Synthetic Pathways of Regioselectively Substituting Cellulose Derivatives: A Review

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Abstract: The nature of cellulose from renewable biomass contains a special chemical structure of showing C2-OH and C3-OH on one side while C6-OH on the other side along the anhydroglucose units. The difference between reactivity of hydroxyl groups located respectively on C2, C3 and C6 makes it possible to functionalize a great variety of cellulose derivatives through regioselective substitution pathways. This paper summarizes the synthetic pathways of regioselectively functionalized cellulose derivatives like 6-O-, 2,3-O-, 3-O-, 2,6-O, 6-O-2,3-O-cellulose esters with or without protecting methods. In regioselectively blocking hydroxyl groups of cellulose, mechanism and routes of functionalizing celluloses by using protecting reagents of Trityl Chloride, Tosyl Chloride, Triphenylmethyl Chloride, Halogenating, and Isocyanate are discussed. It is considerable that no uses of protecting routes regioselectively substituting cellulose can be realized directly on cellulose by the methods of nucleophilic substitution reaction, isocyanate substitution reaction, halogenate substitution reaction, ring-opening copolymerization. The facing problems and suggestions for preparing these functionalized cellulose ethers are pointed out.

Keywords: Anhydroglucose units, Cellulose derivatives, Regioselective substitutions, Protecting groups.

1. INTRODUCTION

As the most abundant biomass in the global environment, cellulose has the annual biosphere production of 90×10^9 metric tons [1]. The celluloses are easily processed to manufacture biocomposites, chemicals, biofuels, papers compared to typical organic polymers [2-6]. Cellulose contains a large number of β-D-glucopyranose (Glc) units linked by glucosidic linkages (C_1-O-C_4) [1]. Generally speaking, about 40-70 cellulose chains are assembled naturally by abundant hydrogen bonds to from microfibrils, which is served as the basic unit that comprises wood matter [7]. Cellulose is served as a green linear polymer with three hydroxyl groups like C6-OH, C3-OH, C2-OH in each Glc, which are located respectively on both sides of cellulose chains [8-9]. It is commonly known that intra-chain hydrogen-bonds are found between C3-OH and O5 of Glc units, while inter-chain hydrogen-bonds are found between C3-OH…O3 and C6-OH…O2 (Seen in Fig. **1**) [10]. The primary hydroxyl group (C6-OH) and secondary hydroxyl groups (C2, 3-OH) are of very special interest due to their differences in the reactivity, which is presently agreed with the order of C6-OH>C2-OH>C3-OH [10-12].

The inevitable challenge for regioselectively substituting celluloses must be considered due to its stiff structure and strong hydrogen bonds. Firstly it is noted that most of hydrogen bonds between cellulose chains must be broken in order to release abundant hydroxyl groups for engaging the regioselectively substituting reaction. It is problematic to break completely the hydrogen bonds between cellulose with less degradation by common pathways, e.g. soda acid hydrolysis. Recently the efficient cellulose solvents like LiCl/DMAc [13], NaOH/urea [14] and especially the green ionic liquids (ILs) [1] were developed, which had made it possible to release desirable quantities of hydroxyl groups from celluloses due to nearly pure physical actions in neutral environments.

Regioselective substitution means a pathway of the substituting reagent attacks an objective hydroxyl group (C6-OH, C2-OH or C3-OH) solely after other hydroxyl group(s) is inactivated [15]. The process of inactivating hydroxyl group(s) of cellulose is mainly realized by protecting reagents and catalysts [16-20]. In this regard, a great variety of cellulose derivatives are synthesized by controlling the process of three hydroxyl groups (C6-OH, C2-OH or C3-OH). This paper summarizes the recent advances in cellulose derivatives via regioselectively substituting pathway. Different pathways of regioselective substituting celluloses are compared. A variety of cellulose eaters like 6-O, 2,3-O, 2,6-O, and 3-O- cellulose derivatives was introduced. Of course, the regioselective substitution of cellulose without protecting groups was also discussed.

2. CELLULOSE SOLVENTS SYSTEM

Cellulose has strong mechanical properties based on the fact of its highly ordered structure and strong hydrogen bonds, which makes it a challenge to find solvents for its desirable dissolution [11, 21]. In past years, the cellulose solvents are mainly consisting of non-derivatizing solvents (e.g. Cuam, Cuen, Mineral acids, Melts of inorganic salt hydrates) and derivatizing solvents (e.g. NaOH /CS_2, NMMO) [14, 22-23]. However, such compulsive cellulose dissolutions could not provide favorable environment for efficient cellulose modifications due to excessive degradations of cellulose. Efforts to develop desirable solvents for efficiently dissolving cellulose biomass were made in recent years. For example, the solvent of DMA/LiCl had been served as the universal cellulose solvent for cellulose modifications recently because it can cleanly and efficiently dissolve cellulose biomass with few degradation and little pollution [24-27]. A great variety of cellulose derivatives had been developed in DMA/LiCl solvent. Recently ILs had been found to have potential for cellulose modifications because they can give a milder condition for physical dissolution of celluloses compared to DMA/LiCl [19, 28-33].

3. PATHWAYS OF REGIOSELECTIVE SUBSTITUTION OF CELLULOSES

The essence of regioselective substitution celluloses is that an introduced reagent attacks preferentially the objective hydroxyl

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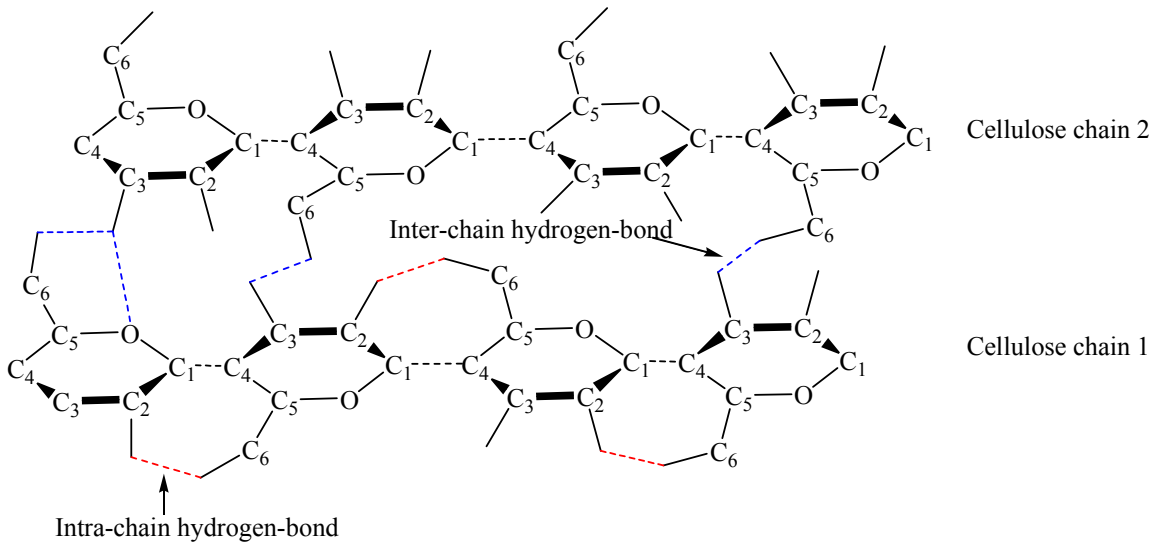

Fig. (1). Illustration of hydrogen-bond structure of cellulose with intrachain positions and interchain positions [10].

group(s) (e.g. C3-OH, C2,3-OH) of cellulose by a pathway. About two pathways are involved for realizing this process. The one pathway by using protecting groups is that the objective hydroxyl group(s) (e.g. C6-OH, C2,6-OH) of cellulose is shielded by a protecting group, which release other free hydroxyl groups for substitution reactions. The other pathway is that the introduced reagent only attacks the objective hydroxyl group(s) (e.g. C6-OH) without any protecting group. An important result in this regard was that the introduced reagent plays a vital important role in regioselectively substituting process.

3.1. Without Use of Protecting Group

The precondition of regioselectively substituting cellulose without protecting group is that the introduced reagents have special chemical attack on the objective hydroxyl group(s), but have no impact on the residual hydroxyl group(s) of cellulose. In past years, scientists have undertaken these works by different pathways like nucleophilic substitution (SN) reaction [34], isocyanate substitution reaction [35-36], halogenate substitution reaction [37-38] and ring-opening copolymerization [39-42].

