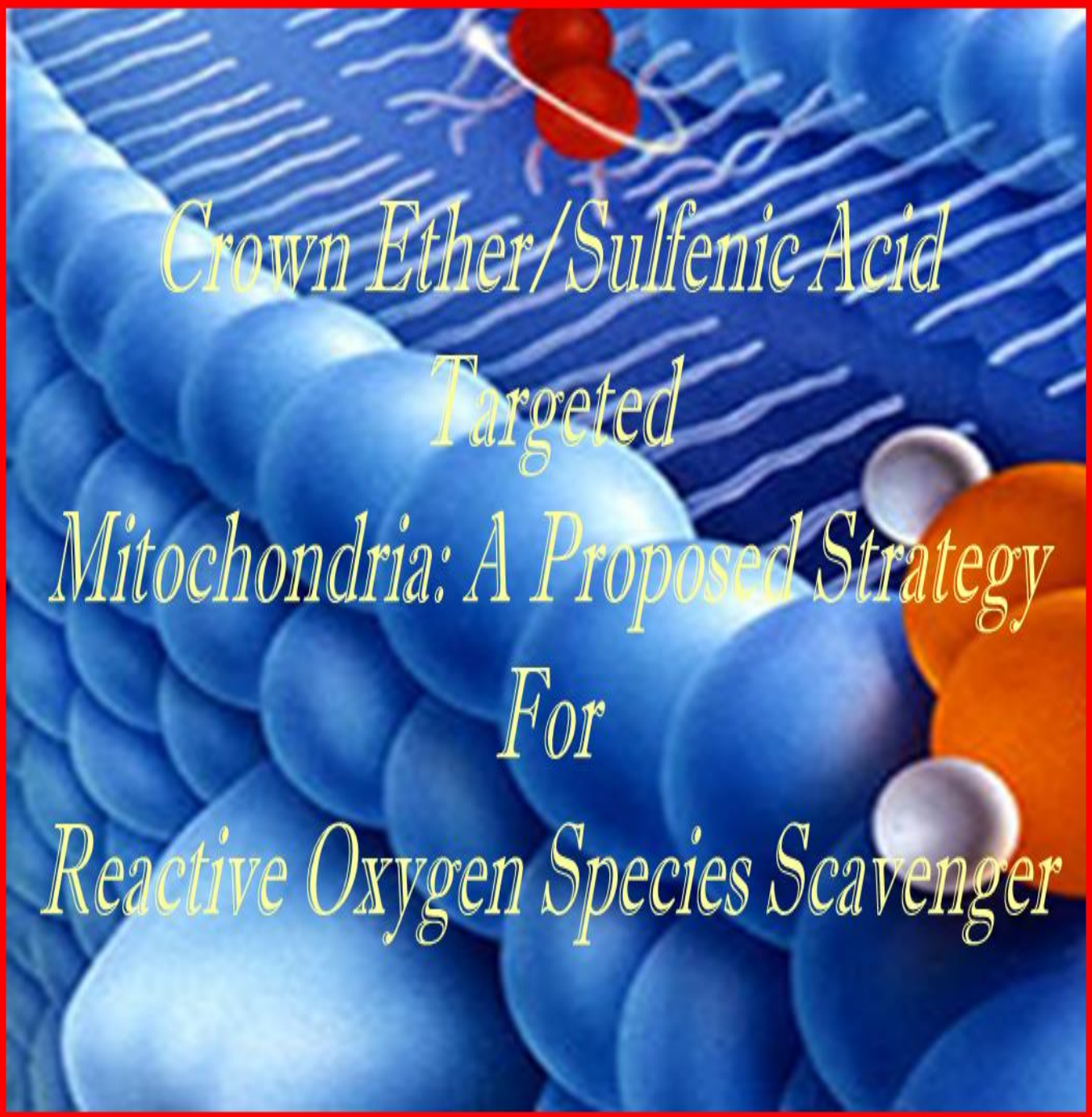

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Crown Ether/Sulfenic Acid Targeted Mitochondria: A Proposed Strategy For Reactive Oxygen Species Scavenger

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Mitochondrial dysfunction leads to a series of diseases as a result of excessive oxygen and nitrogen reactive species (ROS/RNS) caused by mitochondrial metabolism or by-products of oxidative phosphorylation as well as inability of antioxidant defense machinery to control them. This article sheds light on some of antioxidants targeted mitochondria, outlines some important factors in design of synthetic antioxidant compounds, and introduces a novel proposed approach for ROS scavenger based on crown ether/sulfenic acid solution.

Keywords: Antioxidants, Reactive oxygen species, Crown ethers, Sulfenic acids chemistry, Allicin, Antioxidants targeted mitochondria.

1. Introduction

Reactive oxygen and nitrogen species (ROS/RNS) are produced as natural byproducts of normal metabolism and play an important role in cell signaling and homeostasis.[1] They are implicated in intracellular signaling cascades that lead to changes in cell structure, function, and proliferation.[2] However, the imbalance between ROS/RNS generation and their scavenging by different antioxidant mechanisms can be disturbed by the different types of oxidative stress leading to oxidation of DNA, membranes, cellular lipids, and proteins, impairing their normal function and leading ultimately to cell death. Subcellular organelles “mitochondria” are the major production site of ROS where the proteins involved in the mitochondria electron transport chain are probable sites for ROS generation. Many diseases are associated with the increased production of ROS including, among others, atherosclerosis, neurodegenerative diseases, and cancer.[3] The main cause of such excessive production of these reactive species relates to mitochondrial metabolism and the oxidative phosphorylation cascade including the mitochondrial electron transport chain, xanthine oxidoreductase (XOR), NADPH oxidases as well as dysfunctional nitric oxide synthase (NOSs).[4] This article sheds light on some of antioxidants targeted mitochondria, outlines some important factors in design of synthetic antioxidant compounds, and introduces a novel proposed strategy for ROS scavenger based on crown ether/sulfenic acid solution.

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2. Oxidative stress

Mitochondria play a vital role in energy biogenesis *via* the electron transport chain (ETC). Unregulated leakage of electrons out of the ETC during normal aerobic respiration leads to the production of superoxide ($O_2^{\cdot -}$) in the mitochondria.[5] Elevated ROS production can disrupt mitochondrial function and at higher physiological levels may cause extensive damages to cells and the whole organism. These noxious actions, referred to as "oxidative stress", can cause ROS to flow to the cytosol, which in turn results in further increase in ROS production, thus forming a vicious cycle.[6] Therefore, a delicate balance between these radical species and antioxidant defense machinery within mitochondria is essential for the functions of cells, tissues, and organs.

