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Recent Trends on Chemically Modified Chitosan for Biological Interest

Mahmoud A Hussein

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ABOUT THE AUTHORS

Youssef O Al Ghamdi[1]*, Khalid A Alamry[1], Abdullah M Asiri[1,2] and Mahmoud A Hussein[1,3]*

[1]Department of Chemistry, King Abdulaziz University, Saudi Arabia

[2]King Abdulaziz University, Saudi Arabia

[3]Chemistry Department, Assiut University, Egypt

***Corresponding author details**

Mahmoud A Hussein

Chemistry Department, Assiut University, Assiut, Egypt,
Email: mahussein74@yahoo.com; maabdo@kau.edu.sa

Youssef O Al Ghamdi

Youssef O Al Ghamdi Department of Chemistry, King Abdulaziz University, Jeddah, Saudi Arabia,
Email: youssefalghamdi@hotmail.com

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Abbreviations

E. coli	*Escherichia coli* (E. coli)
S. aureus	*Staphylococcus aureus*
DA	Degree of N-acetylation
UV	Ultraviolet-Visible Spectroscopy
IR	Infrared Spectroscopy
CD	Circular Dichroism
NHS	N-Hydroxysuccinimide
NAC	N-Acetyl-L-Cysteine
CAPTCCHT	Chloracetyl Phenyl-Thiosemicarbazone Chitosan
NMP	N-Methyl-2-Pyrrolidinone
GTMAC	Glycidyl Trimethylammonium Chloride
TBAI	Tetrabutylammonium Iodide
TBHP	Tertbutyl Hydroperoxide

Abstract

There is no doubt that, chitosan is considered as one of the most important biopolymers that can easily extracted from nature resources or synthesized in the chemical laboratories. Chitosan also display a suitable number of important properties in different fields of applications. Recently, chitosan has been reported as a perfect candidate as a trestle macromolecule for variable biological fields of study. This include, tissue engineering. cell culture and gene delivery, etc. Furthermore, chitosan has widely used in different types of industries which include: food, agriculture, fragrance, and even cosmetic industries. Besides that, chitosan derivatives is treated as excellent tool in waste water treatment. Therefore, the present work gives a simple selective overview for different modifications of Chitosan macromolecule with a special attention to its biological interest. Prior that, a closer look to its resources, chemical structure as well as general properties has been also determined which include its solubility character and its molecular weight. Furthermore, the chemistry of chitosan has been also mentioned with selected examples of each type of interaction. Finally a brief for sulfone based modified chitosan has been reported including classical methods of synthesis and its experimental variants.

Keywords: Synthesis; Characterizations; Chitosan; Chemical modifications; β-ketosulfone; Biological interest

Introduction

Chitosan is an extremely promising biopolymer that is isolated primarily from sea food processing wastes. This polymer possesses a number of valuable properties. It is practically a single polycation of natural origin [1]. Chitosan is nontoxic, biocompatible, and biodegradable; as a result, it is not accumulated in the body and in the environment [2,3]. Natural polymer of chitin and chitosan have been studied since 1990 due to their different functionals group which show excellent biological properties such as biodegradation in the human body [4,5] and immunological [6,7] antibacterial [8,9] and wound-healing activity [10-12]. Therefore, the development of materials that exhibit antimicrobial activity appears to be highly pertinent in health care. According to Musumeci and his team an antimicrobial agent is a substance that kills or inhibits the development and the multiplication of microorganisms, such as bacteria, fungi, protozoa and/or viruses [13]. Among many abundant natural and biopolymers have a unique structures, chitosan and its derivatives can be addressed. More particularly, a development of chitosan was developed for many applications such as artificial skin, absorbable surgical suture, and a wound healing accelerator, and also as new physiological materials due to their antitumor, immuno enhancing, and hypocholesterolemic properties [14]. Moreover, scitific work on chitosan has focused on a functional, renewable, nontoxic and biodegradable biopolymer for diverse applications, especially in pharmaceutics [15]. Uptodate, chitosan has been found as a good linker as a material for gene delivery [16], cell culture [17], and tissue engineering [18,19]. Moreover, chitosan has found wide use in food [20], fragrance, and cosmetic industries [21]; agriculture; and wastewater treatment [1-3, 22-25]. In the food industry, chitosan is employed as a thickener and stabilizer of dietetic foodstuffs [26] and as a biologically active additive [27] that destroys pathogenic microflora and binds and removes fats, toxins, heavy metal ions, and radionuclides from the body. In the cosmetic industry, chitosan, which efficiently adsorbs on the negatively charged surface of hair to form a protective film, is used as an antistatic and conditioner in the manufacture of shampoos [1,28].

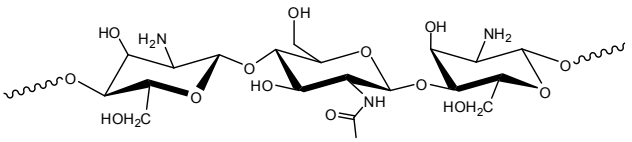
Chitosan is employed for sewage treatment because it can induce the flocculation of emulsions stabilized by anionic surfactants [29] and can bind heavy metal ions [30] surfactants, synthetic and natural polyanions (e.g., proteins), and other contaminants [26]. Public health heads the list of application areas of chitosan [31]. Chitosan is in wide use in the manufacture of weight loss drugs [26] because it binds fats that are contained in food and removes them from the body; in addition, the adsorption layers of chitosan complexes with fatty acids facilitate inhibition of fat hydrolysis by enzymes and thus aggravate its assimilation in the body. However, the most important application of this polymer is its use as a drug carrier [15,32,33]. Most of chitosan functions mainly depend on both their chemical structure and the molecular size which limit the application of this native polysaccharide due to its high molecular weight and highly viscous nature resulting in its low solubility in acid-free aqueous media. In recent years, modification of chitosan and its dervitaves have studied since efficient utilization of marine biomass resources has become an environmental priority and for a better use of chitosan.

Resources, chemical structure and general properties of chitosan

Chitosan structure contains of β-(1→4)-2-acetamido-D-glucose and β-(1→4)-2-amino-D-glucose units, with the latter usually exceeding 80% [34]. The alkaline treatment is responsible on the proportion of the two monosaccharide units in chitosan . Generally, linear structure has the individual chains, which allows a twist every 10.1-10.5 Å along the chain axis. Polymer chains rotate either left or right due to the chirality of each monosaccharide unit. Accordingly, X-ray model and nuclear magnetic resonance (NMR) spectra are good tools to identify the three crystal types of chitosan: α, β and γ type.

Among these, α-type is considered as the most common type obtained from crust of shrimp and crab [35]. Chitosan contains three types of reactive functional groups, an amino/acetamido group as well as both primary and secondary hydroxyl groups at the C-2, C-3 and C-6 positions, respectively. The amino contents mainly contribute for any change in the structures and physico-chemical properties, and its distribution is random, which affect the interaction between hydrogen bonds as given in Figure 1. The molecular weight and its distribution is considered to be the most important characteristic to for these polymers. The solubility of chitosan and its derviaties is always a big challenge with dissociation of aggregates often present in polysaccharide solutions. For this purpose, various method for choosing a solvent were developed , including an acid at a given concentration for protonation together with a salt to screen the electrostatic interaction. The importance of solvent is related with the molecular weight which can be calculated from intrinsic viscosity using the Mark-Houwink relation. The pKa of chitosan plays a role in the solubility where only possible to dissolve chitosan in. Polymeric acidic conditions and is insoluble at pH values above 6.3. However, chitosan oligomer has a low viscosity, and is freely soluble at neutral pH. Chemical or enzymatic methods can be used to produce a low molecular weight chitosan (LMWC) and chitosan oligosaccharides (COS) from the hydrolysis of chitosan. The disadvantage of chemical method requires a high energy and is hard to control, whereas the enzymatic hydrolysis of chitosan offers many advantages. Viscosity plays an important factor for determination different molecular weight chitosan. Unlike most polysaccharides, positive charges on chitosan, LMWC and COS, give an advantage to bind strongly to negatively charged surfaces; which improve for many of the observed biological activities [36]. However, a different biological activity is related to different structures of chitosans, which lead to the ability for various biological activities tests. Each special type of

bioactive has been developed by the chemical modification and enzymatic hydrolysis have been used for enhancement of chitosan medical application. Owing to its ability to bind oppositely charged DNA, chitosan can be used for gene delivery as well [15,37,38].



Chitosan

Figure 1: Chemical Structure of Chitosan.