3.1.1. Nucleophilic Substitution (S_N) Reaction

Nucleophilic substitution (S_N) reaction was reported to prepare directly 6-O-cellulose derivatives by using tosyl chloride without any protecting group, in the presence of triethylamine (TEA)/DMA/LiCl [34,43-44]. The mechanism of S_N reaction is that the tosyl group displaced by NaN_3 was achieved only on C-6 location, whereas the tosyl groups were not displaced at C-2 and C-3 locations at low temperature of 50 °C in Me_2SO. A 6-amino-6-deoxycellulose derivative with about a DS 1.0 at C-6 was synthesized without using protecting group strategy [24] (See Fig. **2**, Route A). In nucleophilic displacement reactions, amine takes great effects on the structure and solubility of cellulose derivatives. It was reported that N,N-dimethyl-1,3-diaminoporopane, 2,4,6-tris (N,N-dimethyl-aminometyl) phenol) have comparably higher DS of 0.27-0.50 comparison to the cationic cellulosics derived from tosyl cellulose and TEA in preparation of water soluble 6-deoxy-6-trialkylammonium cellulose [25]. The result showed that by controlling the appropriate molar ratio of cellulose to tosyl chloride, the exclusive tosylation at C-6 was achieved by controlling the DS of 1.0-1.3 [25]. Pohl and his group also used nucleophilic displacement reaction for synthesizing regioselectively 6-deoxy-6-aminopropargyl cellulose with propargyl amine through 6-O-toluenesulfonyl ester of cellulose with a DS of 0.58 [45] (See Fig. **2**, Route B). They found that by the copper-catalyzed Huisgen reaction the novel 6-deoxy-6-aminopropargyl cellulose derivative with azidopropyl-PAMAM dendrons provides an excellent pathway without any side reactions or impurities [45].

3.1.2. Isocyanate Substitution Reaction

In process of preparing 6-O-cellulose derivatives, isocyanate reagent was also reserved as the advisable reagent for exclusive reaction due to its dominating substitution for the C6 -OH but not C2-OH and C3-OH [35]. As we can know, the -NCO group from isocyanate reagent has strong reactivity which shows potential for introducing directly the objective groups onto the isocyanate group at C6 location. However, it can be problematic to remove the isocyanate group completely from C6 location due to its strong bondings (Newkome *et al.*, 1997; Hassan *et al.* 2004). This method provides interest idea for building ultra-macromolecule cellulose derivatives. By using isocyanate and the dibutyltin dilaurate (DBDL) catalyst, the 6-O-dendritic cellulose carbamate derivatives were synthesized in DMA/LiCl [36] (See Fig. **3**). The molecular volume of the cellulose derivative increases with the increase of reaction time. The stirred reaction mixture was maintained at 65 □ for 12 h for dendron G1, 2 d for the larger G2, and 4 d for the largest dendron G3 [36] (See Fig. **3**). Well-ordered {[$(HO_2C)_{27}$-Den]-cellulose}, CdS quantum dots nanoparticles with dendrimerized chiral cellulose was prepared through the same route, by using DMA/LiCl solvent, G3-NCO Dendron and DBDL catalyst [46]. This achieved cellulose based- ultra-macromolecule biopolymer exhibited luminescence properties.

3.1.3. Halogenate Substitution Reaction

Halogenate substitution reaction is also considered to be a potential pathway of synthesizing 6-O-deoxycellulose derivatives (e.g. 6-O-deoxy-aminocellulose or 6-O-deoxy-mercaptocellulose). In this process, the halogen atom like Bromine (Br) or Chloride (Cl)

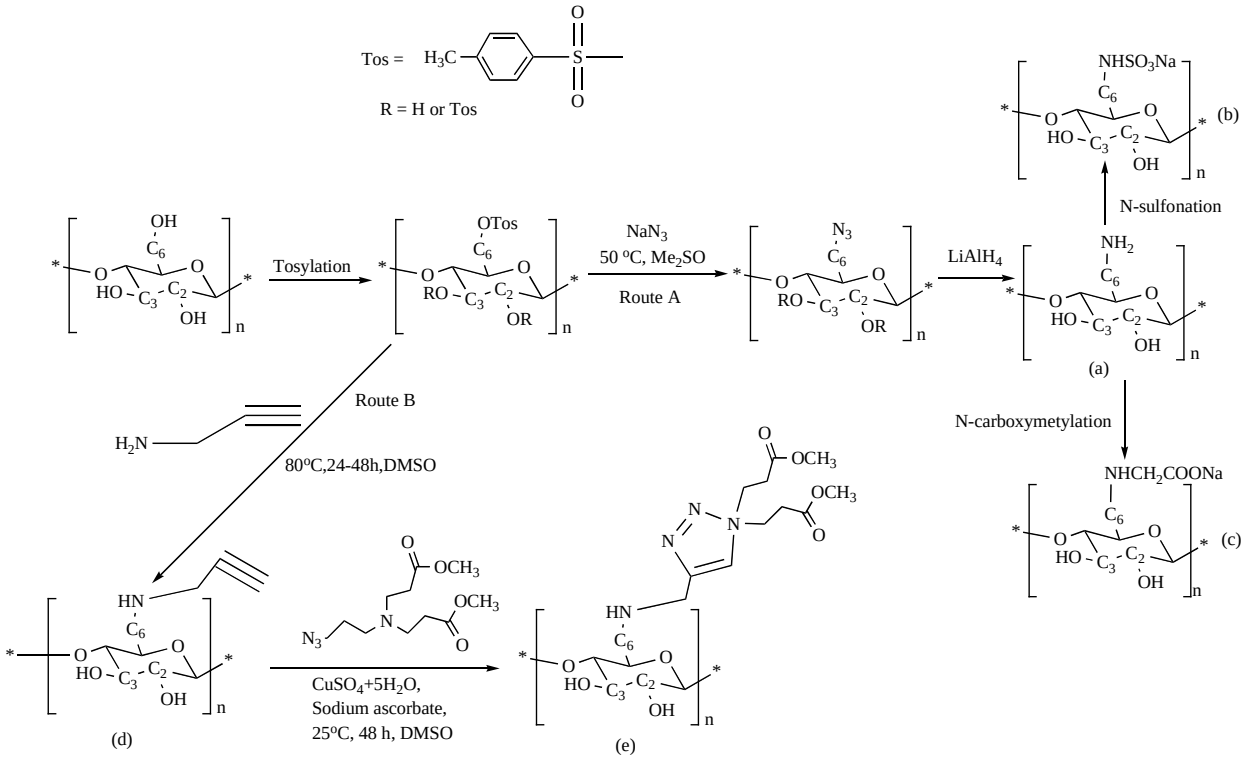

Fig. (2). Scheme of the regioselective synthesis of 6-amino-6-deoxycellulose (**a**) and its sulfonated (**b**) and N-carboxymethylated derivatives (**c**) (Route A) [34], and 6-Deoxy-6-amino-(4-methyl-[1,2,3-triazolo]-1-propylpolyamido amine) cellulose (**d**) from 6-deoxy-6-aminopropargyl cellulose (d) with propargyl amine [45].