2.1. ROS generation

Mitochondria play a crucial role in cellular regulatory processes, such as ATP production, intracellular Ca^{2+} regulation, ROS generation and detoxification and apoptosis. Mitochondria sources of oxygen reactive species include the electron transport chain (ETC), tricarboxylic acid cycle (TCA cycle) [also known as citric acid cycle] and monoamine oxidase (MAO) at the outer membrane. ROS generation is efficiently stabilized by antioxidant enzymatic activity and non-enzymatic low molecular compounds that scavenge overproduced ROS and limits their toxicity. Of most importance enzymatic components are copper-zinc (Cu/Zn) and manganese (Mn) superoxide dismutase (SOD) that dismutate $O_2^{\cdot -}$ to H_2O_2, glutathione peroxidase (GP) and catalase (CAT), which convert H_2O_2 to water.[7] Nitric oxide synthase (NOS) catalyzes the synthesis of nitric oxide ($NO^{\cdot}$), which may react with $O_2^{\cdot -}$ to give peroxynitrite ($ONOO^-$). While the non-enzymatic compounds include reduced glutathione(GSH), flavonoids, and proline. The nature of this antioxidant machinery underlies the necessity of detoxification of ROS for cellular survival. However, the perturbation in the redox balance of the cell, due to the excessive production of ROS that overwhelms the intrinsic antioxidant defenses resulting of aging or pathological processes, needs an external intervention to restrain these harmful endogenous oxidants. In fact, the products of lipid peroxidation that arise from overproduction of ROS have been shown to be mutagenic and carcinogenic and implicated as the underlying mechanisms in numerous disorders and diseases.[8,9] Likewise, mitochondrial Ca^{2+} overload, as a consequence of myocardial ischemia-reperfusion injury, leads to uncontrollable ROS generation and opening of mitochondrial permeability transition pore.[10] Furthermore, calcium has been shown to play a critical role in apoptotic pathway. Ceramide, arachidonic acid, and H_2O_2 stimulate an endoplasmic reticulum (ER)-calcium - dependent apoptosis. Massive calcium influx into mitochondria leads to the activation of mitochondrial permeability transition. The next section tries to touch upon the action of antioxidants.

2.2. *Antioxidant actions*

The characteristic feature of enzymatic oxidation is specificity. Each enzyme oxidizes specific substrate to give *regio*-, *stereo*- and *enantio*-specific products. In addition, the enzymatic oxidation is in general tightly programmed and regulated. On the other hand, free radical mediated lipid peroxidation proceeds randomly to give diverse products. For example, arachidonic acid, one of the major constituents in cell membranes, is oxidized by lipid peroxidation to give mixtures of *racemic* 5-, 8-, 9-, 11-, 12-, and 15-*cis*, *trans*- and *trans*,*trans*-hydroperoxyeicosatetraenoic acid (HPETE), while 15-lipoxygenase (LOX) enzyme gives 15(*S*)-*cis*,*trans*-HPETE exclusively which have potent bioactive signaling capacity.[11] Conse-quently, free radical mediated lipid peroxidation produces diverse products, which the relative import-ance of many competing reactions and distribution of them are determined by many factors at the reaction site and diffi-cult to be regulated.[12] Thus, the lack of regulation and specificity in ROS formation and reactions makes it difficult for lipid peroxidation products to act as physiologically essential signaling messenger. Antioxidants compounds and enzymes with different functions exert their respective roles by scavenging ROS to protect biologically essential molecules from oxidative modification. However, the random behavior of the over-production of free radical mediated lipid peroxidation cannot be controlled with antioxidants and enzymes. Therefore, an external intervention is needed to scavenge the excessive product-ion of these radical comp-onents, taking into consideration, that such an intervention may not scavenge physiologically important signaling ROS, nor inhibit the enzymatic lipid oxidation.

The chain processes of the formation of lipid-derived free radicals, which are the major class of oxid-ants, are involved initiation, propagation and termination steps. The interruption of this process by an anti-oxidant takes place through chain-breaking whether by preventing propagation of the radical chain or by terminating the chain. For example, the antioxidant enzyme superoxide dismutase (SOD) catalyzes the conversion of $O_2^{\cdot-}$ to H_2O_2 and O_2. H_2O_2 may be detoxified by catalase and by the Se-dependent glutathione peroxidase (GPx) (the glutathione disulfide formed in the reaction is reduced to glutathione by NADPH-dependent glutathione reductase (GR)) (Figure 1).

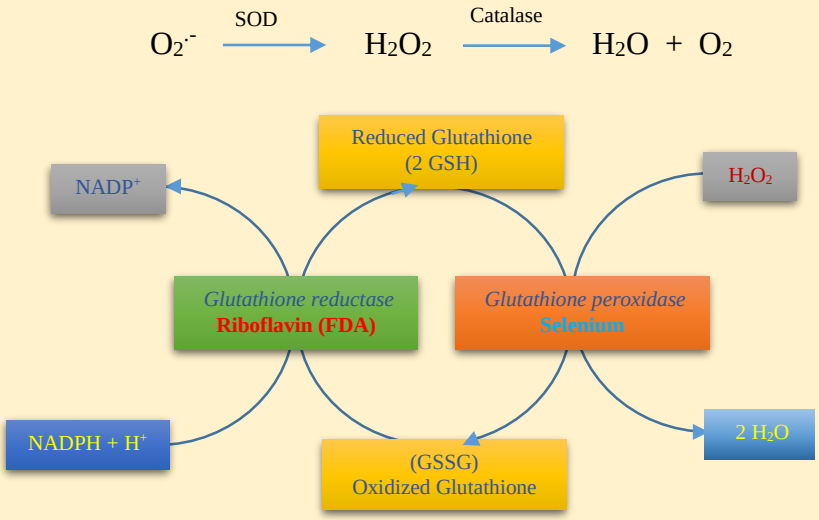

Figure 1. Antioxidant scavenging reactions.

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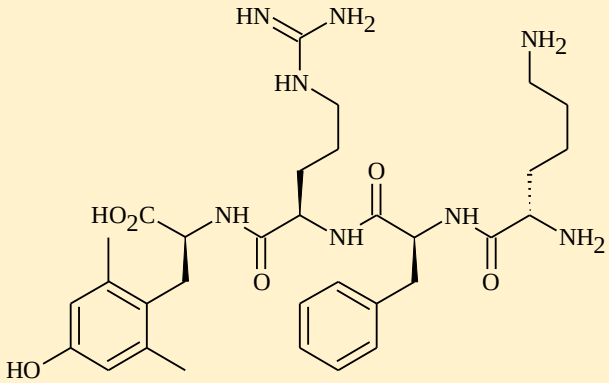
Indeed, a range of natural and synthetic antioxidants functions well to inhibit ROS generation, however, some of them such as vitamin E proved ineffective due to the fact that they cannot accumulate in the mitochondria, the major site of ROS generation. Thus, targeting an antioxidant component to the cellular and mitochondrial membranes is a paramount step to quench the excessive radical species.