Sources of chitosan

Chitosan occurs in nature in some fungi [39] however, its main source is chitin. This polysaccharide is second in abundance in nature to cellulose. Chitin is one of the main components of the exoskeleton of arthropods (crustaceans, arachnids, and insects); it enters into the composition of the cell walls of fungi, bacteria, and some algae [2,3,39]. The main source of raw material for the commercial production of chitin is provided by the shells of crustaceans (crabs, lobsters, krill) [40] which are waste products of their processing. Shells are comprised of three main components: chitin, calcium carbonate, and protein. In addition, they contain small amounts of lipids and pigments. The mean content of chitin in shells does not exceed 20-25% [40]. Chitin is insoluble in most solvents; therefore, it cannot be isolated directly from shell [41]. Chitin is obtained through the successive separation of the mineral and protein components of the shell. For this purpose, the shells are treated with hydrochloric acid (for demineralization) and then caustic soda (for deproteination). The precipitate is washed with water and then the fats and the pigments are removed from it, for example, via extraction with ethyl acetate [41]. Chitosan in turn is prepared by the deacetylation of chitin, that is, by its chemical modification leading to the splitting off acetyl groups. The acetyl groups of chitin are stable against hydrolysis owing to the presence of hydrogen bonds between C=O and N-H fragments of amide groups of neighboring chains. Therefore, deacetylation is conducted under severe conditions [42] through treatment with a concentrated aqueous solution of NaOH at a high temperature (110-140°C) for 4-6 h. Under these conditions, not only acetyl groups are eliminated but also glycoside bonds between repeat units are ruptured; that is, deg radation of the polymer occurs Thus, chitin isolated from shells of crustaceans has a molecular mass of nearly (2.0-2.5) × 106 whereas the molecular mass of chitosan is usually an order of magnitude lower. Both chitin and chitosan are crystallisable polymers. On average, the degree of crystallinity of chitin is 70%; in the case of chitosan, it is lower: 30-45% [43]. This fact is explained by the distortion of the regular structure of the polymer during deacetylation. Despite the severe conditions of deacetylation, it is frequently impossible to attain full splitting of all acetyl groups. As a result, the final polymer (chitosan) contains intact chitin N-acetyl-D-glucosamine units along with D-glucosamine units. The mean content of acetyl groups is characterized by the degree of acetylation. It is impossible to cite a certain DA value below which the polymer is regarded as chitosan and above which the polymer is regarded as chitin as illustrated in Figure 2. These polymers are usually distinguished by their abilities to dissolve in dilute aqueous solutions of organic acids, because chitosan is soluble, while chitin is insoluble in such a medium. Solubility appears, as a rule, at DA < 50-60%. Depending on deacetylation conditions, a copolymer with a micro block or statistical distribution of acetyl units can be prepared. The micro block distribution is observed if the reaction is conducted under het erogenous conditions, when the chitin powder in the solid state is treated with concentrated alkali. The statistical distribution of acetyl units is obtained if the dissolved chitin is treated with alkali under homogeneous conditions [44].

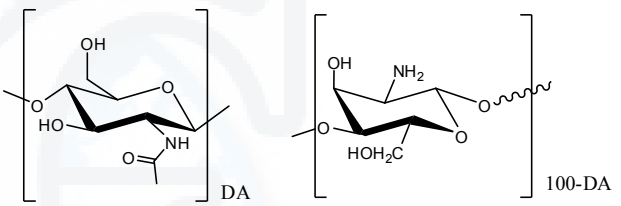


Figure 2: Degree of acetylation (DA) of chitosan.

Chemistry of chitosan

Investigations of chitosan have been concerned with its preparation from chitin and its resultant degree of deacetylation and molecular weight, as well as their effects on solution properties, since these chemical properties may significantly affect the biological properties and applications of chitosan and its derivatives. The effects and characterizations of such properties (DD, molecular weight and solubility) are briefly discussed below.

Degree of N-acetylation and degree of deacetylation: Takahashi et al. [45] & Chiu et al. [46] reported that a higher DD would lead to a higher antibacterial efficacy against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*). According to Je et al. [47], chitosan with a DD of 90% has a higher scavenging reactive oxygen species (ROS) efficacy compared to those with DDs of 75% and 50%. Degree of N-acetylation (DA) is commonly determined as the ratio of 2-acetamido-2-deoxy D-glucopyranose towards 2-amino-2-deoxy-D-glucopyranose structural units. On the other hand, another term DD, which is defined as the proportion of nitrogen which is in the form of amine groups, is more commonly used. DD can be determined by methods including NMR, ultraviolet-visible spectroscopy (UV), infrared spectroscopy (IR), circular dichroism (CD), colloid titration, etc [48-51]. So far, the most reliable method seems to be 1H NMR [1].

The impact of molecular weight: The molecular weight of chitosan affects the antimicrobial ability. Such observation

has been mentioned by many researchers which include Guo and his research team in 2008 [52], Seyfarth and his co-workers in 2007 [53] and Tsai and his group in 2006 [54]. More particularly, other properties have been also affected by chitosan molecular weight such as: drug delivery behaviour by Zhou et al. [55], Gupta & Jabrail [56]. Hemostasis by Yang et al. [57] as well as the antioxidant ability of chitosan and its derivatives which has been detected by Kim & Thomas & Je et al. [58]. Thus, molecular weight is another important property of chitosan. The molecular weight distribution can be determined by high performance liquid chromatography (HPLC) [59]. The term average molecular weight is often used and it can be simply and rapidly determined by viscometry using the Mark-Houwink equation [60]. The Mark-Houwink equation displays a relation between intrinsic viscosity [η] and molecular weight M and is expressed as:

$[\eta] = KM\alpha$

Where K and α have been estimated in acetic acid (0.1 M) and sodium chloride solution (0.2 M): K=1.81× 10-3 and α = 0.93. η is the intrinsic viscosity of chitosan solution and M is the average molecular weights results were detected by Kumar [60].

Solubility behaviour

Chitin turn into soluble product in aqueous acidic solution once its deacetylation degree arrives to about 50%, and directly its name is converted to chitosan [1]. Chitosan in acidic media becomes a polyelectrolyte because of the protonation of the amine ($-NH_2$) groups. The degree of protonation increases progressively, in tandem with the progressive solubilization of chitosan. Complete solubilization is obtained when the degree of protonation exceeds 50% and the stoichiometric ratio ([AcOH]/[Chit-NH_2]) is 0.6 [61]. The solubility limits the applications of chitosan, thus various modification techniques and derivatives have been developed to improve its solubility. Copolymerization of maleic acid (sodium salt) onto hydroxypropyl chitosan and carboxyethyl chitosan (sodium salts) yielded the water-soluble chitosan derivatives with antioxidant activity [62] and antibacterial activity [63].

Chemical modification of chitosan

Since chitosan is extraditing bigger awareness as one of the most important novel materials that can be easily functionalized. Utilization of chitosan and its derivatives has been rarely determined and developed regardless of its amazing biological behaviours. Furthermore, its practical and/ or commercial utilization has been restricted only to the pristine chitosan. In order to go closer and give more permeation throughout utilization in different fields, the researchers concentrate on its chemical modification to introduce a assortment of functional groups. Such new created groups will act as a key point in the expected future applications. Therefore, an extensive essential studies based on how to do such chemical modification in a correct way will be in demand. Just for a comparison, the chemical modification of cellulose as an examples has been studied well and consider as an active field as yet [60,64,65].

Chitosan based modified sugar

Hall & Yalpani [66,67] succeeded to synthesize sugar restricted chitosan by reductive N-alkylation procedures in the presence of unmodified sugar and using NaCNBH3 or in the presence of a sugar-aldehyde derivative as given in Figure 3 method A and method B respectively. Similar synthesis of sugar based chitosan derivatives has reported by Morimoto. Molecules such as those with D- and L-fucose, and their specified interactions with lectin and cells have been synthesized. Besides that, Kato synthesized lactosaminated N-succinyl based chitosan and its fluorescein thiocarbanyl derivative as a liver-specific drug carrier in mice through a sialoglyco protein receptor as shown in Figure 4 [68-72]. Galactosylated chitosan which illustrated in Figure 5 synthesized by the interaction of lactobionic acid and chitosan and in the existence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and N-hydroxysuccinimide (NHS). Such interaction give a great advantage as a synthetic extracellular matrix for hepatocyte attachment Figure 5 [73]. Sialic acid bound chitosan have been prepared as a novel member of sialic acid that based polymers in the presence of p-formylphenyl-a-sialoside using reductive N-alkylation procedure [74,75]. Since the first derivative was insoluble in water, whereas, consecutive N-succinylations were carried out to produce water-soluble derivative as a final product (Figure 6). Water-soluble β-galactosyl chitosan that has been prepared in the previous section, has been also synthesized by nearly similar synthetic rout. Sialic acid displayed specified binding against β-galactosyl specified lectin (Griffonia simplicifolia). Variable sort of spacer has been reported on sialic acid or β-galactosyl epitope based chitosans as given in Figure 7 [76,77]. Such modifications display a significant effect on the whole chemical as well as physical properties, it can easily protonated in acidic pH. Polycationic chitosan derivatives is known as efficient drug absorber by modulating the tight junctions of the gastrointesential epithelial barrier. Chitosan based β-galactosyl as well as variable spacers easily water soluble molecules. Such segments act as attached side chains over chitosan backbone which lead to increase the chain packing distance, decrease the inter molecular chain interaction, and hence make the salvation easier.

Chitosan based dendrimer hybrid

Dendronized polysaccharides that attached to chitin and chitosan macromolecules are limited and only few reports are examined in the literature. of A diverse number of chitosan based dendrimer hybrids have been synthesized which are basically designed by two important synthetic procedures as shown in Figure 8 [78-81]. Method A mainly based on, synthesis of dendrimers molecules which carried out an aldehyde group and somewhat a spacer. These are after that interacted with chitosan by normal reductive N-alkylation procedure. Whereas, in method B chitosan can easily attached to the dendrimer surface.

This method permits the utilization of commercially available amino dendrimers such as poly (ethylene-imine) or poly (amidoamine) dendrimers. High generations of dendronized products are possible throughout this process. But unfortunately, method B has one weak point which is related to the side cross-linking reaction may be occasionally occurred due to the presence of two or more binding points. An ideal representative example of a hybrid dendrimer obtained by method A is shown in Figure 9 [78,81]. We visualize This type of hybrid compounds can be considered like a tree type molecules. Whereas, the functional sugar represents the leaf, the spacer represents the master branch, the dendrimer represents a subsidiary branch, and finally chitosan represents the trunk. Figures 9-11 represent variable examples of chitosan based dendrimer hybrid as reported in the literature [79,80].