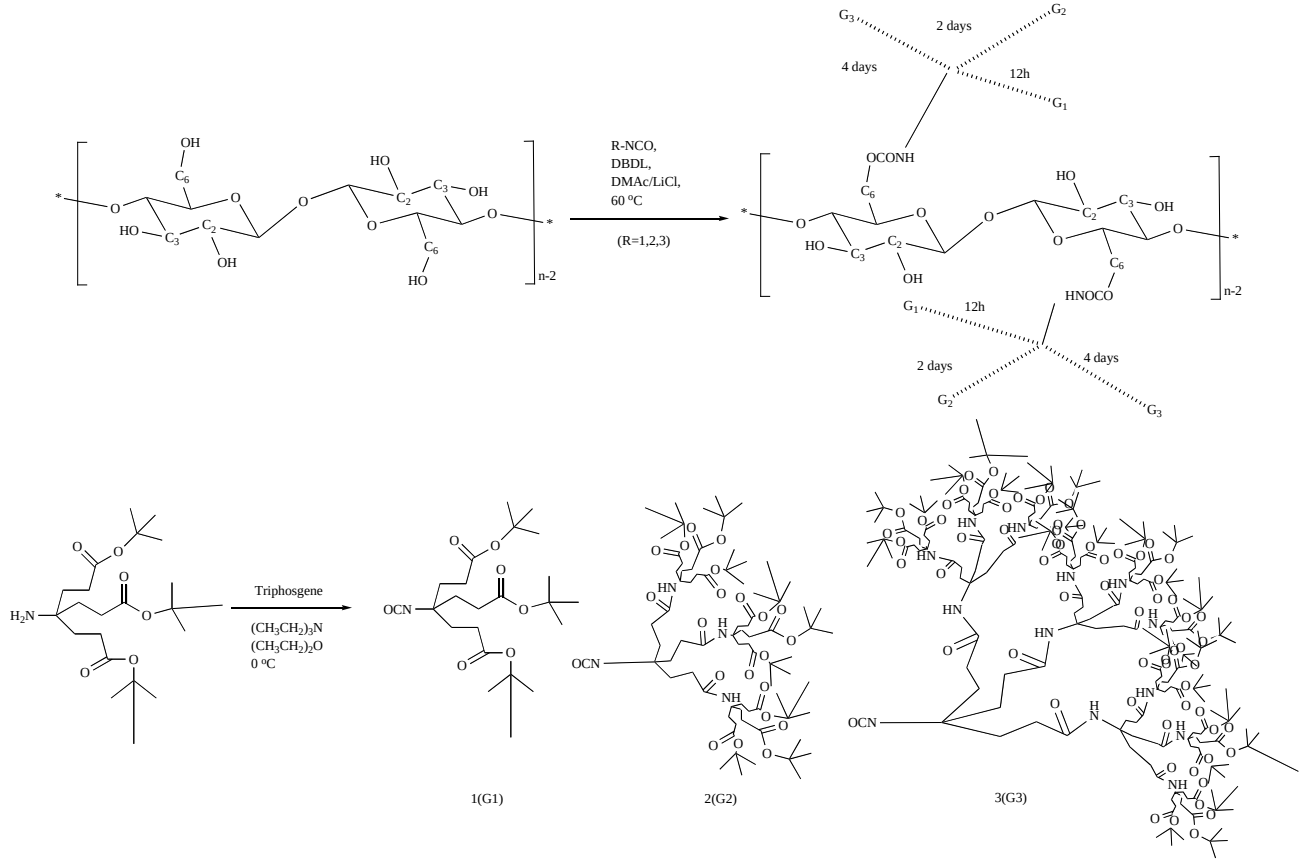

Fig. (3). Pathway of preparing the dendronized cellulose derivatives through isocyanate substitution reaction; DBDL-dibutyltin dilaurate [36]; The G1-, G2- and G3-NCO resulted from Behera's Amine, $(CH_3CH_2)_3N$, $(CH_3CH_2)_2O$, triphosgene at 0 °C, is respectively introduced onto C_6 location of cellulose as a result of reaction time (12 h, 2 days, 4 days) [35]. In Chemical reaction, isocyanate to cellulose anhydroglucose unit (AGU) was 3:1 and the catalyst concentration was 2% based on cellulose.

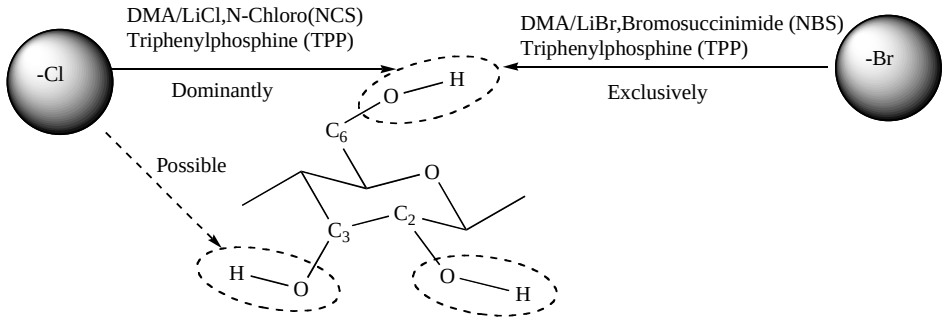

Fig. (4). Pathway and action of Halogenate substitution reaction on cellulose [37, 48].

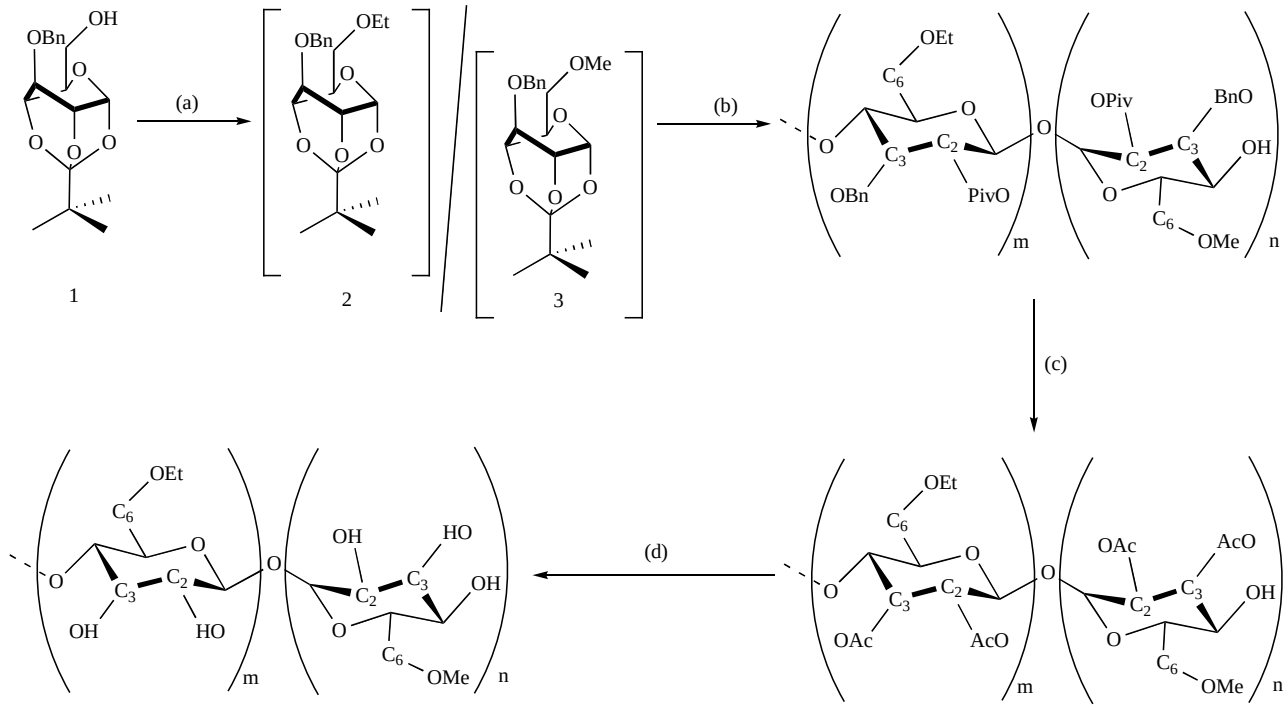

Fig. (5). Synthetic route for 6-O-ethyl/methyl-celluloses from 3-O-Benzyl-6-O-ethyl-a-D- glucopyranose 1,2,4-orthopivalate (1) and 3-O-Benzyl-6-O-methyl-a-D-glucopyranose 1,2,4-orthopivalate (2) based on 3-O-Benzyl-a-D-glucopyranose 1,2,4-orthopivalate (1); Bn and Piv is indicative of benzyl, pivaloyl respectively; Regents and conditions: (**a**) NaH, $(Bu)_4NI$, DMF, r.t., overnight; the m:n molar ratio of Ethyl halide to Methyl halide is 1:9, 5:5, 9:1 and 10:0 respectively; (**b**) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 24 h; (**c**) Pd-C, AcOH/THF (1/1, v/v), under H_2 gas, 60 °C, overnight; (**d**) $NaOCH_3$, CH_3OH/CH_2Cl_2 (1/4, v/v), r.t., overnight, 80 °C, 1h [41, 52].

attacks exclusively the primary hydroxyl group at C6 of cellulose [37-38, 47-49]. It was reported that chloro substituted reaction can substitute regioselectively and quantitatively hydroxyl groups at C6 location only or both at C6 and C3 locations [50-51]. Compared to chloro substitution, bromo substitution has more efficient and exclusive ability for regioselectively substituting the primary hydroxyl group at C_6 location [37] combining with DMAc/LiBr solvent (See Fig. **4**). The rate for bromodeoxysaccharides on cellulose is reported about 1000 times higher than those of corresponding chlorodeoxysaccharides [37]. The reactions of chloro, bromo substitution was commonly carried out with N-chloro, bromosuccinimide (NCS, NBS)/triphenylphosphine (TPP) under cellulose solvents like DMA/Lithium halide (e.g. LiCl, LiBr) due to their high concentrations of halide ion. Furuhata and this group prepared the 6-bromo-6-deoxycellulose (DS=0.91) by NBS/TPP reagents, and further studied the sample samples with higher DS of 1.6 by regulating high molecular ratios of bromination reagents to the repeating unit of cellulose in LiBr/DMA [48].