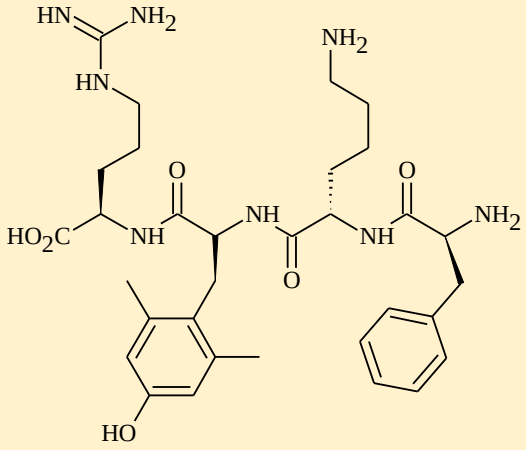
3. Antioxidants targeted mitochondria

Changes in the functions of mitochondria in cellular energy metabolism, apoptotic, Ca^{2+} homeostasis, cell signaling, and mutations in mitochondrial DNA under the influence of ROS lead to abnormal physiological activity, and are a cause of various pathologies. Many developing strategies to target components with therapeutic potential to mitochondria have been proven with their potentially beneficial effects as a therapy for ameliorating mitochondrial dysfunctions.[13]

Recently, most strategies have been based on engineering mitochondria-targeted antioxidants.[14,15] Since the mitochondria membranes spans across a negative potential, most of engineered antioxidants have a positively charged moiety in order to penetrate the mitochondrial phospholipid bilayer.[16] For example, the SS tetrapeptides such as SS-02 and SS-31 (Figure 2), have been proven to be effective in scavenging H_2O_2 and inhibiting Linoleic acid oxidation *in vitro*. Their antioxidant properties attribute to 2´,6´-dimethyl-tyrosine (Dmt) residues[17], which induce localization in the inner mitochondrial membrane, and the Dmt phenol moieties are likely responsible for the chemical reduction of ROS and peroxide bonds.[18]



SS-02



SS-31

Figure 2. Structures of *SS-02* and *SS-31*.

Among the synthetic approaches of antioxidants targeted mitochondria are lipophilic cationic compounds, that based on the negative mitochondrial membrane potential ($\Delta\Psi_m$) of 150-180 mV. This high potential generated by proton pumps (Complexes I, III and IV) is an essential component in the process of

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energy storage during oxidative phosphorylation, and together with the proton gradient (Δ pH) it forms the trans-membrane potential of hydrogen ions which is harnessed to make ATP. In addition, this high negative potential that generated across the inner mitochondrial membrane is the driving force to deliver cations and proteins which are necessary for healthy mitochondrial functioning. Based on this characteristic property, the lipophilic cations were developed as selective targeting components, such as rhodamine 123 and triphenylphosphonium (TPP^+). For example, MitoQ {mixture of [10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl]triphenylphosphonium bromide (Figure 3) and [10-(2,5-dihydroxy-3,4-dimethoxy-6-methylphenyl)decyl]triphenylphosphonium bromide}, have been proven to be effective antioxidant therapies against the damage caused by enhanced ROS generation. MitoQ is a derivative of ubiquinone conjugated to triphenylphosphonium, a lipophilic cation that enables this molecule to enter and accumulate within the mitochondria, which it accumulates 5- to 10-fold within the cell cytoplasm and several hundredfold within mitochondria, as a result of its cationic side group and the negative membrane potentials across both of these membranes.[19,20] The feature of this moiety is attributed to ubiquinone, which serves as an electron carrier and reducing the production of lipid peroxyl radicals within the mitochondria.[21]

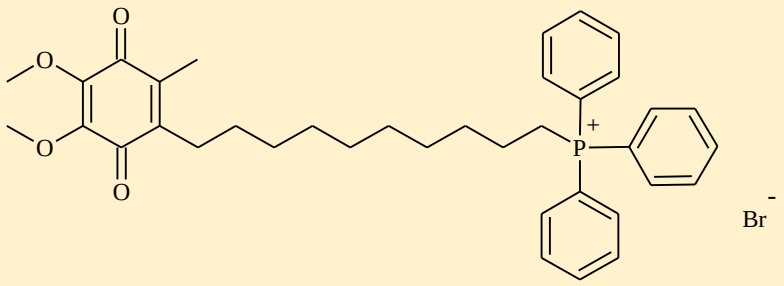

Figure 3. Structure of MitoQ.

4. Proposed Approach of Antioxidants targeted mitochondria

In a situation where the defense network of multiple antioxidant compounds and enzymes with their differ-ent functions are unable to exert their respective roles against oxidative stress, the external intervenetion becomes inevitable. Hence, there is a great interest in developing approaches to design radical scavenging compound or antioxidant to protect biological essential molecules from oxidative modification. Indeed, some of developed antioxidants have demonstrated their potency of both cellular and mitochondria-localization, and exhibited their effective role against the damage caused by the enhanced ROS generation. As an added engineering of these compounds, I introduce a proposed approach that could serve as a therapy for ameliorating mitochondrial dysfunctions.

The approach is based on crown ether/sulfenic acid solution. Crown ethers display ionophoretic properties in cell membranes and facilitate diffusion carriers that transport ions down their electrochemical gradient. They behave similar in function to natural product valinomycin, a known cyclic depsipeptide antibiotic, that stimulated K^+ uptake and H^+ efflux from mitochondria.[22] They are used in cancer treatment[23]

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and as drug delivery via vesicular formations.[24] Their ionophoric properties could potentially enhance antioxidants transport across the lipid bilayer. On the other side, sulfenic acids have been shown to play important roles as a catalytic center in enzymes and participated in signal transduction and transcription regulation events.[25]

They have a unique antioxidant activity and serving as the most powerful reactive radical-trapping angents.[26,27] But as far as I know crown ethers have not been investigated for their ability to localize within mitochondria and to sequester Ca^{2+} ions in order to quench their overload that leads to uncontrollable ROS production, as well as serving as antioxidant carrier. Even sulfenic acids have not been investigated to target mitochondria.

In view of the salient features of both crown ethers and sulfenic acids, I hypothesized that, if crown ethers can form complexes with calcium ions, they should be able to quench the burst intracellular Ca^{2+} level that caused by ischemic injury, and their ionophoric properties could assist sulfenic acid across mitochondria membranes where it can serve its function as scavenging of ROS and ameliorate oxidative damage.

4.1. Crown ethers

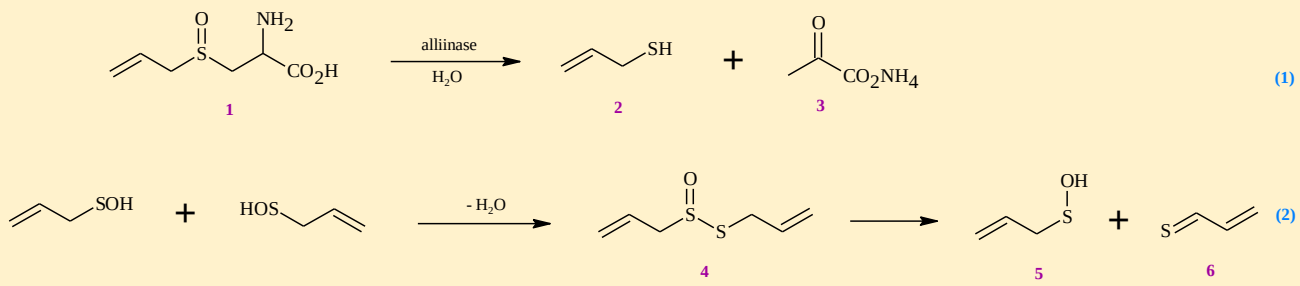
Crown ethers are cation complexing agents which the exterior of their ring is hydrophobic, allowing them to dissolve in the membrane lipid bilayer while caring the sequestered cation down its electrochemical gradient. They are able to form guest-host complexes with metal ions and neutral organic molecules. Their inherent flexibility allows to adapt to a range of environments, displaying solubility in aqueous and lipophilic solvents and rapid, reversible ion binding characteristics.[27] For instance, according to the Hansch lipophilicity scale, 18-crown-6 has a value of zero, indicating a perfect hydrophilic/lipophilic balance. This is due to the ligand's ability to flex according to the medium it encounters, exposing either hydrophilic oxygen atoms or lipophilic ethylenic groups.[27] Moreover, it is well known that they have the ability to increase binding affinity and to enhance solubility properties for a range of organic molecules.