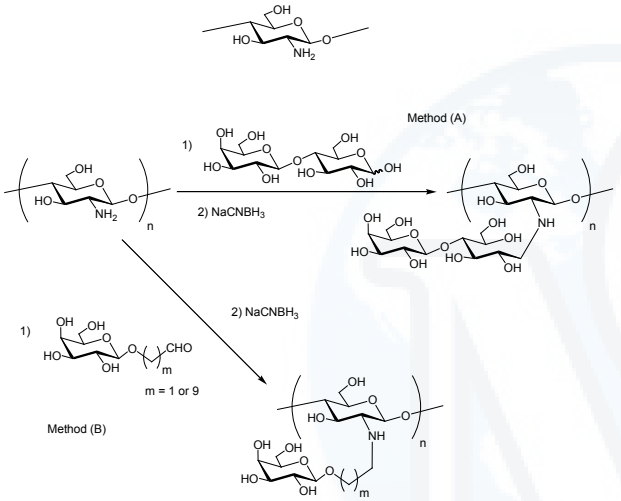


Figure 3: Method for the formation of un-modified sugar (method A) and modified sugar (method B).

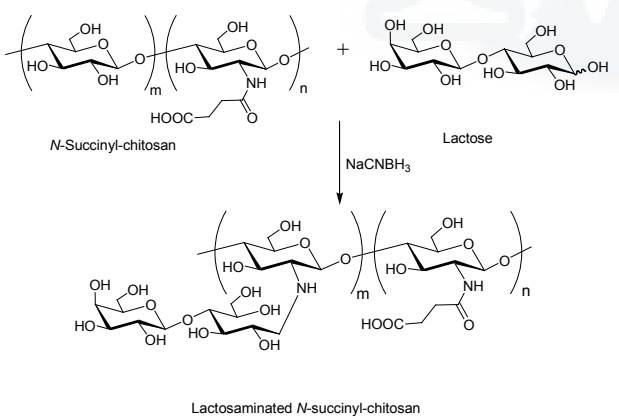


Figure 4: Method for the synthesis of Lactosaminated N-succinyl-chitosan.

Chitosan based cyclodextrin

Chitosan based cyclodextrin is believed to be as enjoyable corner stone in the field of pharmaceutics, which include: analytical chemistry, cosmetics and drug delivery. The functionalization position at the 6-C of OH in cyclodextrin is comparatively easy than the secondary 2 or 3 position, however these two positions display the efficient site of cyclodextrin in bonding studies. A chitosan based α-cyclodextrin has been prepared by Sakairi using 2-O-formylmethyl-α-cyclodextrin followed by reductive N-alkylation and the formation of host guest complex with p-nitrophenol. Tosylated β -CD is also salutary to connect chitosan at the 2-position of CD, for slow liberation of radioactive iodine in rats. An insoluble cross-linked chitosan bearing β -CD is synthesized by the interaction of N-succinyl chitosan and aminated- β -CD throughout amide formation. The β -CD linked chitosan using 1,6-hexamethlene diisocyanate as a spacer is also synthesized as given in Figure 12 [82].

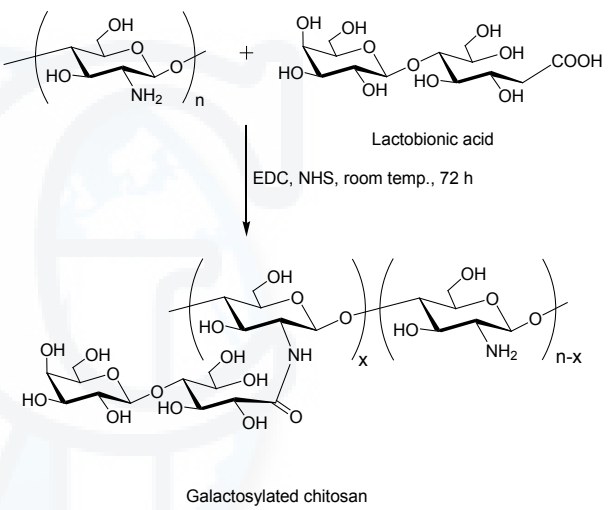


Figure 5: Method for the synthesis of Galactosylated chitosan.

Crown ether restricted chitosan

The literature shows new synthetic polymers carrying out both types of structures as well as general properties of both chitosan and crown ethers as well. Such macromolecular structures are formed basically by the help of stronger complexes with metal salts and display preferable selectivity for certain metal ions. This behaviour is mainly attributed to the synergistic effect of its high molecular weight. Tang and his research group synthesized a crown ether restricted chitosan of N-Schiff base-type and its reduced corresponding analog as illustrated in Figure 13 [83]. Whereas, the first synthesis of chitosan based calixarene has been reported by Li. The collected products found to be easily converted to powder and did not dissolve in common organic solvents, which reflect its usage impediments. This observation enhance their use as adsorbents than unmodified chitosan as shown in Figure 14 [84].

Chemical grafting of chitosan

In order to produce practically beneficial derivatives for chitin and/or chitosan it is easy to go straight forward to

graft copolymerization which represent an essential way for the functionalization of chitin and chitosan. Grafting process can be achieved by variable synthetic routes, such as: Fenton's reagent, ceric ion, various radicals, ring-opening, and gamma-irradiation [85]. An interesting feature of polyoxazoline chains is the fact that they are regarded as pseudo-peptides having considerable chain flexibility. It has also been detected that chitosan based oxazoline by grafting has the susceptibility of combining lipase P and catalase and displays increased hydrolytic activity compared with free enzymes as given in Figure 15 [86-88]. Physically cross-linked hydrogels are synthesized as new pH-sensitive without using any catalyst by grafting procedures of D,L-lactic acid onto amino groups in chitosan as given in Figure 16 [89]. Kurita [90] synthesized graft copolymers on chitin. The grafting depend mainly on SH mercapto group as illustrated in Figure 17 [90].

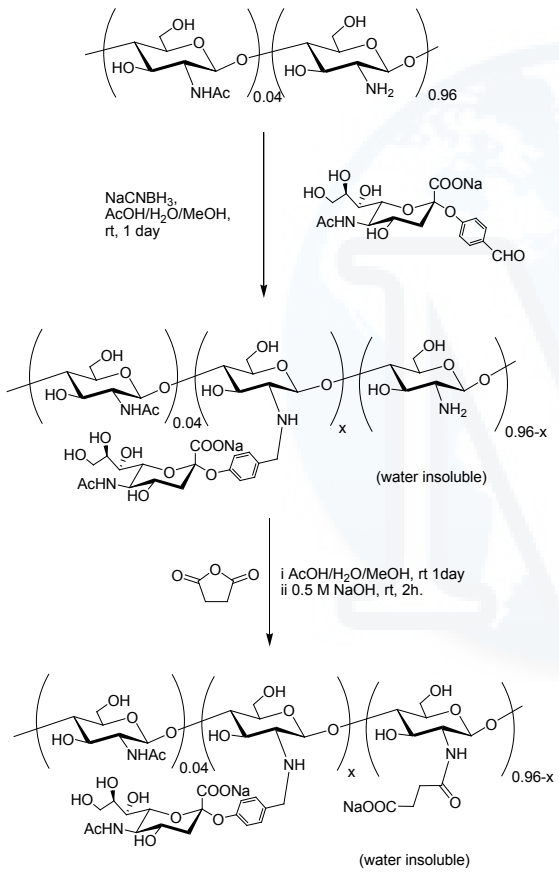


Figure 6: Consecutive N-succinylations for making water soluble chitosan.

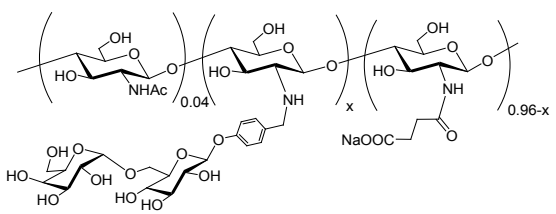


Figure 7: Structure of chitosan with variable spacer molecules.

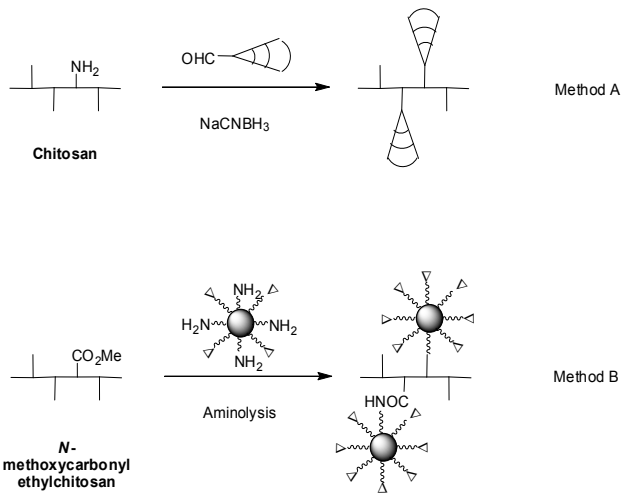


Figure 8: Synthesis of chitosan dendramites through method A and method B.

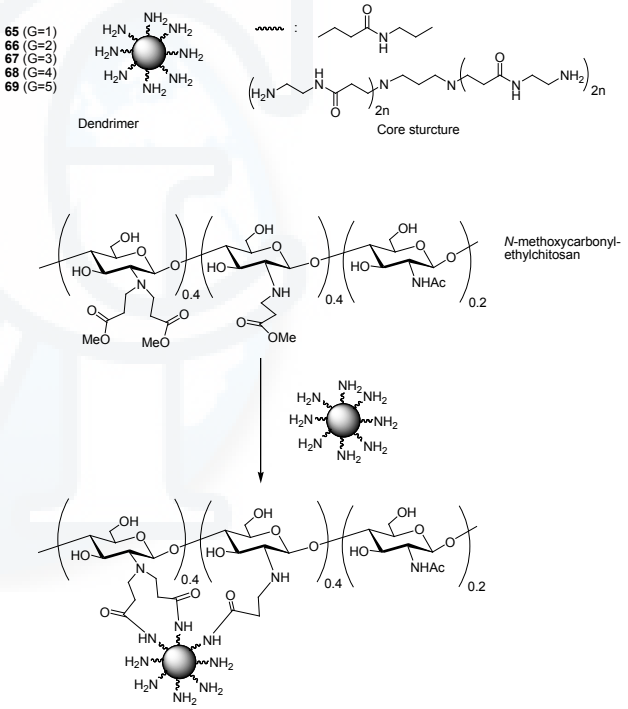


Figure 9: Crossed linked chitosan hybride.