3.1.4. Ring-opening Copolymerization

Ring-opening polymerization reaction is also regarded as an effective method for regioselectively and quantitatively substituting the objective hydroxyl groups of cellulose [39-42, 50-52], such as 6-O-cellulose esters. The scientists' reports showed that 6-O-Alkyl-cellulose derivatives were synthesized with well-defined ratio of ethyl and methyl groups at C-6 location by the pathway of ring-opening copolymerization for investigating the relationships between structure and property of cellulose derivatives [41-42]. They used 3-O-Benzyl-6-O-ethyl-a-D-glucopyranose 1,2,4-orthopivalate and 3-O-Benzyl-6-O-methyl-a-D- glucopyranose 1,2,4-orthopivalate as the basic matters, and regioselectively substituted hydroxyl groups at C-6 locations of celluloses with ethyl and methyl groups simultaneously [41, 52] (See Fig. **5**). In addition, the regioselective synthetic route of preparing 2, 3, 6-O-alkylcellulose derivatives can be achieved respectively via cationic ring opening polymerization approaches starting from 3-O-Benzyl-a-D-

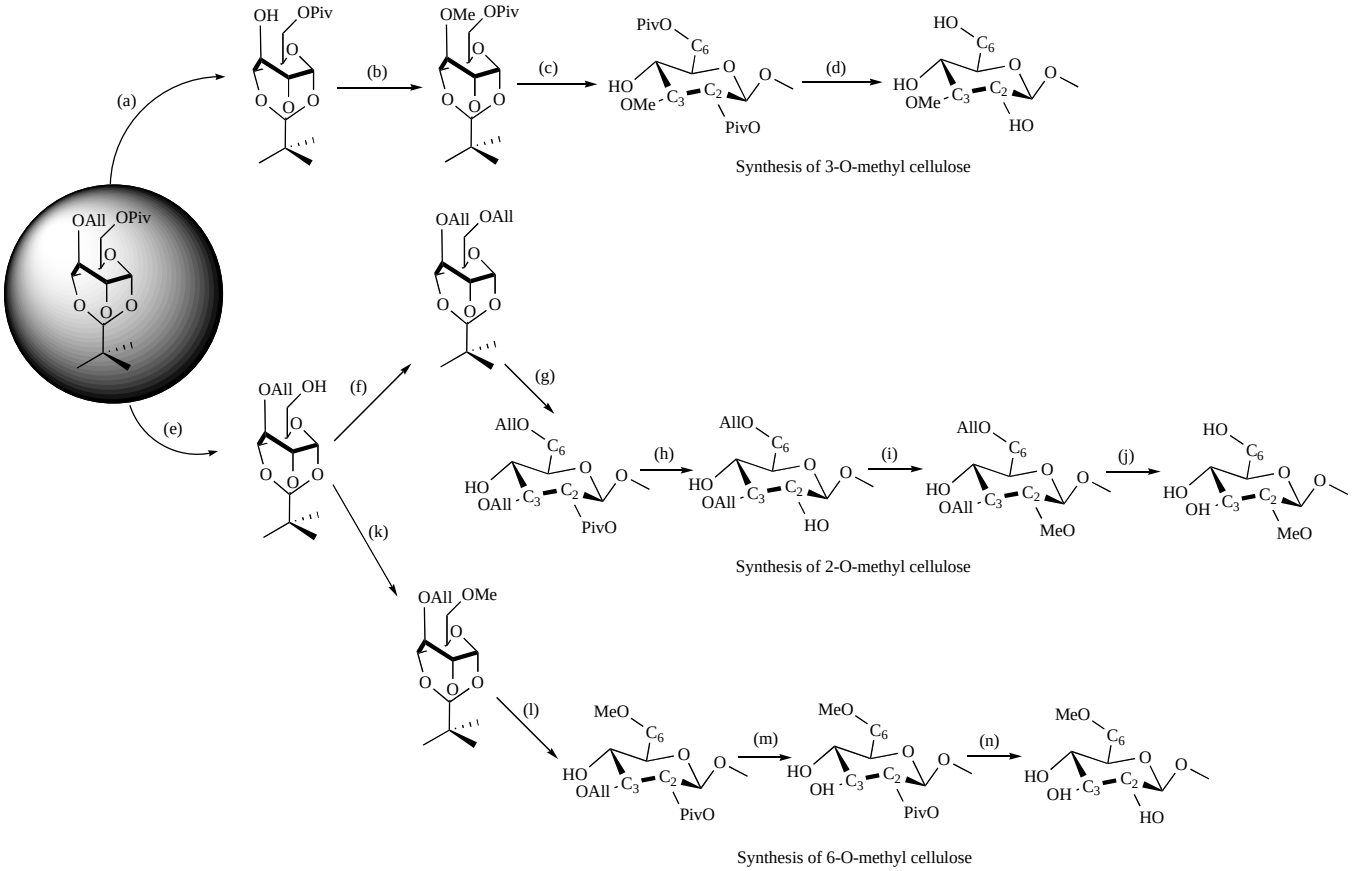

Fig. (6). Synthetic route for preparing 2, 3, 6-O-methylcelluloses respectively from 3-O-Allyl-6-O-Piv-a-D-glucopyranose 1,2,4-orthopivalate; All, Bn and Piv is indicative of Allyl, benzyl, pivaloyl respectively; Regents and conditions: (**a**) $PdCl_2$, MeOH:CH_3Cl (v/v = 1/1), 60 °C, 10 h; (**b**) CH_3I/Ag_2O/DMF, r.t., 12 h; (**c**) BF_3•Et_2O (cat.), CH_2Cl_2, r.t., 10 h; (**d**) NaOMe/THF:MeOH (v/v = 4/1), r.t., 10 h, overall 12%; (**e**) NaOMe/THF:MeOH (v/v = 4/1), Rt, 10 h; (**f**) All–Br/NaH/DMF, r.t., 4 h; (**g**) BF_3•Et_2O (cat.), CH_2Cl_2, 10 h, r.t. (**h**) NaOMe/THF:MeOH (v/v = 4/1), r.t., 10 h; (**i**) CH_3I/NaOH/DMF, r.t., 3 d; (**j**) $PdCl_2$, MeOH:$CHCl_3$ (v/v = 1/1), 60 °C, 4 h, overall 8%; (**k**) CH_3I/Ag_2O/DMF, r.t., 12 h; (**l**) BF_3·Et_2O (cat.), CH_2Cl_2, r.t., 10 h; (**m**) $PdCl_2$/MeOH:CH_3Cl (v/v = 1/1), 60 °C, 10 h; (**n**) NaOMe/THF:MeOH (v/v = 4/1), r.t., 10 h, overall 9% [41-42].

glucopyranose 1,2,4-orthopivalate, such as 2, 3, 6-O-methylcellulose derivatives [41-42] (See Fig. **6**).

3.2. Use of Protecting Group

The previous literatures reported that not only degree of substitution (DS) but also species of substituted groups can influence the properties of cellulose derivatives [53-54]. As a general rule, the introduced reagents react simultaneously with all hydroxyl groups at C-6, C-2 and C-3 locations of cellulose despite of their slight reactivity differences. This makes it a challenge to synthetize cellulose derivatives regioselectively on one or two hydroxyl groups located on C-6, C-2 and C-3 locations of cellulose. By achieving the regioselectively substituted cellulose derivatives, protecting groups are required besides of the abovementioned four special pathways [15, 55]. The protecting group seems to be easier to react exclusively with the targeted one or two hydroxyl group of cellulose. However, the use of protecting group strategy must overcome the following challenges like selective introduction, stability during subsequent reactions, and also removability easily without influence on other substituents [15]. In past years many efficient protecting groups had been investigated for regioselectively substituting celluloses. In this article, three main kinds of efficient protecting groups like trityl group, tosyl group and trimethylsilyl (TMS) group as well as their derivative groups are discussed [15, 19, 25-27, 56-59].

3.2.1. Trityl Group and their Derivative Groups

Trityl Chloride (TC), as a typical protecting group, has been used to protect the primary hydroxyl group (C6-OH) of celluloses [19, 54, 60-63]. This protecting reagent like TC reacts exclusively with the C6-OH besides that it blocks a very small amount of C2-OH of cellulose, in view of that natural steric demands resulting from its three benzene rings at least [15,19] (See Fig. **7**). The regioselective substituting accuracy and efficiency of protecting group in the process of blocking C6-OH are influenced by solvent mediums (e.g. DMA/LiCl or ionic liquid), catalysts (e.g. pyridine) and molar ratio of protecting group [19].

In past years many studies had reported that this protecting reaction was popularly carried out in DMA/LiCl solvent system at tempertures of 100 – 150 °C [24-27]. Compared to harsh conditions resulted from cellulose solvent of DMA/LiCl, the ionic liquids (e.g. AMIMCl and BMIMCl) are of special interest for they can give a milder condition for regioselectively blocking C6-OH of cellulose, and also achieves higher degrees of distribution (DS) and substituting efficiency [12,19,28,30-33]. For example, the fact that DS did not exceed 1.3 in the tritylation of cellulose with a p-methoxytrityl group in DMA/LiCl solvent system was reported, whereas the DS reaches about 2.0 in ionic liquid of AMIMCl [19, 24].