4.2. Sulfenic acids

Reactive oxygen species-mediated cysteine sulfenic acid (Cys-SOH) modification has been implicated in several biological events. The antioxidant activity of many proteins is related to the oxidation of cysteine to sulfenic acid during the catalytic cycle, in which the Cys-SOH could act as an intermediate in disulfide bond formation during nonenzymatic protein folding.[28,29] Sulfenic acids have also been associated with cellular signaling and oxidative stress sensing.[30] Sulfenic acid formation is involved in H_2O_2-mediated inactivation of protein tyrosine phosphatases (PTPs). Tyrosine phosphorylation plays a central regulatory role in cell metabolism, growth, proliferation, differentiation, immune response, motility, tissue homeostasis and apoptosis. This redox reaction of catalytic Cys-SOH has been shown to be an important mechanism for the regulation of cellular PTP activity.[31] Human serum albumin, the most abundant protein in plasma, possesses a single free thiol which has been shown to form a stable sulfenic acid.[32] Also, reversible sulfenic

acid modification is shown to switch on or off the enzymatic activity of transcription and transduction factors including, among others, *Escherichia coli* OxyR.[33]

Sulfenic acids have been considered as transient species that lead to the formation of more stable disulfide bond. Such bond formation is mostly considered thiol oxidation reaction, which may proceed via thiol-disulfide exchange or condensation of a thiol with sulfenic acid. In fact, sulfenic acids have the unique ability to function as both a nucleophile and an electrophile due to the fact that the formal oxidation state of sulfur in sulfenic acid is 0. As an example for such dual nature is *Allicin* chemistry. Allicin is derived from Alliin **1** [(+)-*S*-allyl-l-cysteine *S*-oxide], which is found predominantly in garlic. Upon the homogenization of garlic, alliin is cleaved by alliinase to yield ammonium pyruvate (**3** Eq. 1) and 2-propenesulfenic acid (**2** Eq. 1). Self-condensation of **2** forms thiosulfinate allicin (**4** Eq. 2), which provides garlic with its odor and flavor. Allicin is known to undergo Cope elimination readily at room temperature to yield 2-propenesulffenic acid (**5** Eq. 2) and thioacrolein (**6** Eq. 2).



Sulfenic acids are powerful peroxyl-radical-trapping agents. Such antioxidant activities are attributed to alkanesulfenic acids that arise from the decomposition of the thiosulfinate precursors. The reaction of alkanesulfenic acids with peroxyl radicals is envisage to be diffusion-controlled and takes place by a common proton-coupled-electron-transfer mechanism.[34]

4.3. Synthesis of stable sulfenic acids

Owing to their high reactivity, most of sulfenic acid molecules are unstable under laboratory conditions due to the tendency to undergo self-condensation to afford thiosulfinate. However, many approaches have been developed to prepare stable sulfenic acids. It has been demonstrated that a major factor in the stabiliza-tion of sulfenic acid in proteins is the structural geometry where it is embedded in cavity and shielded from other reactive groups.[35] Thus, the steric factors play an important role in stabilizing sulfenic acids. Okazaki and Goto reported a readily accessible chemical system which simulates the environment of clefts present in protein sulfenic acids.[36] The stability of these molecules is related to the kinetic stabilization produced by bulky bowl-type environment of cyclophanes (Bmt). The Bmt-SOH was accomplished by the reaction of

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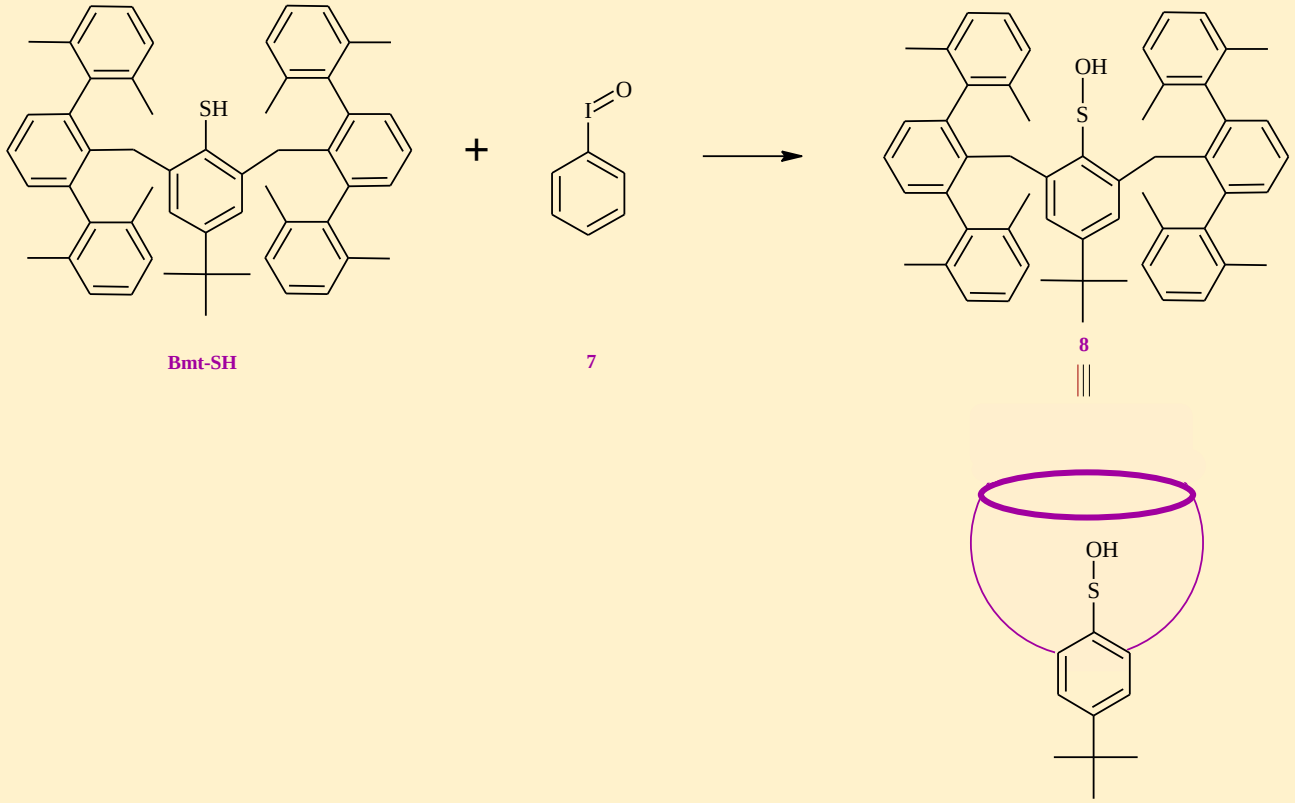
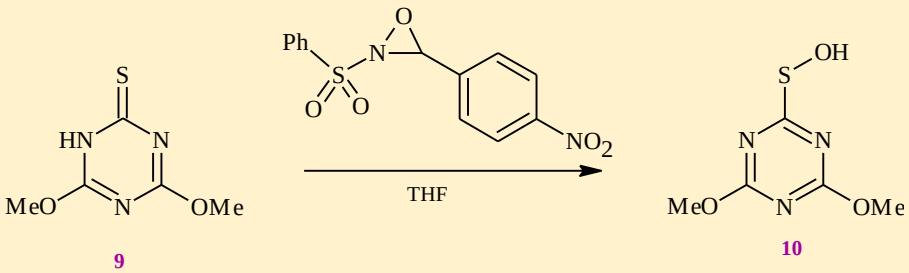
iodosobenzene **7**, a mild oxidant, with Bmt-SH to afford pure Bmt-SOH as a crystalline solid in 41%yield, in which the generation of symmetrical disulfide (Bmt-S-S-Bmt) **8** is sterically hindered (Scheme 1).[36]