Enzymatic modification of chitosan

The enzymatic pathway to the modification of chitin and/or chitosan is motivating referring to its particularity and environmental characteristics compared with chemical modification. By putting in our consideration human health and safety, enzymes suggest the possibility of eliminating the hazards attached to reactive reagents. Payne and co-workers determined enzymatic grafting of phenolic compounds onto chitosan to confer water solubility under essential stipulations as clarified in Figure 18 [91].

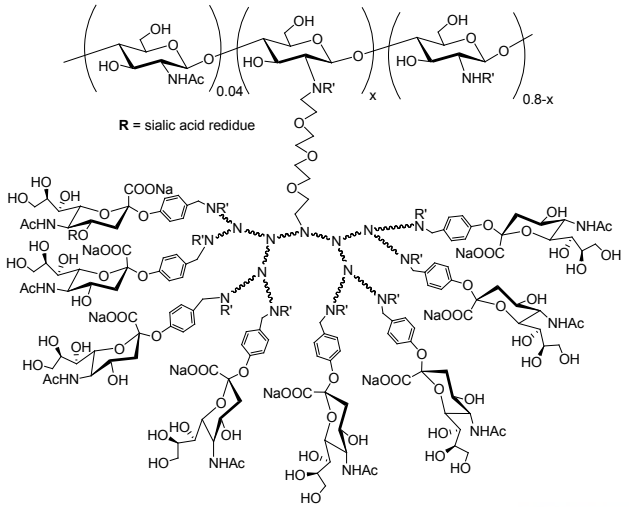


Figure 10: Hybrid chitosan dendrimers.

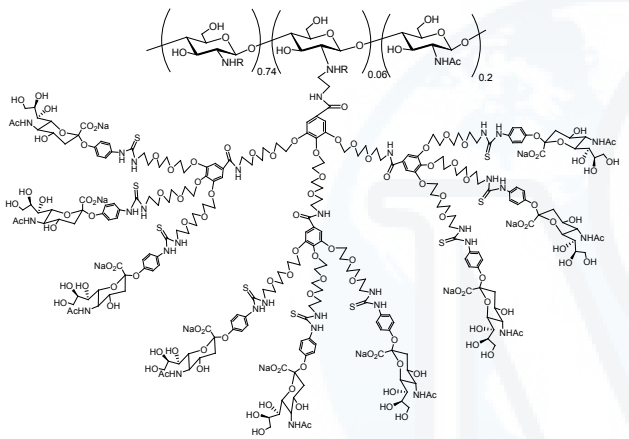


Figure 11: Chitosan dendrimers hybrid molecule.

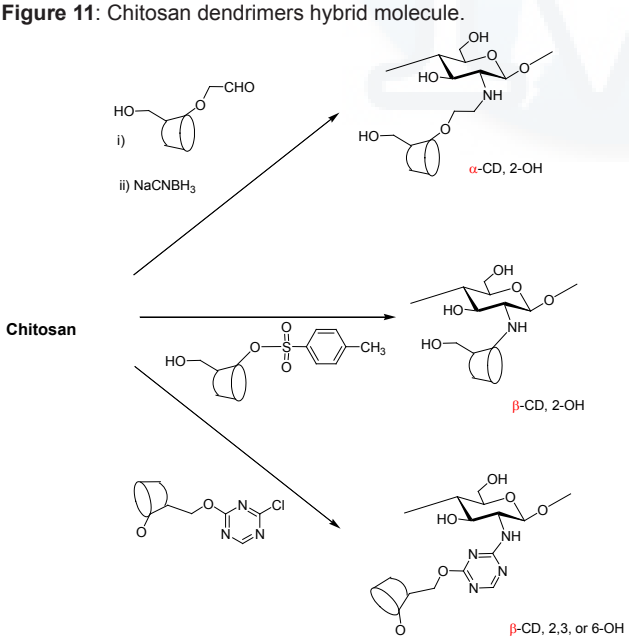


Figure 12: Cyclodextrin-linked chitosan.

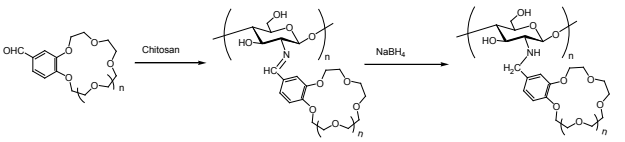
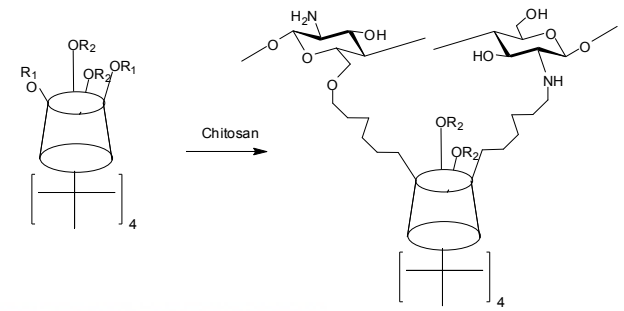


Figure 13: Crown ether bound chitosan.



(I) $R_1 = (CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}Cl$, $R_2 = H$

(II) $R_1 = (CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}Cl$, $R_2 = Bz$

Figure 14: Crown ether bound chitosan.

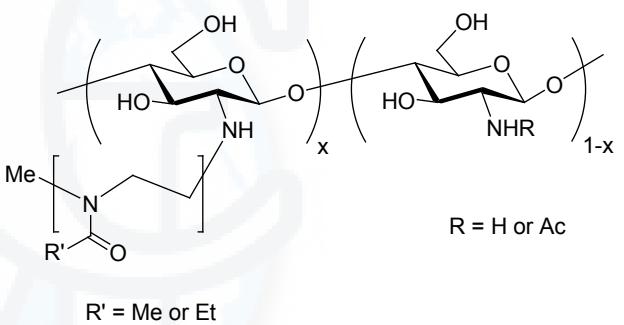


Figure 15: Chemical grafting of chitosan.

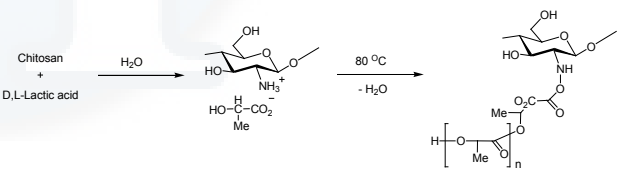


Figure 16: Hydrogel made of D,L-lactic acid grafting on chitosan.

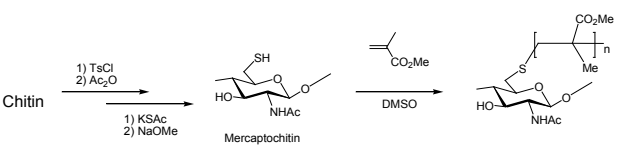


Figure 17: Grafting of mercepto group onto chitosan polymer.

Arginine functionalized chitosan derivatives

Arginine functionalized chitosan-derivatives were prepared through reaction with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), using N-hydroxysulfosuccinimide sodium salt (NHS) as a catalyst agent in 2-(N-morpholino) ethanesulfonic acid sodium salt buffer solution (MES) (Figure 19) [92]. Other chitosan-

derivatives were obtained from N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDAC) [93]. In this case, N-acetyl-L-cysteine (NAC) functionalized chitosan was obtained (Figure 19). Li et al. [94,95] was able to graft biodegradable and biocompatible chitosan derivatives with poly (lactic acid) via EDC and NHS in order to activate carboxyl groups of lactic acid.

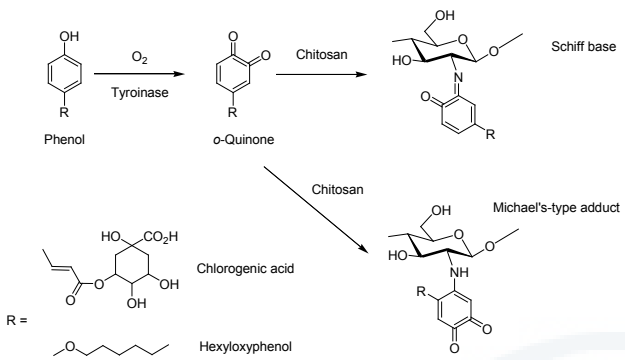


Figure 18: Enzymatic modification of chitosan by grafting it with phenolic compounds.

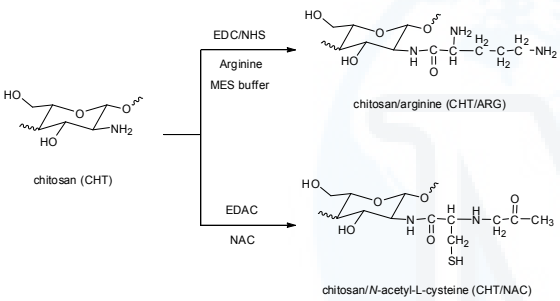


Figure 19: Arginine and Cysteine modified chitosan.

N-substitution of chitosan

The process of making direct N-substitution of chitosan can be done between the primary amino groups and alkyl halides, which require a strong base under heterogeneous conditions (Figure 20). Vigorous conditions are essential to perform this reaction , such as high concentration of base and fixed temperature, which effect in molecular depolymerization and chitosan-derivatives with low substitution degree (DS = 24.5%) [96,97]. On the other hand, selective N-alkylation and N-arylation can be synthesized via Schiff base intermediates. The primary amino groups on chitosan backbone reacts with some aldehydes, under homogeneous acidic conditions, followed by Schiff base reduction agent [96]. Figure 21 lists a series of N-substituted chitosan-derivatives obtained from Schiff base reduction.