In regioselectively substituting process, deprotecting the blocking groups on cellulose is very important for the subsequent process

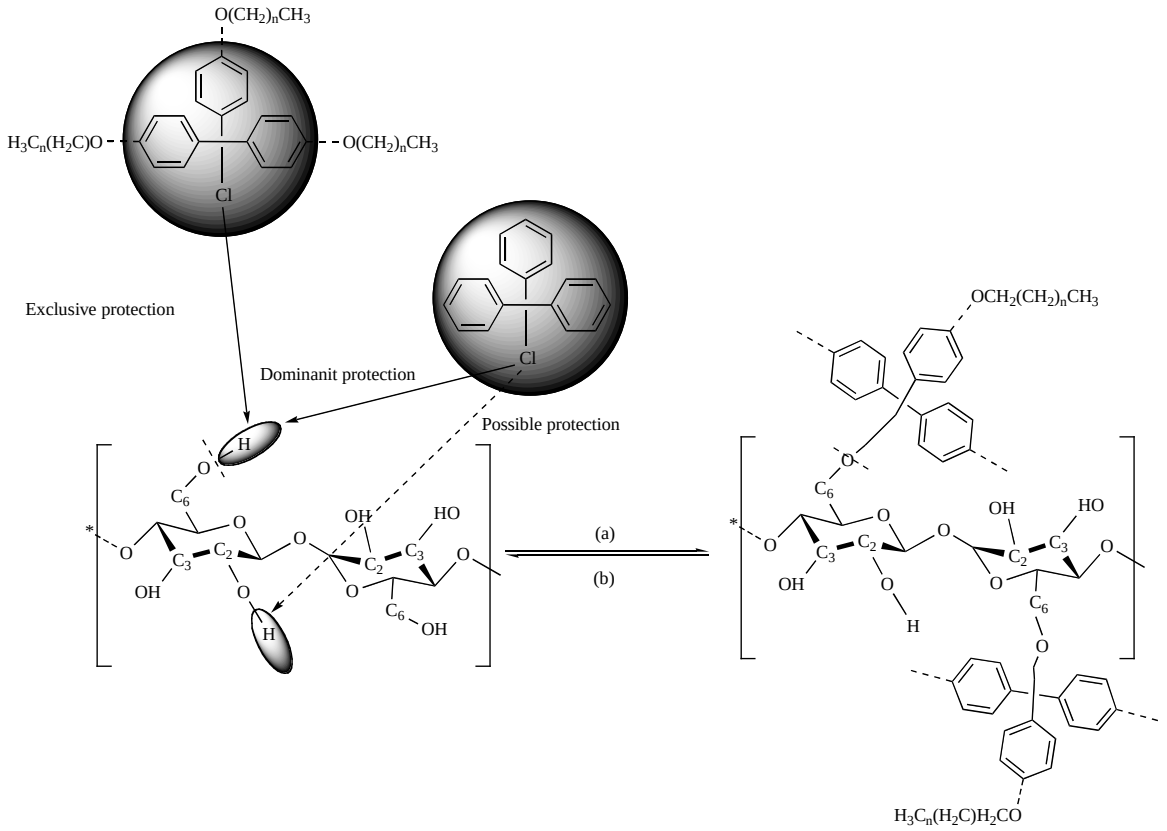

Fig. (7). General protecting and deprotecting process of the primary hydroxyl group at C6 of cellulose by trityl chloride, monomethoxytrityl chloride, dimethoxytrityl chloride, trimethoxytrityl chloride and 4-Alkoxytrityl chloride; n=0, 1, 2, …n. Regents and conditions: (**a**) 4-methoxytriphenylmethyl chloride, pyridine, AMIMCl; (**b**) Concd HCl, THF/Fe(III)Cl·6H_2O, CH_2Cl_2/1% I_2/MeOH, CH_2Cl_2, (**c**) Acetic anhydride, pyridine, [Amim]Cl [15,19, 65, 67].

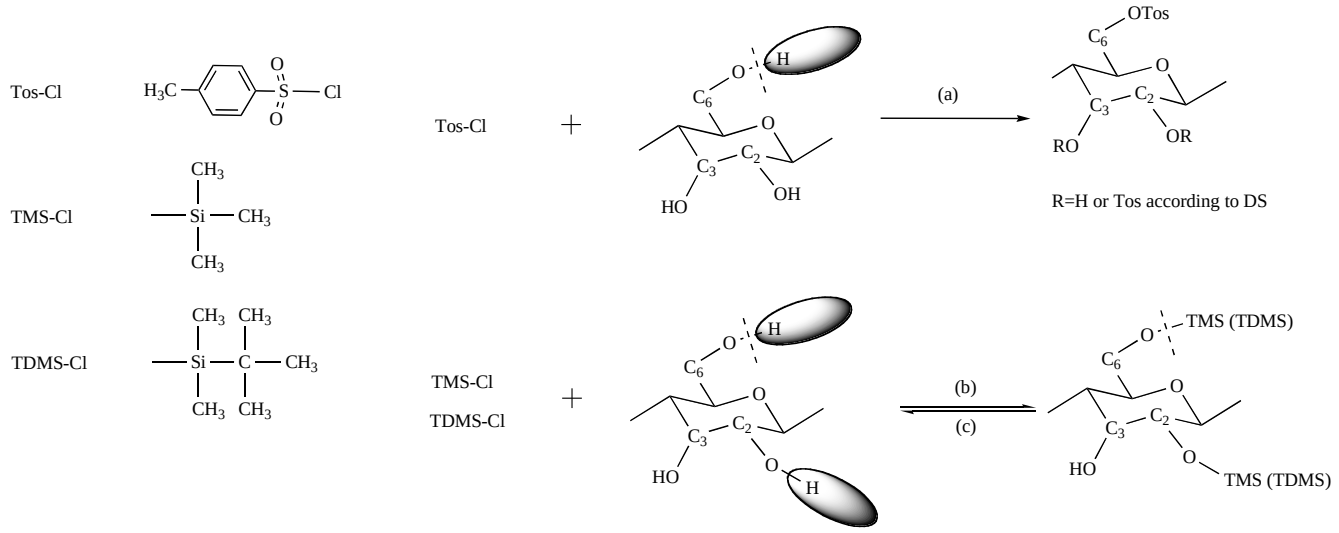

Fig. (8). General protective route of tosyl group, and trimethylsilyl group on $C_{6\text{-}OH}$ of cellulose; Regents and conditions: (**a**) Tos-Cl, triethylamine, DMA/LiCl, 24 h, 8 °C; (**b**) TDMS-Cl, imidazole, 24 h, 100 °C, DMA/LiCl; (**c**) TBAF·3H_2O, 24 h, 50 °C, THF, DMSO [25, 43].

because the regioselectively blocking is only served as a temporary alternative for the convenience of introducing other reagents onto cellulose. However the complete deprotection of the trityl group from cellulose is almost impossible [64]. This fact makes it a challenge to prepare accurate cellulose derivatives up to now. Recently the TC derivatives like methoxy-substituted triphenylmethyl chlorides were reported to exhibit higher efficiency for blocking hydroxyl groups at C6 location of cellulose [19, 52, 65-66]. For example, by achieving the same DS value of 1.0, only 4 h was required by a protecting reagent of 4-alkoxytritylation, compared to which much longer time of about 48 h was required by typical trityl chloride [52]. The reaction efficiency of tritylation as well as detritylation process are proved to be increased in the order of typical trityl chloride, monomethoxytrityl chloride, dimethoxytrityl chloride, trimethoxytrityl chloride [65]. The chain length of 4-O-alkoxytrityl chlorides are proved to have no effect on the reactivity at the same condition for 4-O-alkoxytrityl chlorides, but gives much higher regioselectivity of 97 % quantitative yields than trityl groups [24,66] (See Fig. **7**). At the same time, the detritylation of p-methoxy substituted trityl groups located on cellulose seems to be

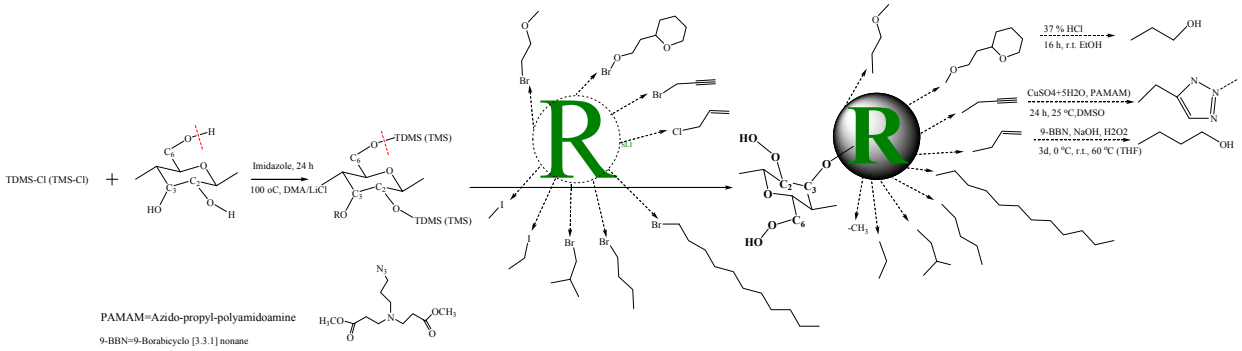

Fig. (9). General synthetic route of 3-O cellulose derivatives [15, 25-26, 69, 81-82].

easier compared to typical trityl group [66]. This pathway provides a faster and removed easier technology for achieving higher DS of 2, 3-functionalized cellulose derivatives [24].