Scheme 1. Synthesis of Bmt-SOH.

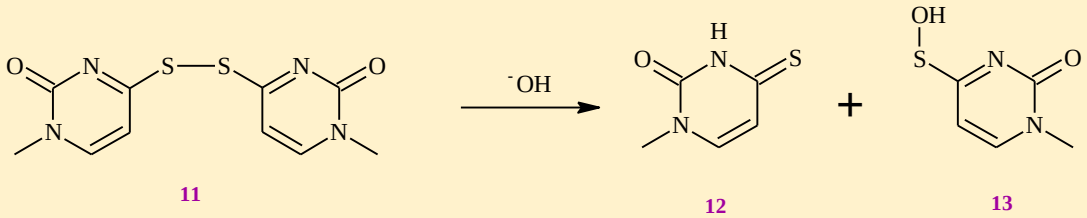
Furthermore, other factors must also be taken into consideration in order to isolate stable sulfenic acids.[29] First, for aromatic sulfenic acids, presence of electron-withdrawing-substituents diminishes the nucleophilicity of sulfenic acid sulfur, thus stabilizing the aromatic sulfenic acids as shown in the oxidation of 4,6-dimethoxy-1,3,5-triazine-2(1H)-thione **9** with 2-benzenesulfonyl-3-*p*-nitrophenyloxaziridine in THF solution to afford 4,6-dimethoxy-1,3,5-triazine-2-sulfenic acid **10** as a stable crystalline solid (Scheme 2).[37]



9 10

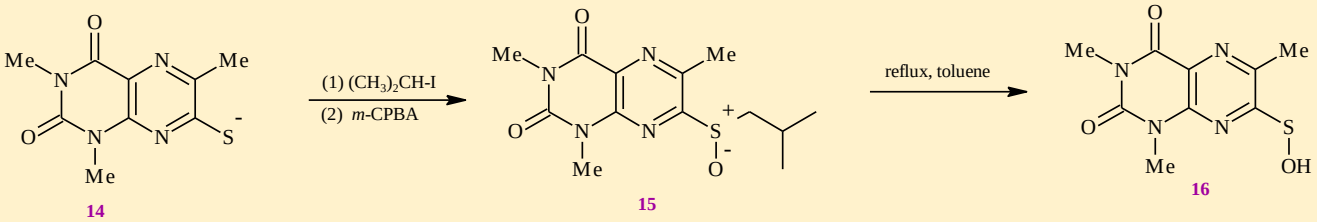
Scheme 2. Synthesis of 4,6-dimethoxy-1,3,5-triazine-2-sulfenic acid.

Second, intramolecular hydrogen bonding between sulfenic acid and a nearby hydrogen bond acceptor also imparts substantial stability. This is illustrated in two subsequent reactions: i) the synthesis of pyrimidine sulfenic acid **13** *via* alkali-mediated scission of disulfide in methyl analog of bis(4-thiouridine)disulfide **11** (Scheme 3);[38] and ii) the stable lumazinesulfenates were prepared from corresponding disulfides, in which



Scheme 3. The isolation and characterization of a pyrimidine sulfenic acid.

the disulfide bond was cleaved under alkaline conditions to yield the silver salt of 1,3,6-trimethyllumazine-7-thionate **14** followed by alkylation with *i*-propyliodide then by *m*-CPBA mediated oxidation to afford the corresponding sulfoxide **15**. Thermal cleavage of sulfoxide **15** resulted in the cope elimination and gave analytically pure 1,3,6-trimethyllumazine-7-sulfenic acid **16** (Scheme 4).[39]



Scheme 4. Synthesis of 1,3,6-trimethyllumazine-7-sulfenic acid.

Finally, the formation of thiosulfinates would be suppressed if the sulfenic acid is present in the form of sulfenate anion as the ionization reduces the hydrogen bond donating potential which is key to thiosulfinate formation. This is exemplified by the enhanced stability of 1-methyluracil-4-sulfenic acid **13** (Scheme 3) (pK_a 6.3) and lumazine sulfenic acid **14** (Scheme 4) (pK_a 4.8) in alkaline solutions.[38,39]

In another interesting study, Baldwin and co-workers reported the synthesis of unusually stable azitidinone sulfenic acid **18** (Scheme 5), which they attributed the stability of these sulfenic acids to both steric bulk of azetidinone moiety that prevents the thiosulfinate synthesis and to the relative thermodynamic instability of the substrate **17**.[40]

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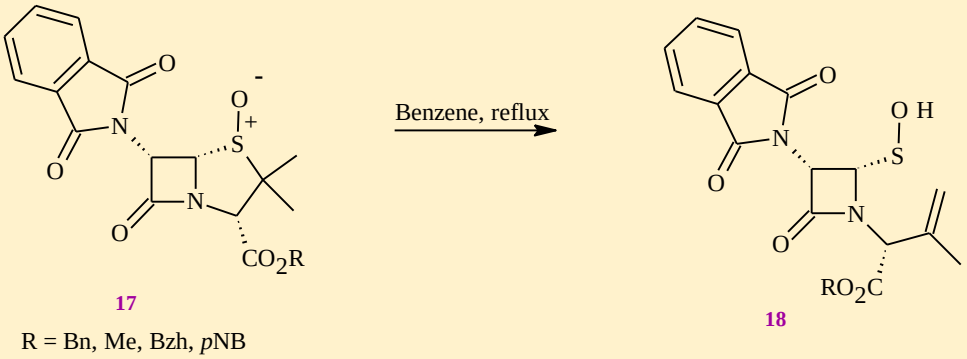

17

R = Bn, Me, Bzh, *p*NB

18

Scheme 5. Synthesis of azitidinone sulfenic acid.