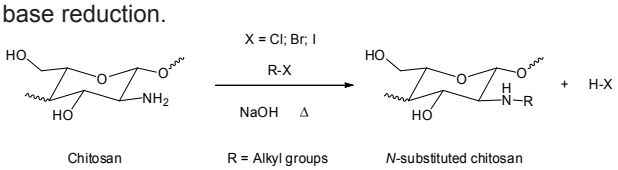


Figure 20: Synthesis of N-substitution of chitosan.

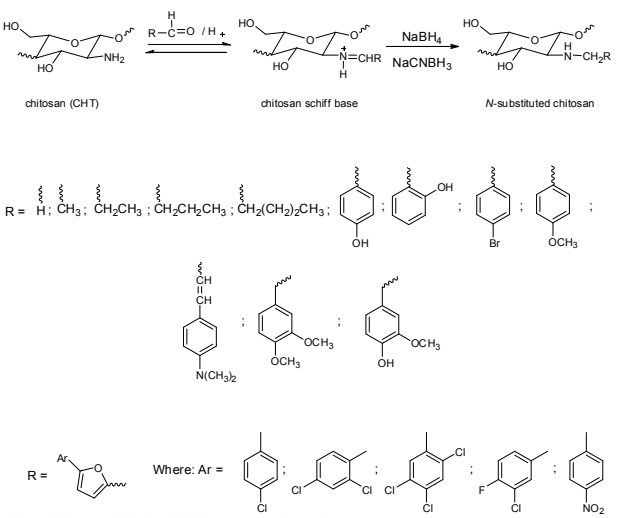


Figure 21: Synthesis of various N-substituted derivatives of chitosan.

Chitosan thiosemicarbazones

Mohamed et al. [98] was able to prepare a different novel thiosemicarbazone O-carboxymethyl chitosan derivatives (TCNCMCHT) through condensation reaction of thiosemicarbazide O-carboxymethyl chitosan (TCDCMCHT) with O-hydroxybenzaldehyde, p-methoxybenzaldehyde and p-chlorobenzaldehyde as given in Figure 22 [98]. Zhong et al. [99] showed the synthesized acetyl and phenyl-thiosemicarbazone chitosan-derivatives and further evaluation of antimicrobial activities. The antimicrobial action of the derivatives showed a relationship between the grafted groups and different inductivity. In another study, Zhong et al. [99] prepared chloracetyl phenyl-thiosemicarbazone chitosan (CAPTCCHT) derivatives with different R-substituent groups as also illustrated in Figure 22 [99,100].

Synthesis of N,N,N-trimethyl chitosan (TMC) and its antimicrobial activity

The use of iodomethane in alkaline solution of N-methyl-2-pyrrolidinone (NMP) is considered to be a method for synthesizing the N,N,N-trimethyl chitosan (TMC) (Figure 23a). The quaternization is performed from nucleophilic substitution of the primary amino group at the C2 position of chitosan with iodomethane and sodium iodide [101-103]. More homogenously N-quaternized chitosan derivatives, in this case TMC free of O-methylation, could be synthesized by protecting the hydroxyl groups present at the C3 and C6 positions on the chitosan backbone (Figure 23b) [104]. The synthesis of chitosan-derivatives were performed using a group protection strategies and, as consequence, these compounds present good solubility in organic solvents, because the H-bond intensities among chitosan chains decreased substantially [105]. Di-tert-butyl-dimethylsilyl (di-TBDMS) groups can be used as a protector for hydroxyl groups on chitosan backbone, which present good stability

under basic conditions and moderately acidic conditions, and can still be removed under strongly acidic conditions without affecting other functional groups. TBDMS-protected chitosan was used as a precursor in the synthesis of fully trimethylated TMC and consequently TMC free of O-methylation was obtained (Figure 23c) [105]. Other method of synthesizing N-quaternized chitosan-derivatives can be formed by reductive alkylation by a series of different aldehydes via the formation of Schiff base intermediates, and making a methylation with methyl iodide or ethyl iodide (Figure 24). The improvement of antibacterial activity of the chitosan-derivative, especially in a neutral environment is caused by a positive charges on the chitosan-derivative surface [106].

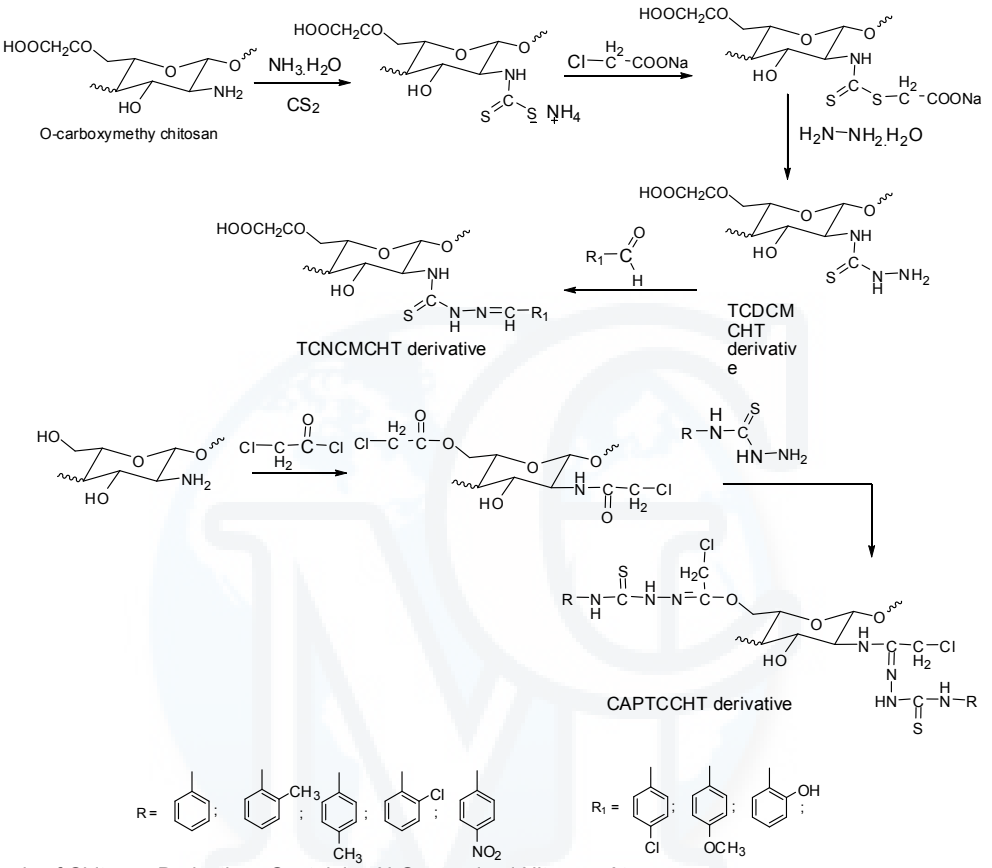


Figure 22: Synthesis of Chitosan Derivatives Containing N-Quaternized Nitrogen Atoms

Quaternization of chitosan using glycidyl trimethylammonium chloride

Glycidyl trimethylammonium chloride (GTMAC) can be used as quarternizing agent [107-111]. When a primary amino group of chitosan reacts with GTMAC, the chains of the chitosan-derivative obtained are longer when associated to respective TMC. In this case, the complete N-monoalkylation can be performed in water at 60 °C during 15 h as shown in Figure 25.

Quaternization of chitosan from schiff bases and glycidyl trimethylammonium chloride

Sajomsang and co-workers synthesized diverse chitosan alternatives depending on a variety of N-aryl substituent's bearing both electron donor and electron acceptor groups besides chitosan alternatives that mainly based on monosaccharide and disaccharide moieties in their main chain [112]. The synthesis was successfully completed by reductive N-alkylation from Schiff bases, and then the O,N-quaternization was carried out using Quat-188 (Figure 26). The resulting quaternized products are found to be water soluble at neutral condition (pH ≈ 7) [112]. Whereas, Mohamed et al. inserted quaternary ammonium moieties into carboxymethyl chitosan based on electron donor and electron acceptor groups on the benzyl substituent introduced on carboxymethyl chitosan chains from Schiff base reduction (Figure 26) [113]. Figure 27 shows a simple route for synthesis of O,N-quaternized chitosan alternatives produced by reductive N-alkylation from Schiff bases, then of O-quaternization from GTMAC and N-quaternization from ethyl iodide reducing agent [114]. Fu et al. [114] corroborative the N-quaternization of the nitrogen atom attached to the benzyl radical by reaction with ethyl iodide in the presence of base and sodium iodide at 36 °C.