3.2.2. Tosyl group and their Derivative Groups

Compared to trityl group, tosylation group seems to have lower ability for regioselectively blocking the primary hydroxyl groups at C6 of cellulose. It was reported that a faster tosylation group reacts faster with C6-OH compared to the C2,3-OH by ^{13}C NMR spectroscopy [43] (See Fig. **8**). However, tosyl group can be used to regioselectively substitute C6-OH of cellulose by the pathway of controlling the DS from 1.0 to 1.3 as a result of the molar ratio of cellulose to tosyl chloride [25].

3.2.3. Trimethylsilyl (TMS) Group and their Derivative Groups

Different to the trityl and tosyl groups of showing regioselectively blocking C6-OH, the trimethylsilyl (TMS) group is also served as the most popular protecting group with high regioselectively substitution of C2,6-OH of cellulose, but not C3-OH [15, 46, 57-58, 68]. The Trimethylsilyl (TMS) groups are mainly consisting of Trimethylsilyl Chloride (TMS-Cl) [46], Thexyldimethylsilyl Chloride (TDMS-Cl) [69], Hexamethyldisilazane Chloride (HMDS-Cl) [46], Dimethylthexylsilyl Chloride (DS-Cl) [46], dimethylthexylsilyl chloride (DS-Cl) [70]. The abovementioned silyl groups play different roles in blocking hydroxyl groups at C2,6 of cellulose (See Fig. **8**). It was reported that the desilylation of cellulose are mainly completed in tetrahydrofuran (THF) combining with tetrabutylamonium fluoride trihydrate (TBAF) at low temperature of 0 ~ 50□ for 24 h [26, 69]. However, the desilylation of cellulose was usually carried out in ethanol or THF by using concentrated hydrochloric acids (HCl, 35 - 37 %) [27, 65]. But it was still problematic to remove these blocking groups completely from cellulose derivatives up to now.

In silylation of cellulose, the catalyst of imidazole shows more effective compared to pyridine regarding to trityl of cellulose [15]. By using DMA/LiCl system and imidazole catalyst, the DS of 2, 6-O-silylation celluloses have DS of about 1.8 [58], and have higher DS of 2.0 by controlling molar ratio 1:4:4.7 of cellulose/trimethylsilyl (TMS) group/imidazole catalyst at 100 °C for 24 h [25-26]. In addition, the reaction medium has great influence on the regioselective silylation of cellulose. In a heterogeneous phase reaction (N-methylpyrrolidone (NMP)/NH_3), the silylation at C-6 by TDMS-Cl with pyridine or imidazole catalyst reaches 96%, which was more than that of 85% at C-6 in a homogenous phase reaction of DMA/LiCl [26, 71].

4. REGIOSELECTIVELY SUBSTITUTED CELLULOSE DERIVATIVES

In past years, the scientists synthesized a great variety of cellulose derivatives like Nitrocellulose (NC), Cellulose Ether (CE), Cellulose Acetate (CA), Methyl Cellulose (MC), Ethyl Cellulose (EC), Carboxymethyl Cellulose (CMC), Hydroxyethyl Cellulose (HEC), and Hydroxypropyl–Methyl Cellulose (HPMC) and Sulfated Cellulose (SC) as prospective applications on many industries [17, 72-79]. Most of abovementioned cellulose derivatives were synthesized with random substitutions at C2, C3 and C6 locations of cellulose without regioselective substitutions. Regioselective functionalization of natural celluloses are directing the development of the next design of special biomaterials, medicals, chemicals and beautiful organic architectures in interdisciplinary researches [46], although this work has been experimentally realized 150 years long ago [80]. The studies indicated that the cellulose derivatives showed different special properties when they were prepared through regioselectively substituting hydroxy groups located at C2, C3 or C6 locations of cellulose respectively [11].

4.1. 3-O-cellulose Derivatives

In preparation of 3-O-cellulose derivatives, the main approach is to use TMS group to block hydroxyl groups at C2 and C6 locations of cellulose which is convenient for further substitution of hydroxyl groups at C3 location of cellulose [25, 56, 70, 81]. Finally the blocking groups located at C2,6 of cellulose are removed. In these processes the DMA/LiCl is regarded universally as the common cellulose solvent for silylation, and imidazole is used as efficient catalyst for regioselective silylation of cellulose at C2, C6 locations [46, 82]. The desilylation at C2, C6 locations was mostly carried out in THF solvent by using tetrabutylammonium fluoride trihydrate (TBAF) reagent [25, 26, 69, 81]. The results showed that the completed desilylation of 2,6-di-O-thexyldimethylsilyl cellulose can be realized by repeatedly desilylation method at the nearly same condition [25, 69].

The type of hydrogen bond bridges and the alkyl units introduced groups at C3 of cellulose was reported to control the characterization of the solution structure and properties of cellulose derivatives [25] (See Fig. **9** and Table **1**). For example, by introducing methyl (CH3-) and allyl (CH2=CH-CH2-) group respectively at 3-O-position of cellulose via the 2,6-di-O-thexyldimethylsilyl cellulose, the obtained products of 3-O-methyl cellulose exhibits lower solubility in typical solvents compared to 3-O-allyl-cellulose [25] (See Table **1**). By the similar pathway, the synthesized 3-mono-O-

Table 1. Solubility of Synthesized 3-O, 2,6-O, 3-O-2,6-O- Cellulose Derivatives

No.	Cellulose Derivatives	Solubility in Water and Solvents							Ref.
		THF	DMSO	Chloroform	Water	Toluene	Acetone	DMA	
1	3-O-methyl cellulose	-	-	-	-	-	-	-	[25]
2	3-O-ethyl cellulose	-	+	-	+	-	-	+	[15]
3	3-O-propyl cellulose	-	+	-	+	-	-	-	[83]
4	3-O-allyl cellulose	-	+	-	-	-	-	+	[25]
5	3-O-pentyl cellulose	+	+	+	-	+	+	+	[81]
6	3-O-isopentyl cellulose	+	+	+	-	+	+	+	[81]
7	3-O-dodecyl cellulose	+	-	-	-	-	-	-	[81]
8	3-O-(2-methoxyethyl)-cellulose	-	+	-	+	-	-	+	[82]
9	3-mono-O-hydroxyethyl cellulose	-	-	-	+	-	-	-	[26]
10	3-O-(4-methyl-1-N-propyl-PAMAM-[1,2,3-triazole]) cellulose	-	+	-	-	-	-	+	[26]
11	2,6-Di-O-TDMS cellulose	+	-	+	-	+	-	-	[82]
12	2,6-Di-O-methyl cellulose	-	-	-	-	-	-	-	[42]
13	2,6-Di-O-ethyl cellulose	-	-	+	-	-	+	-	[42]
14	2-O-ethyl-6-O-methyl cellulose	-	-	-	-	-	+	-	[42]
15	3-O-allyl-2,6-Di-O-acetyl cellulose	-	-	+	-	-	-	-	[25]
16	3-O-methyl-2,6-Di-O-acetyl cellulose	+	-	+	-	-	-	-	[25]
17	3-O-(2-methoxyethyl)- 2,6-Di-O-TDMS cellulose	+	-	+	-	+	-	-	[82]
18	3-mono-O-(30-hydroxypropyl)- 2,6-Di-Othexyldimethylsilyl cellulose	+	-	+	-	+	-	+	[69]
19	3-mono-O-(2-(tetrahydropyran-2-yloxy)ethyl)-2,6-Di-O-thexyldimethylsilyl cellulose	+	+	+	-	-	-	-	[26]

+ soluble; - insoluble;

ethyl cellulose (EC), 3-O-(2-methoxyethyl) cellulose in DMA/LiCl was found to be easily soluble both in aprotic-dipolar organic media and water [15, 82] (See Fig. **9**), and 3-O-propyl cellulose with DS of 0.19 - 1.02 was smart water soluble [83]. Increasing carbon chain on alkyl located at C3 cellulose derivatives brings distinct changes to the solubility in typical organic solvents. For example, 3-O-Dodecyl cellulose shows good solubility in only THF, however, it is surprisingly to find the prepared 3-O-pentyl or isopentyl cellulose derivatives can be seen to form visually clear solutions in nearly all the typical solvents [81] (See Fig. **9** and Table **1**).