4.4. Crown ether/sulfenic acid targeted mitochondria

The most important factors that control the binding strength and selectivity of crown ethers, are preorganization and complementarity; solvation and chelate ring size.[41] Crown ethers are known for their ability to sequester alkali metal cations, the efficiency of this effect depends mainly on cavity size besides enthalpy and pH. 18-crown-6 has high affinity for Ca^{2+} ions, where its cavity diameter is 2.6 Å (Figure 4). Thus, 18-crown-6 has the ability to bind and extract Ca^{2+} ions at physiological pH.

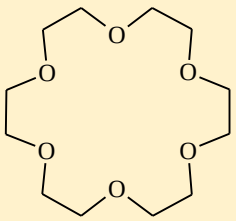

Figure 4. Structure of 18-crown-6.

Owing to their important role in redox regulation, synthetic sulfenic acids can be penetrated cellular and mitochondria membranes using crown ethers. I hypothesize that crown ethers ionophoric properties may enhance synthetic sulfenic acids permeability due to increasing their binding affinity and solubility enhancing properties as well as their strong tendency to act as hydrogen bond acceptors. For example, the sulfenic acid Bmt-SOH **8** (Scheme 1) is too large to reside within the cavity of 18-crown-6 because of the fact that complex formation depends on the relative size of the host cavity and the gust molecule.[42] However, partial complexation is possible with larger molecular variants as a result of hydrogen bonding interactions.[41]

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5. Conclusion

The burst of mitochondrial ROS generations that leads to large number of disease states, prompted a therapeutic intervention based on controlling the mitochondrial route for apoptosis. Antioxidants targeted mitochondria, the major site of ROS production, is a crucial step to reduce or eliminate the excessive generation of ROS. In this context, I proposed a novel approach based on crown ether/sulfenic acid solution to act as a therapeutic compound for ameliorating mitochondria dysfunctions. This approach has not previously been investigated as antioxidants targeted mitochondria or as an agent transport through mitochondria membranes. I hypothesize that crown ethers "18-crown-6" have the ability to sequester Ca^{2+} ions at physiological pH. Such important function may lead to quench the overload of Ca^{2+} ions that cause uncontrollable ROS production. Moreover, the ionophoric properties of crown ethers could enhance antioxidants transport across the lipid bilayer of mitochondria. Sulfenic acids have a unique antioxidant activity and play an important role in redox regulations. Albeit their propensity to undergo self-condensation to form thiosulfinates, many strategies have been developed to prepare stable sulfenic acids. These synthetic compounds could localize in mitochondria using crown ethers "18-crown-6" which may enhance the solubility and permeability of sulfenic acids across cell membranes due to their ionophoric properties. Crown ethers can form partial complexation with larger molecular variants, namely, sulfenic acids regardless their relative cavity owing to their strong tendency to serve as hydrogen bond acceptors.

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Snapshots of some topics of interest of recent notable advances in chemistry

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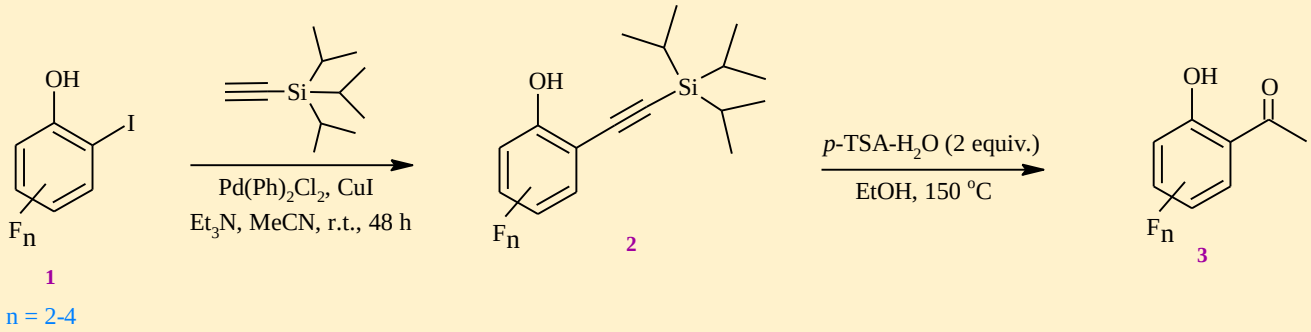
Synthesis of Polyfluorinated *o*-Hydroxyacetophenones: Precursors of 3-Benzylidene-2-phenylchroman-4-ones

A simple and metal-free synthetic route for fluorinated *o*-hydroxyactophenones is described. The procedure involved the replacement of iodine atom of fluorinated *o*-iodophenols with acetyl group *via* triisopropylsilyl moiety followed by hydrolysis using *p*-toluenesulfonic acid monohydrate. The product can act as a precursor of polyfluorinated 3-benzylidene-2-phenylchroman-4-ones.

As versatile precursors in synthesis of a range of biologically active molecules, Politanskaya and co-workers demonstrated a simple and efficient procedure for the synthesis of fluorinated *o*-hydroxyacteophenones. The cross-coupling of fluorinated *o*-iodophenols **1** with triisopropylsilyl acetylene (TIPS-acetylene) was accomplished in the presence of bis(triphenylphosphine)pallafium dichloride, copper (I) iodide, and trimethylamine as catalysts in dry acetonitrile as a solvent at room temperature in an argon atmosphere to afford TIPS-ethynylphenols **2** in high yields (Scheme 1).

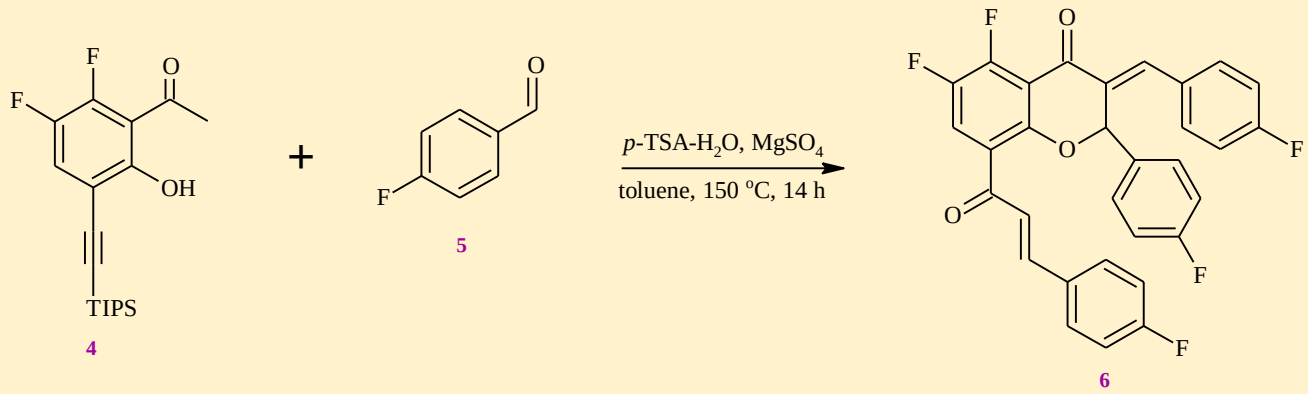


Scheme 1. Synthesis of fluorinated *o*-hydroxyacetophenone.