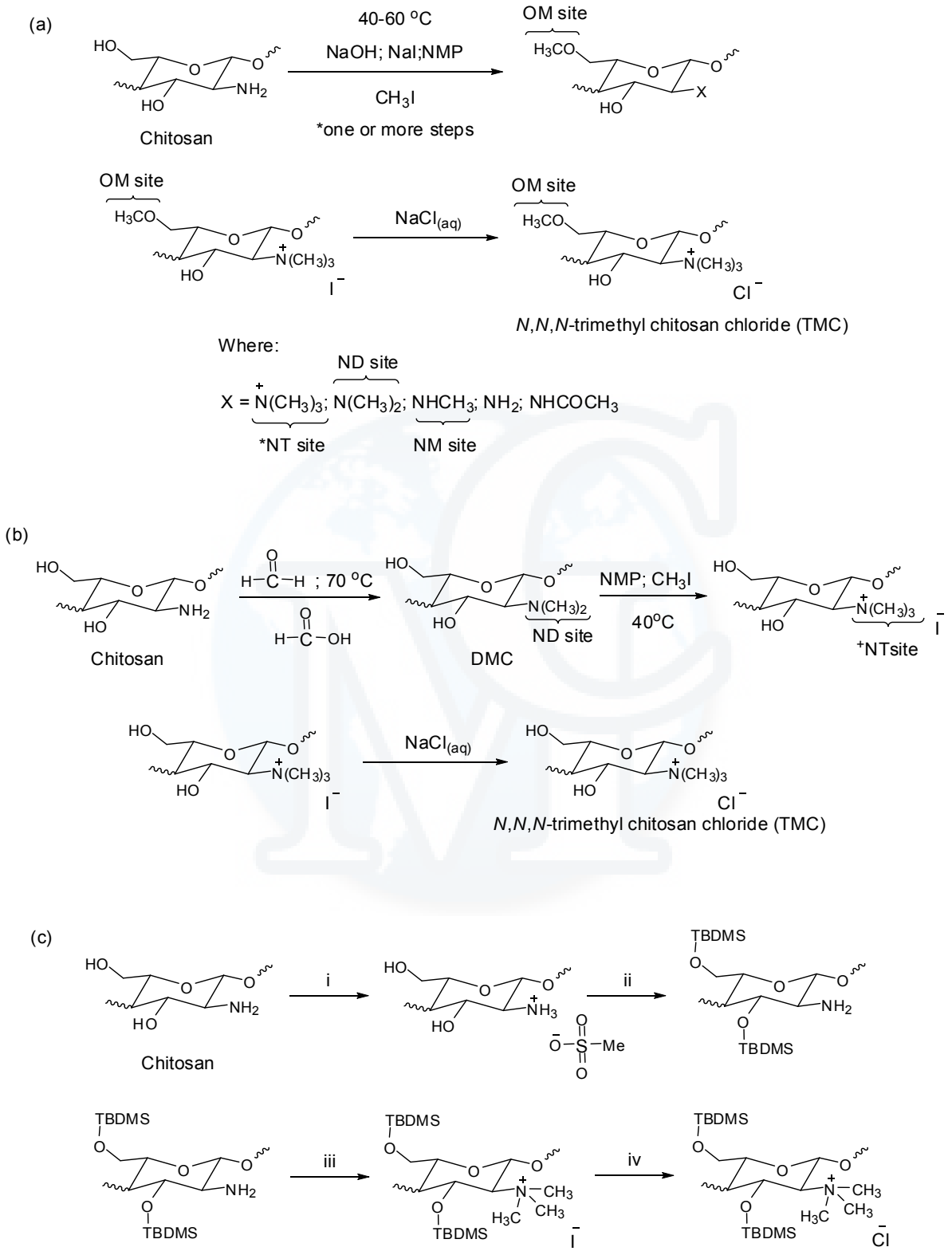


Figure 23: Quaternization of Chitosan from Schiff Bases and Iodomethane/Iodoethane.

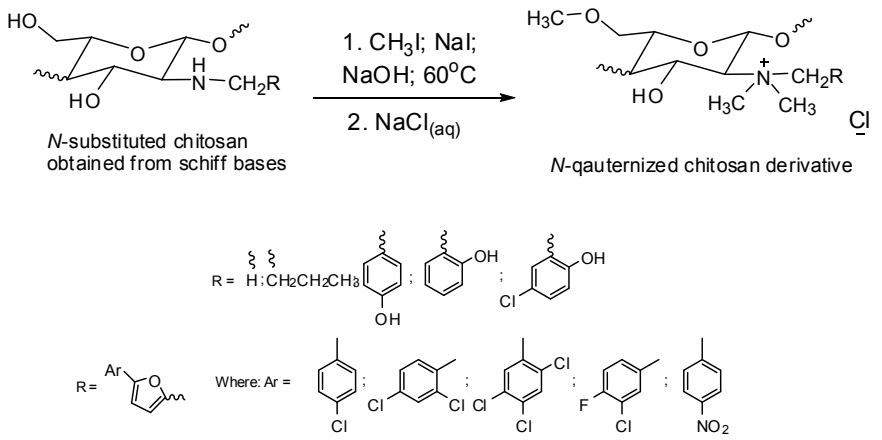


Figure 24: Quaternization of Chitosan using various aldehyde.

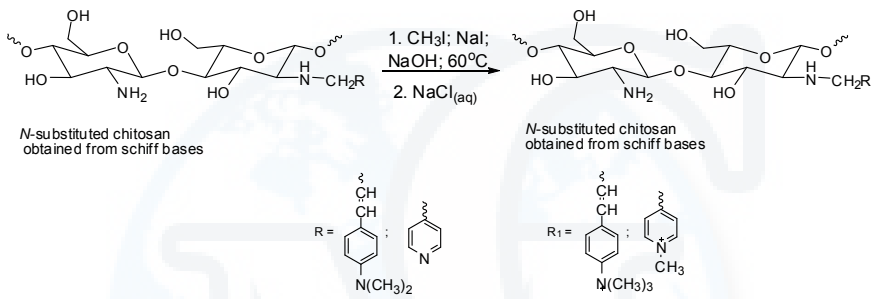


Figure 25: Quaternization of Chitosan Using Glycidyl Trimethylammonium Chloride.

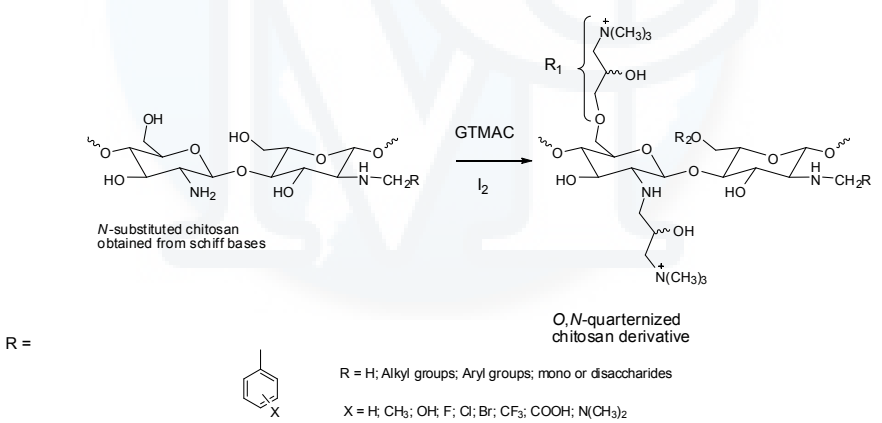


Figure 26: Quaternization of Chitosan from Schiff Bases and Glycidyl Trimethylammonium Chloride

Specific quaternization of chitosan

Glycidyl trimethylammonium chloride and iodomethane are used in a specific quaternization of chitosan. N,N,N-trimethyl-O-(2-hydroxy-3-trimethylammonium propyl) chitosan derivative (TMCTPCHT) with different O-substitution degrees (DS) was synthesized by reacting TMC free of OM sites with Quat-188 [115] (Figure 28).

Quaternization of chitosan through other methods

Benediktsdottir et al. [105] & Runarsson et al. [116] synthesized Quaternary chitosan alternatives putting in their mind to investigate the structure activity relationship for the antibacterial effect [105,116]. Novel methods using protection strategies were used in such synthesis as illustrated in Figure 29.

Sulfone derivatives based chitosan

Sulfone derivatives display a distinguished impact in diverse fields of applications which mainly attributed to their obvious distinct structural as well as electronic behaviours. The literature observe a considerable number of biologically active compounds which carry out similar functional group [117]. The sulfone scaffold represents a specific connection

in medicinal chemistry. Besides that, such compounds are utilized versus different medical references. This is include: eletriptan which is used in the treatment of migraine and bicalutamide which is used in treatment of prostate cancer or the antibacterial dapsone feature a sulfone unit [118,119]. The sulfone group is also firmed in variable fundamental agrochemicals, such as: mesotrione, pyroxasulfone or cafenstrole [120-122]. Furthermore, sulfone containing polymers display interesting properties and bisphenol S is used replacement for bisphenol A [123].

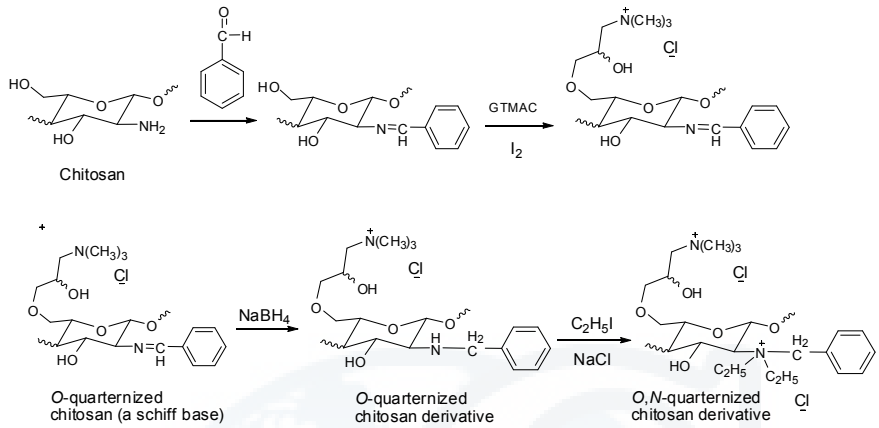


Figure 27: Synthesis of O,N-quaternized chitosan-derivatives performed by reductive N-alkylation from Schiff bases.