In synthesis of 3-O-cellulose derivatives, other typical chemical reactions are also can be carried out directly on the objective group located C-3 location of cellulose derivatives except for introducing directly method. Based on the hydroxypropyl cellulose (HPC), 3-mono-O-(3'-hydroxypropyl) cellulose was prepared by conversion of allyl group to hydroxypropyl group directly on C3 location of cellulose in DMA/LiCl, [69] (See Fig. **9**). In this case, cycloaddition reaction of the triple bond of the propargyl group with azido-propyl-polyamidoamine (PAMAM) dendrons can be achieved on 3-O-propargyl cellulose in DMA/LiCl [26] (See Fig. **9**). By introducing 2-(2-bromoethoxy) tetrahydropyran onto the objective C3 location of 2, 6-di-O-thexyldimethylsilyl cellulose, 3-mono-O-hydroxyethyl cellulose was realized in DMA(120℃, 2h)/LiCl solvent [84] (See Fig. **9**). The further oxidizing reaction on water insoluble 3-O-alkyl (e.g. methyl, butyl groups) cellulose derivatives results in water soluble 3-O-alkyl-6-carboxy celluloses [85-86].

4.2. 2,6-O-cellulose Derivatives

The preparation of 2,6-O-cellulose derivatives can be realized by using main two pathways including direct silylation reaction and ring opening polymerization. For preparing 2,6-di-O-methylcellulose, the cellulose is firstly converted to 2,6-di-O-thexyldimethylsilylcellulose by TDMSCl in DMAc/LiCl, then to 3-mono-O-allyl-2,6-di-O-methylcellulose, and finally to 2,6-di-O-methylcellulose by desilylation method (See Fig. **10**). In other pathway, the 3-O-Benzyl-6-O-pivaloyl-a-D-glucopyranose1,2,4-Orthopivalate from glucose was firstly converted to 3-Mono-O-benzyl-2,6-di-O-pivaloylcellulose, then to 3-Mono-O-benzyl-2,6-di-O-methylcellulose, and finally to the 2,6-di-O-methylcellulose by deacetylation reaction (See Fig. **10**). Moreover, different alkyl groups (i.e. Methyl and Ethyl) can be regioselectively introduced at C2 and C6 locations of cellulose respectively for synthesizing 6-O-ethyl (methyl)-2-O-methyl (ethyl) celluloses by ring opening polymerization, which exhibits better solubility than 2,6-di-O-methyl cellulose (See Fig. **10**) [41].

4.3. 6-O-cellulose and 2,3-O-cellulose Derivatives

In order to achieve regioselectively 6-O-cellulose derivatives, two pathways were involved generally as following (See Fig. **11**): Firstly the hydroxyl groups at C2,3 are blocked by transitional groups (e.g. Acetyl or Phenylcarbamoyl groups) after the method of blocking primary hydroxyl at C6 by protecting group (e.g. Trityl

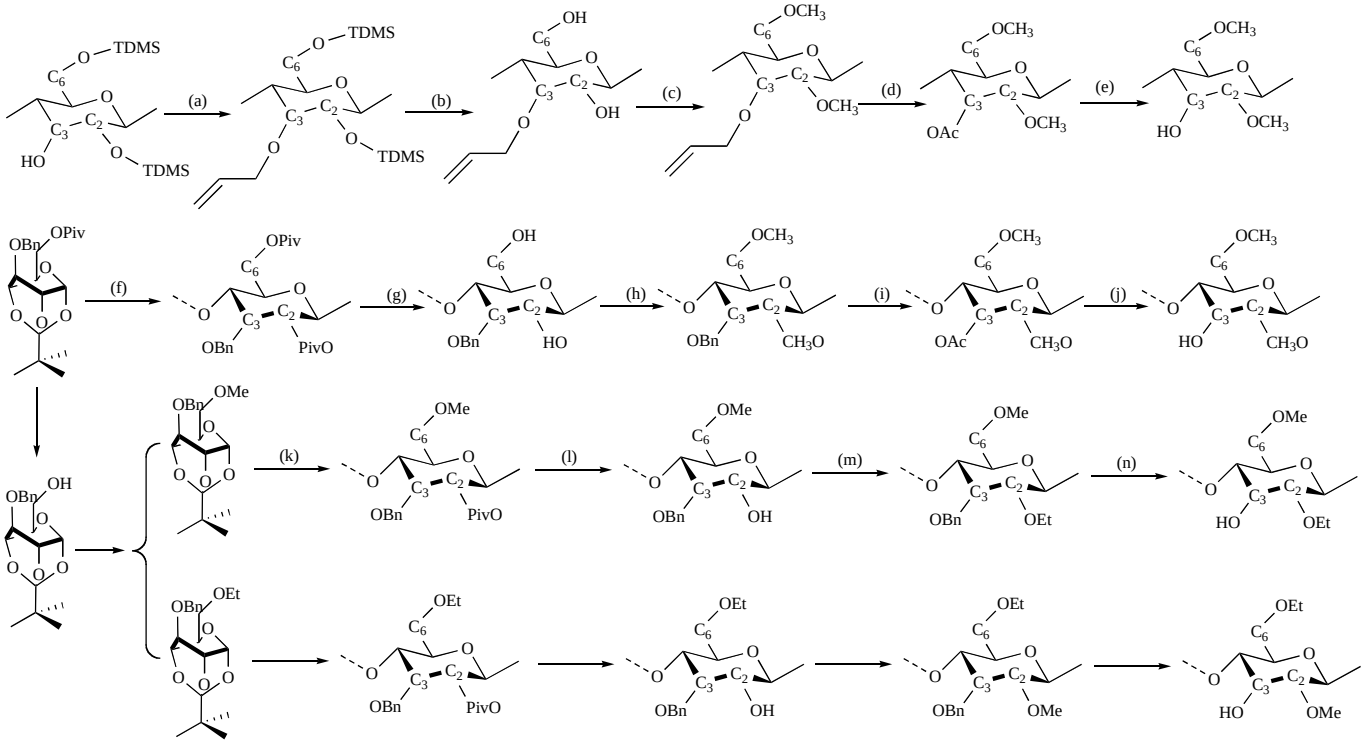

Fig. (10). General synthetic route of 2,6-di-O methylcellulose and 2-O-methyl (Ethyl)-6-O-Ethyl (methyl)cellulose derivatives by silylation reaction and ring opening polymerization; Regents and conditions: (**a**) Allyl chloride, NaH, THF, 1 day, 25 °C, 3 day/50 °C; (**b**)TBAF, THF, 1 day, 50 °C; (**c**) Methyl iodide, NaH, DMSO, 1 day, 25 °C, 3 day/50 °C; (**d**) PdCl2, MeOH, CHCl3, 1.5 day; Ac2O, Pyridine, PMAP, r.t., 1.5 day; (**e**) NaOCH3 in MeOH/MeOH: CHCl3=1:4 (v/v)/r.t./29 h; (**f**) Ph3CBF4, CH2Cl2, r.t.; (**g**) NaOCH3/THF:MeOH (4:1, v/v)/50 °C /15 h; (**h**)Methyl iodide, NaH, DMSO, 1 day, r.t./1 day 50℃; (**i**)H2/Pd(OH)2 on carbon/THF:AcOH (1:1, v/v)/4.5 kgf/cm2/80 °C/38 h; Ac2O/pyridine/50°C/1 day; H2/Pd(OH)2 on carbon/THF:MeOH:AcOH (1:5:5, v/v)/4.5kgf/cm2/80°C/27h; Ac2O/pyridine/50°C/19 h; (**j**) NaOCH3/THF:MeOH:CHCl3 (1:1:1, v/v)/reflux/over nigh; (**k**) -30 °C, 24 h; (**l**) THF/methanol (10 mL, 4:1 (v/v)), 28% sodium methoxide in methanol (0.40 mL), r.t., 60 °C /15 h; (**m**) DMSO (5 mL), 60 % sodium hydride/mineral oil/ethyl iodide/r.t./26h, sodium hydride/mineral oil/ethyl iodide/50 °C/46h/methanol; (**n**) THF/methanol (4:1, v/v), sodium methoxide/r.t./60 °C/ca.1.25 h, r.t./6.75 h [41-42].

Chloride), subsequently the clearage of protection group at C6 gives a reaction site at C6 location which aims at introducing the objective substituting groups. The second pathway is that the direct substituting objective groups at C6 just reported by no use of protecting group (e.g. Isocyanate, Nucleophilic, Halogenate substitution reactions). As we can see from Fig. (**11**), it indicates that the second direct pathway exhibits easier and shorter synthetic route than the first indirect pathway for preparing 6-O-cellulose and 2,3-O-cellulose derivatives.

In fact, 6-O cellulose is found to be prerequisite for preparing 2,3-O-cellulose derivatives, although the 6-O cellulose can be realized by the pathways with or without protecting group as discussed above. The synthesis of 2,3-O-methyl celluloses with regioselective substitutions at C2,3 starting from trityl blocking cellulose in DMA/LiCl was reported [27] (See Fig. **11**). By using 6-O-(4-monomethoxytriphenylmethyl) cellulose as basic matter, 2,3-O-carboxymethylcellulose (CMC) was synthesized by introducing sodium monochloroacetate at C2,3 locations of cellulose, in which the carboxymethylation is more effective at C2-OH compared to C3-OH of cellulose [88]. Novel water soluble 2,3-O-hydroxyethyl- and 2,3-O-hydroxypropyl cellulose products with DS of 0.25-2.00 based on the 6-O-(4-monomethoxytrityl) cellulose was prepared in the presence of a detergent mixture [89]. The same 2,3-O-hydroxyethyl cellulose product was carried out, and was found that the trityl at 6 position and tetrahydropyran at the hydroxyethyl substituent can be simultaneously cleaved off by acidic hydrolysis [27]. In this similar pathway, on an Au-coated substrate, 2,3-Di-O-octadecylcellulose resulted from 6-O-triphenylmethylcellulose (tritylcellulose) was applied by arranging long alkyl side chains in a Langmuir–Blodgett (LB) film, in which hydrophobic long alkyl side chains were forced to be repellent to the surface of water [90].