In the hydration step, TMS group activates the triple bond in arylacetylene *via* the action of *p*-toluenesulfenic acid monohydrate (*p*-TSA-H_2O) to give fluorinated *o*-hydroxyacetophenone **3**.

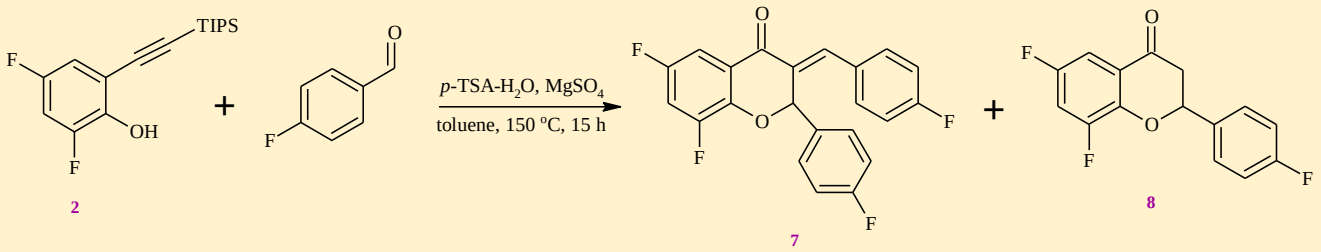
Synthesis of polyfluorinated 2-arylchroman-4-ones:

The interaction of *o*-hydroxyacetophenone **4**, which contains a triple-bond moiety, with an excess of 4-fluorobenzaldehyde **5** in the presence of *p*-TSA-H_2O and drying agent ($MgSO_4$) furnished the desired product **6** in good yields (Scheme 2). The exocyclic double bonds have *E*-configuration.



Scheme 2. Synthesis of fluorinated 3-benzylidene-8-cinnamayl-2-phenyl-chroman-4-one (**6**).

TIPS-ethynyl derivatives **2** can also be used as substrates to produce fluorinated chroman derivatives (Scheme 3).



Scheme 3. Synthesis of fluorinated 3-benzylidene-2-phenylchroman-4-one **7** and 2-phenylchroman-4-one **8**.

Review

L. Politanskaya, E. Tretyakov, C. Xi, *J. Fluorine Chem.* **2020**, *229*, 109435.

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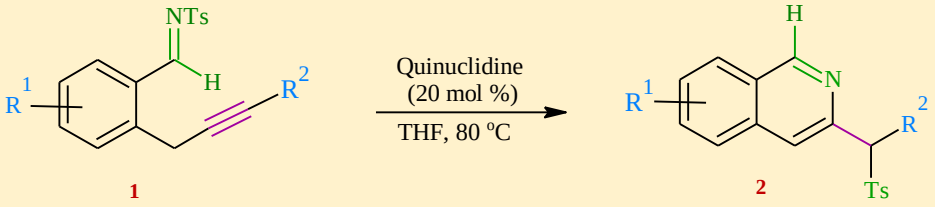
Organo-catalyzed Synthesis of Isoquinolines

The synthesis of isoquinolines from 1,5-yne-imines *via* the intramolecular migration of *N*-aryl sulfonyl substituent to the carbon atom of the alkyne moiety is reported. The utility of non-toxic amines such as NEt_3 and quinuclidine has been proven excellent atom efficiency.

The unique structures of isoquinoline derivatives display a variety of bioactive properties. Thus, the development of new approaches for their preparation based on non-toxic organocatalysts is worthwhile. Ogoshi and his team reported a facile quinuclidine-mediated synthesis of isoquinolines **2** that proceeds *via* the formal *exco*-cyclization of 1,5-yne-imine **1**, followed by intramolecular migration of an *N*-aryl sulfonyl group to the carbon center of the alkyne moiety (Scheme).



1

R^1 = F, Cl, MeO, Ph
R^2 = Me, Ph, *n*-C_5H_{11}, TMS

2

up to 86% yields

Scheme. Quinuclidine-catalyzed synthesis of isoquinoline derivatives.

The introduction of *meta*-fluorine or *para*-chlorine substituents with respect to the propargyl group accelerated the reaction.

Review

Y. Hoshimoto, C. Nishimura, Y. Sasaoka, R. Kumar, S. Ogoshi, *Bull. Chem. Soc. Jpn.*, **2020**, *93*, 182–186.

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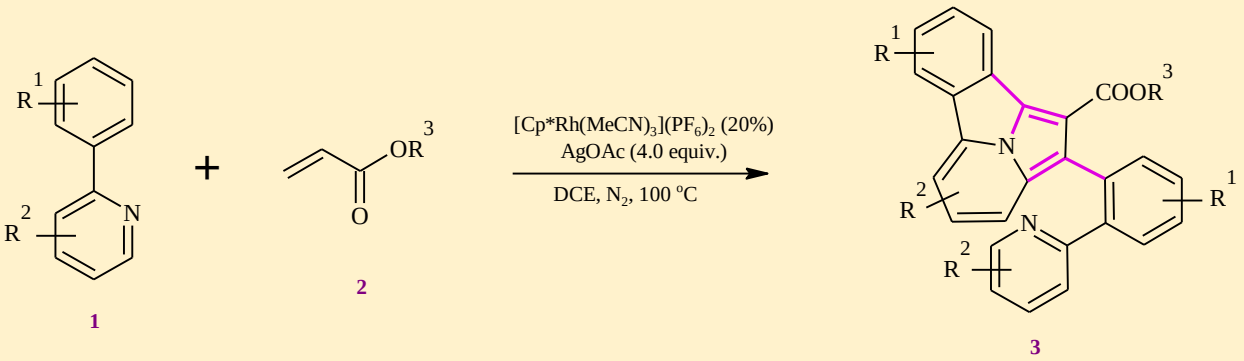
Construction of Indolizino[3,4,5-*ab*]isoindoles

A facile synthesis of indolizino[3,4,5-*ab*]isoindoles *via* rhodium(III)-catalyzed tandem reaction is highlighted. The reaction involved tandem C-H activation, Michael addition, [12+2] cycloaddition and oxidative aromatization.

Indolizino[3,4,5-*ab*]isoindoles exhibit high fluorescent quantum yields in blue to green regions and are found to be candidates for applications in electroluminescence materials and sensors. The current synthetic pathways of these compounds suffer from many drawbacks. In this regard, Liu and co-workers reported a facile synthetic procedure which proceeded *via* the tandem reaction of two molecules of 2-phenylpyridines **1** and two molecules of acrylates **2** in the presence of $[Cp^*Rh(MeCN)_3](PF_6)_2$ (20 mol %) and AgOAc (4 equiv.) as an additive in DCM at 50 °C to furnish indolizino[3,4,5-*ab*]isoindoles **3** in good to moderate yields (Scheme). This tandem reaction involved the formation of two C-C bonds, two C=C bonds, one C-N bond and two rings.



Scheme. Construction of indolizino[3,4,5-*ab*]isoindoles.