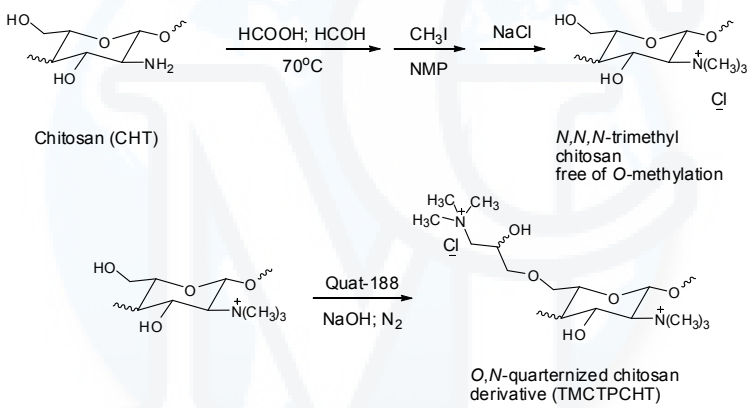


Figure 28: Specific Quaternization of Chitosan.

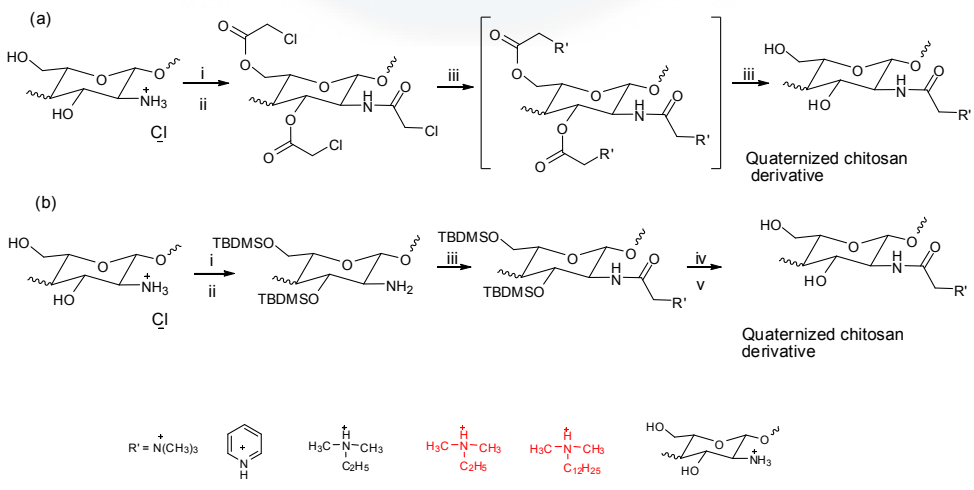


Figure 29: Quaternization of Chitosan by different route.

Considering this plethora of possible, It is not a surprise, if we can say that, a significant number of effective procedures has been reported for the synthesis of sulfone derivatives as a result of such overabundance of conceivable applications have which are listed in the literature. All right, the 19th century determine the first synthetic steps. But, recently number of considerations have been examined for the preparation of sulfone derivatives which lead to develop other research activities in this field. This consideration include: a fixed request for effective, strong and more prospective approaches.

Synthesis of sulfone derivatives: traditional procedures and variants

There are almost four major classical procedures that have been usually and commonly utilized in the synthesis of sulfone derivatives in the literature. These approaches include: alkylation of sulfinate salts, Friedel-Crafts-type sulfonylation of arenes, the oxidation of the corresponding sulfides or sulfoxides, and finally addition reactions to alkenes and alkynes [124]. All of these procedures are find out long time ago, but of course the researchers still have abilities to upgrade them for valuable reuse. Such upgrades are based on novel variants with somewhat significant amended substrate domain, functional group possibility and effectiveness, as well as new chemicals to be used as reagents. Consequently, other procedures, such as cycloaddition reactions, rearrangements, and/or reactions of sulfonic acid derivatives with nucleophiles, have been reported in past few decades, but unfortunately still rare in common use. Figure 30 shows a comparison between old and new procedures for the synthesis of sulfone derivatives. Yadav [126] and his research team find out a confirmed synthesis of β-keto sulfone derivatives by the interaction of alkenes and sodium sulfinates catalyze by silver nitrate and potassium persulfate. Similar keto sulfone compounds can be also synthesized by the oxygen-initiated addition of sulfinic acids to alkynes as illustrated in Figure 31 [125,126].

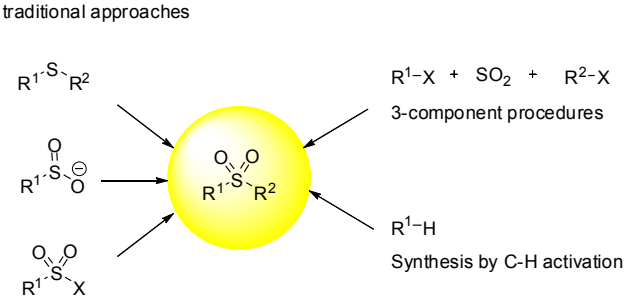


Figure 30: Comparison between old and new procedures for the synthesis of sulfone derivatives.

The interaction of sulfonyl hydrazides with alkynes in the existence of catalytic amounts of copper acrylate and iron (II) chloride estimates (E)-vinyl sulfones. Moreover, the reaction of sulfonyl hydrazides with alkenes in the presence of iron-catalyst as well as air yields β-hydroxy sulfones. Whereas, the reaction of sulfonyl hydrazides with alkenes in the presence of $Cu(OAc)_2$ as a catalyst, gives the corresponding β-keto sulfone derivatives as shown in Figure 32 [127-129]. Copper-catalysed synthesis of (E)-vinyl methyl sulfone derivatives from alkynes in DMSO have been reported by Chen & Qu [131] & Loh [131] research teams using two different procedures. Chen & Qu [131] utilized diethyl H-phosphonate which acts as terminal reducing agent; whereas, Loh [131] shows that, the reaction of alkenes under conformable conditions gives β-keto sulfones as shown in Figure 33 [130,131]. Lei and his research group promote a copper-catalyzed decarboxylative oxosulfonylation of arylacrylic acids with sulfinic acids. They also show a clear evidence for a single-electron transfer procedure between sulfinic acid and copper by comprehensive spectroscopic examinations as given in Figure 34 [132]. Vinyl acetates are also suitable olefinic molecule that can easily used in the synthesis of β-keto sulfone derivatives. Sulfonylation of vinyl acetates with sulfonyl hydrazides in the existence of either iron (III) chloride over air atmosphere or tetrabutylammonium iodide (TBAI), and tertbutyl hydroperoxide (TBHP) as mediators gives the corresponding oxidative coupling products throughout a radical addition mechanism as shown in Figure 35 [133,134]. The synthesis of β-keto sulfone derivatives by the addition of sulfonyl chlorides to vinyl acetates using a photoredox catalyzed procedure has been examined by Zhang & Yu [135] and co-workers as illustrated in Figure 36 [135]. Oxidative coupling of enamides with sulfonyl hydrazides using TBAI as a mediator gives β-keto sulfone derivatives in a similar procedures as also shown in Figure 37 [136]. N-sulfonylbenzotriazoles have been reported by Katritzky as useful chemical reagents for the sulfonylation of lithiated heterocycles or lithium enolates as shown in Figure 38 [137]. Figure 39 shows the copper catalyzed oxidative coupling of oxime acetates in the presence of sodium sulfinates which provides access to sulfonylvinylamines and keto sulfones via a formal C(sp3)-H bond activation [138]. One of the first research teams who to examine the potential of sulfur dioxide as a chemical reagent in the synthesis of complex compound is Vogel and his research group. They also show a Lewis acid corroborative ene reaction of enoxysilanes and allylsilanes or allylstannanes. As well as the formed sulfinates can be trapped in situ with a variety of electrophiles, enabling a one-pot, three-component synthesis of poly functional sulfones as given in Figure 40 [139,140]. Un-functionalized alkenes can react with sulfur dioxide in the presence of stoichiometric amounts of boron trichloride to form sulfinic acid-boron trichloride adducts, which can be hydrolyzed with base to generate sulfinates. Reaction of the latter with alkyl halides yields α, β-unsaturated sulfones in a one-pot transformation as illustrated in Figure 41 [141].

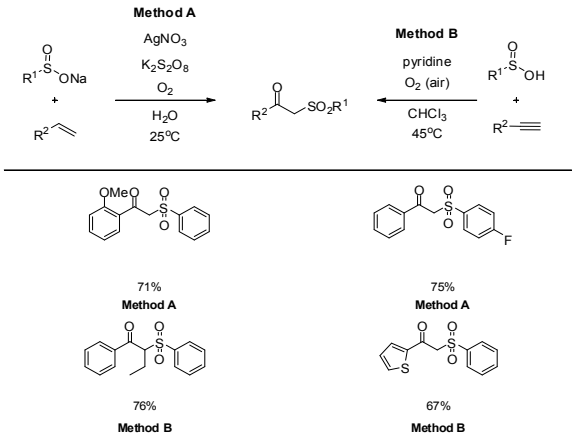


Figure 31: β-keto sulfone derivatives synthesis via various procedures.

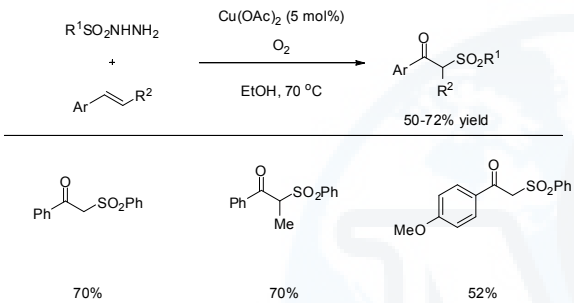


Figure 32: Copper acrylate catalyzes β-keto sulfone derivatives.