Various electron-withdrawing and electron-donating substituents residing at different positions on either the benzene ring or the pyridine ring of 2-phenylpyridines were compatible, providing the desired products.

Mechanistically, the reaction involved tandem C-H activation, conjugate addition, [12+2] cycloaddition and oxidative aromatization.

Review

C. Liu, S. Wu, W. Sun, H. Meng, S. Xing, B. Zhu, *Asian J. Org. Chem.*, **2020**, *9*, 68 –72.

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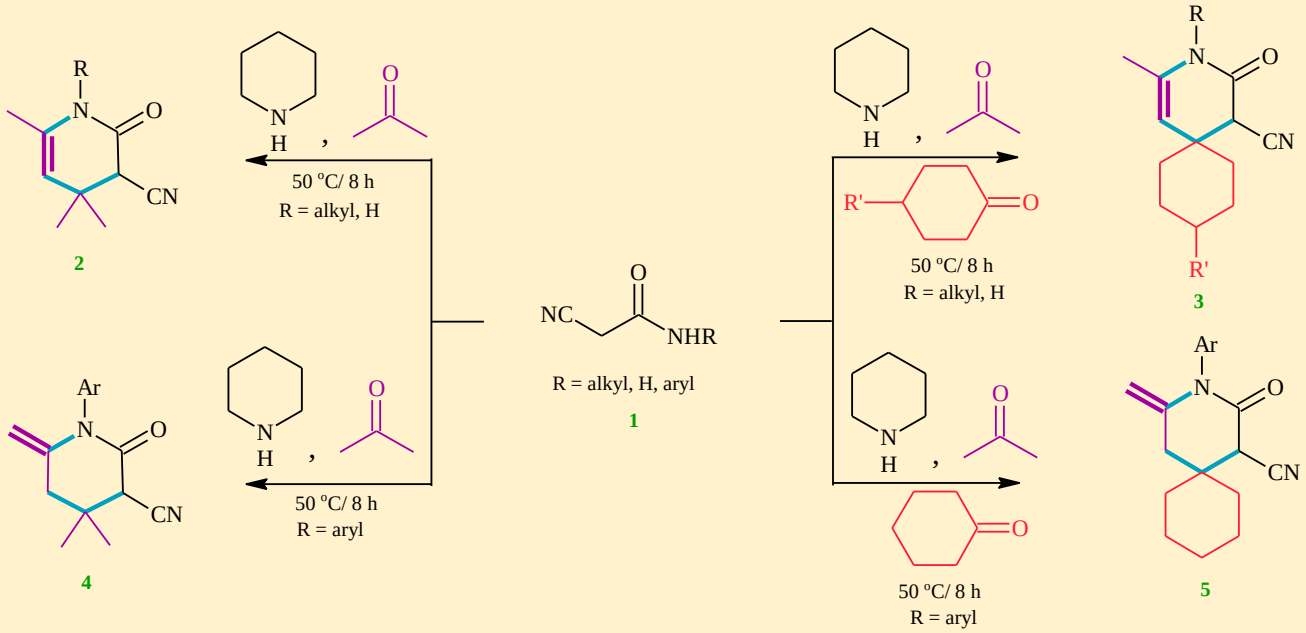
Simple Synthetic Route for Pyridin-2-ones Bearing Quaternary Centers

A multicomponent one-pot synthetic procedure is described for the synthesis of four types of pyridin-2-ones bearing quaternary centers including spiropyridin-2-ones. The synthetic pathway is accomplished *via* the solvent-free cascade reaction of 2-cyanoacetamides, cyclohexanone / cyclopentanone and acetone using piperidine as a promoter.

Lin and his team demonstrated a simple and practical operated route for the synthesis of four types of functionalized pyridin-2-ones. The characteristic features of the approach are green, practical operation (multi-component one-pot) with high yields (up to 95%) and employing the low reactive acetone/cyclic ketone to prepare compounds with quaternary carbon centers or spirocompound libraries.

The reaction of three component 2-cyanoacetamides **1**, cyclohexanone, and acetone was reacted in the presence of piperidine as a promoter at 50 ^{o}C for 8 h to furnish the functionalized pyridin-2-ones **3 & 5** in excellent yields (Scheme 1). Aryl substituted 2-cyanoacetamides gave a double bond functionalized products **5** under the same reaction conditions. While the reaction of 2-cyanoacetamides **1** with acetone in the presence of piperidine produced pyridin-2-ones bearing quaternary centers **2 & 4** in higher yields than those of compounds **3 & 5** under the same reaction conditions.



Scheme 1. The synthesis of pyridin-2-ones bearing quaternary centers.

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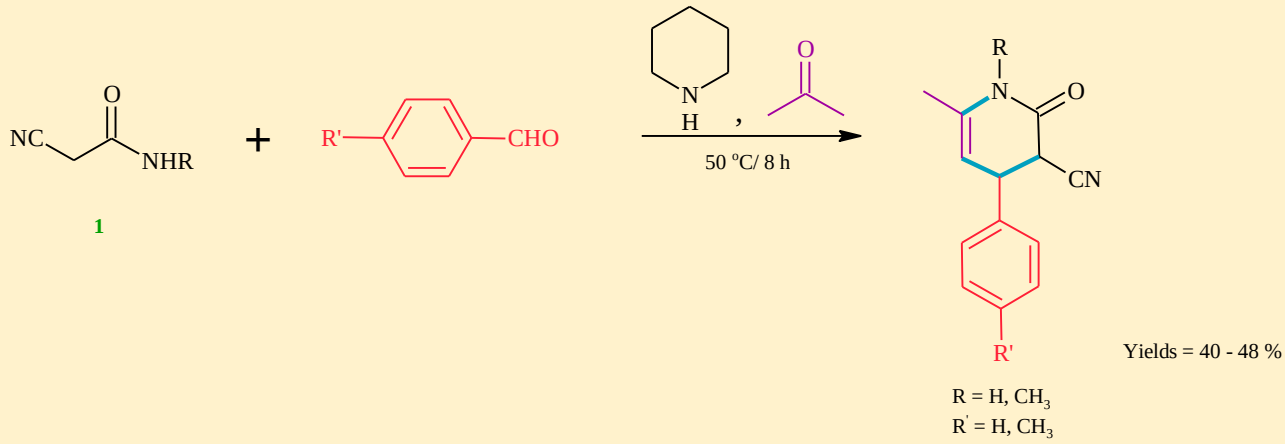
Cyclopentanone proceeded the reaction well, but produced the target compound in lower yield compared to cyclohexanone. Aromatic aldehydes were reacted with 2-cyanoacetamides **1** and acetone under the same reaction conditions to yield the target compounds in lower yields than those of cyclic ketones (Scheme 2).



Scheme 2. Synthesis of pyridin-2-ones from aromatic aldehydes.

Mechanistically, the reaction is achieved *via* the knoevenagel reaction, Michael addition reaction, and intramolecular cyclization. This reaction is a regio-selective dehydration reaction that depends on the stability of the target products.

Review

L. Kong, R. Huang, H. He, Y. Fan, J. Lin, S. Yan, *Green Chem.*, **2020**, *22*, 256–264.