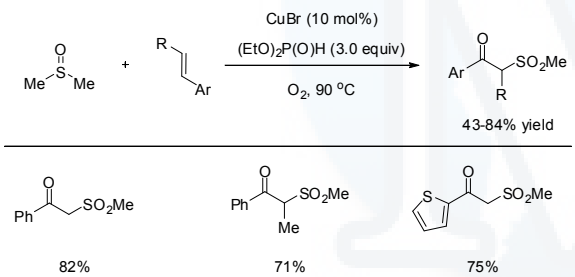


Figure 33: Copper-catalysed the synthesis of (E)-vinyl methyl sulfone derivatives.

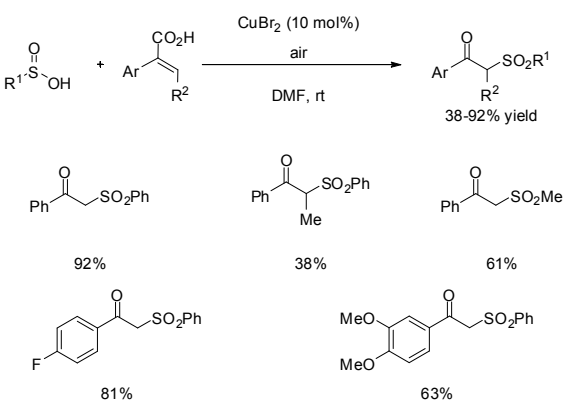


Figure 34: Copper-catalyzed decarboxylative oxosulfonylation of arylacrylic acids with sulfinic acids.

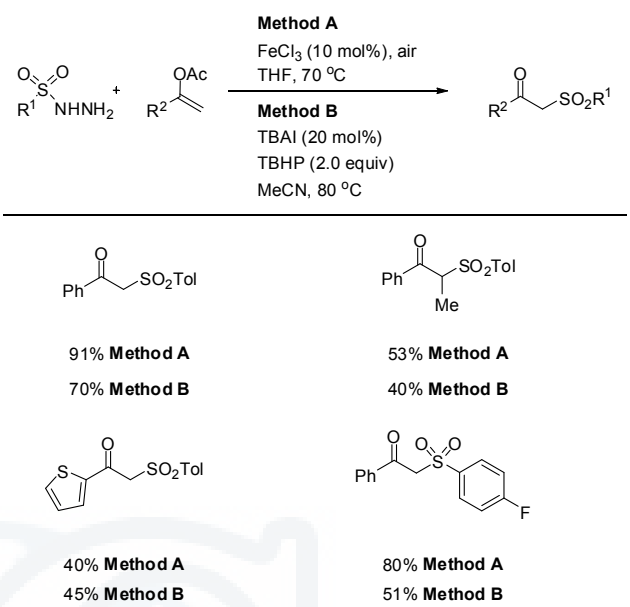


Figure 35: Sulfonylation of vinyl acetates with sulfonyl hydrazides in the presence of either iron (III) chloride / air as a mediator.

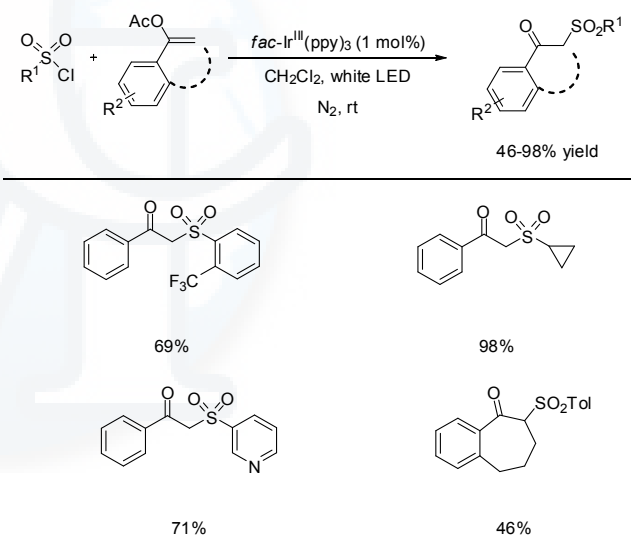


Figure 36: Photoredox catalyzed addition of sulfonyl chlorides.

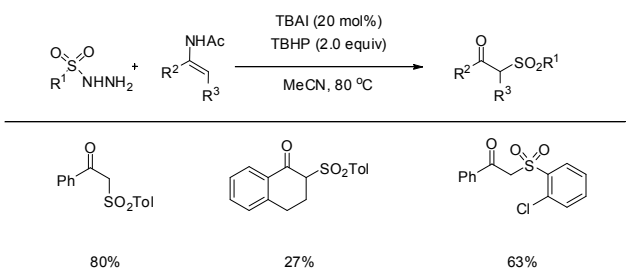


Figure 37: Oxidative coupling of enamides with sulfonyl hydrazides mediated by TBAI.

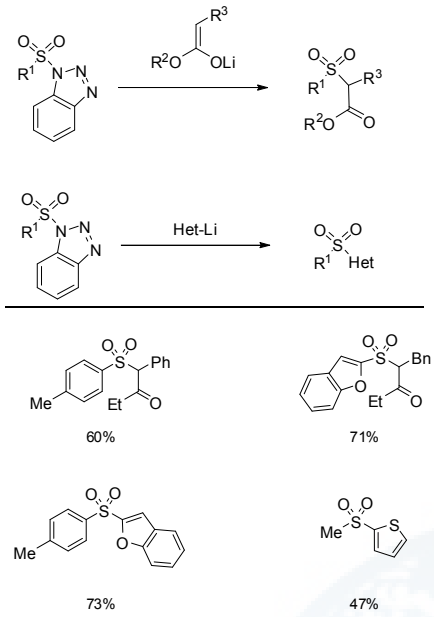


Figure 38: Sulfonylation of lithiated heterocycles on N-sulfonylbenzotriazoles.

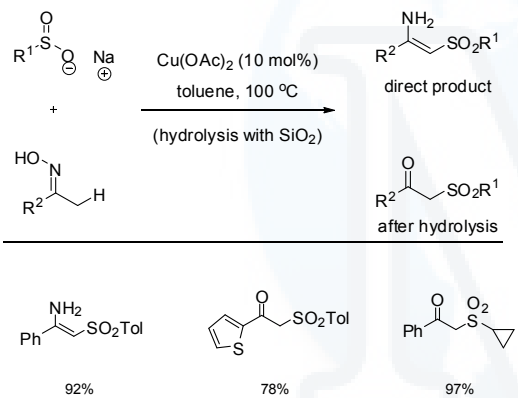


Figure 39: Copper catalyzed oxidative coupling of oxime acetates with sodium sulfinates.

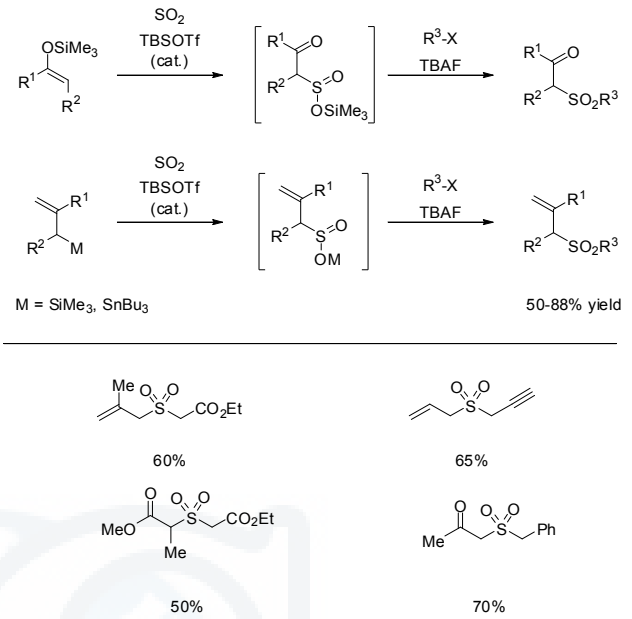


Figure 40: Ene reaction of enoxysilanes.

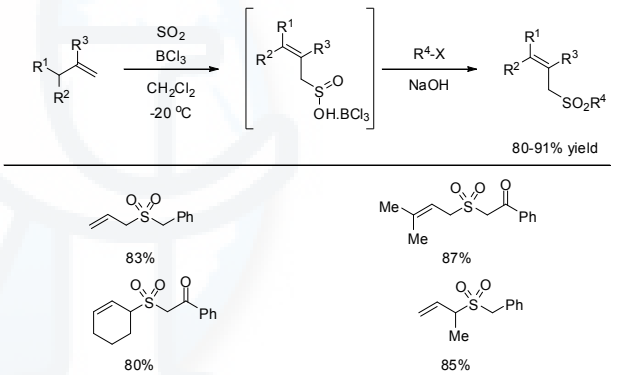


Figure 41: Sulfinic acid-boron trichloride adducts, which on hydrolyzed with base to generate sulfinates.

Conclusion

Chitosan is an important commercially available biopolymer which can readily synthesized or isolated from variable nature resources. Chitosan is applied in different fields of applications due to its versatile physical as well as chemical properties. Utilization of chitosan and its derivatives has been rarely determined and developed regardless of its amazing biological behaviours. So that, a general overview for the biological benefit of chitosan derivatives throughout chemical modifications is displayed and summarized. Firstly, chitosan chemical structure, resources, solubility character and molecular weight are also shown. After that, variable chitosan derivatives out of chemical modification procedures as well as their biological interest are illustrated. This is include: chitosan based modified sugar, dendrimer hybrid, cyclodextrin, crown ether restricted chitosan, chemical grafting of chitosan, enzymatic modification of chitosan, arginine functionalized chitosan derivatives, N-substitution of chitosan, chitosan thiosemicarbazones and TMC synthesis. In addition to that, quaternization of chitosan using glycidyl trimethylammonium chloride & from Schiff bases and specific quaternization through other methods. At the end, a concise view for sulfone based modified chitosan is notified including its conventional methods of synthesis and its experimental variants as well.

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