4.4. 6-O-2,3-di-O-cellulose Derivatives

In synthesis of 6-O-2,3-di-O-cellulose derivatives, about two pathways of regioselective substitutions are generally considered based on the pathway of preparing 6-O-cellulose and 2,3-O-cellulose derivatives. Ifuku and his group used atom transfer radical polymerization to prepare water insoluble 6-O-polyNIPAM-2,3-di-O-methyl cellulose copolymers via a regioselectively modified 6-O-bromoisobutyryl-2,3-di-O-methyl cellulose macroinitiator [54]. This complex copolymer exhibits favorable temperature sensitivity in which copolymer shows stable suspensions to precipitation in water at 30 °C likely arising from the hydrophilic-to-hydrophobic transition of the polyNIPAM graft component [54] (See Fig. **12**). In spit of the tritylation method, nucleophilic substitution reaction is carried out for preparing complex 6-O-2,3-di-O-cellulose derivatives from cellulose tosylates. These derivatives are able to form clear and thin films on glass surfaces and show remarkable complexation properties concerning nickel (II) in the cellulose solvent system DMA/LiCl with triethylamine and tosyl chloride as reagent [91].

5. CONCLUSION

This review work discussed a great variety of cellulose derivatives prepared by regioselective substitutions with different path-

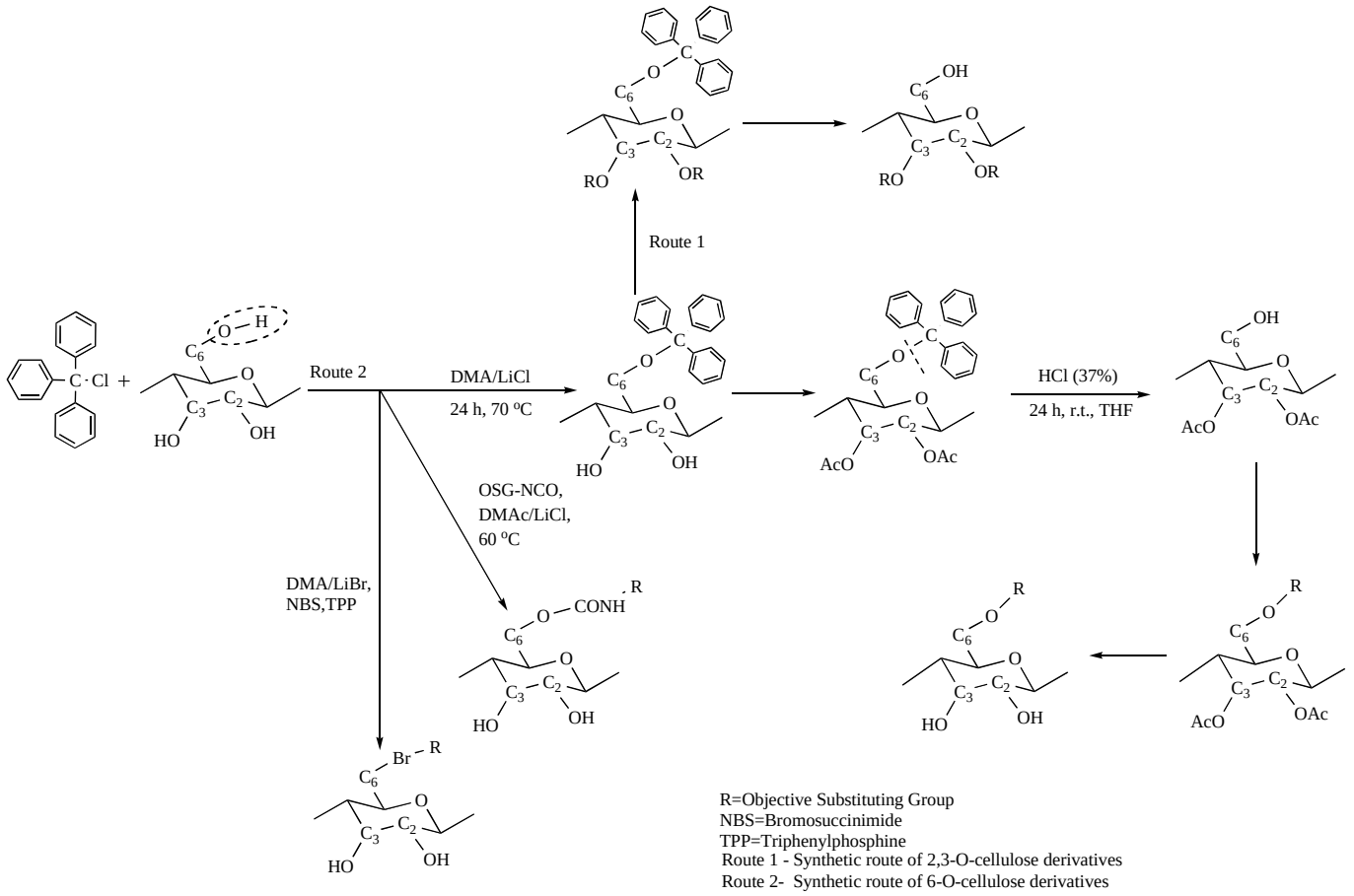

Fig. (11). Synthetic route of 2, 3-O-cellulose and 6-O-cellulose derivatives [27, 37, 36].

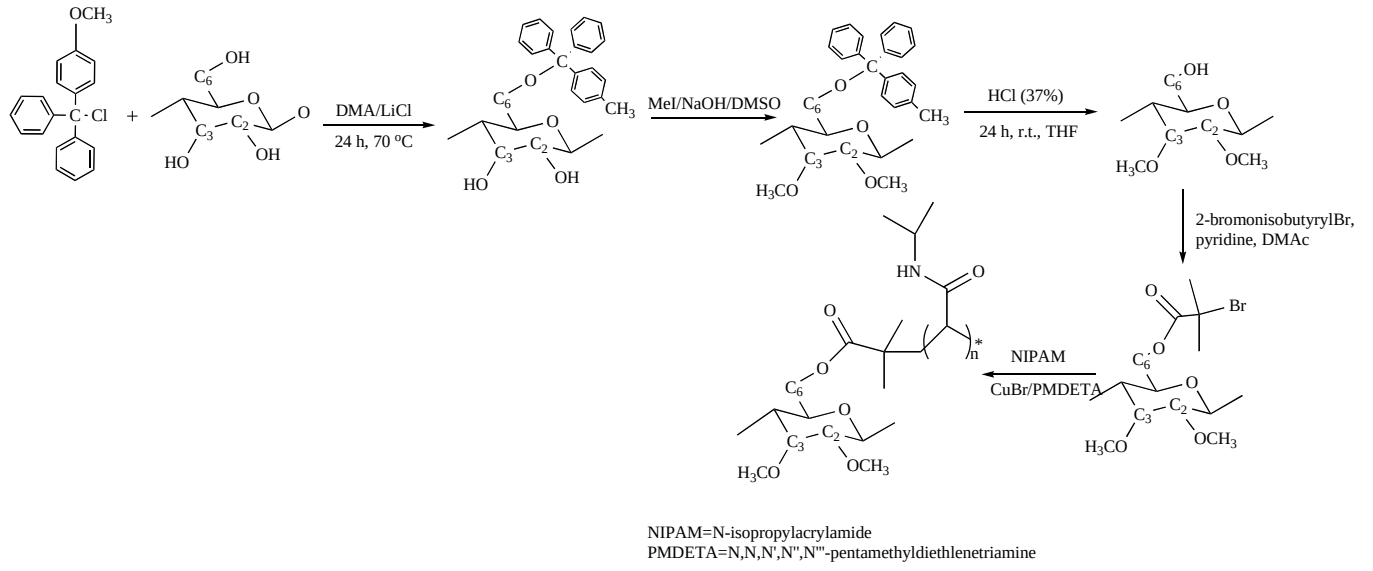

Fig. (12). Synthetic scheme for the preparation of 6-O-PolyNIPAM Cellulose Copolymer and its visual appearance of phase transition [54].

ways and reaction mediums. An important result is that structure-property model of cellulose derivatives can be accurately established since the objective group can be regioselectively introduced onto C2, C3 and C6. There has been an increasing worldwide interest in developing these green biopolymers. It was know that many undiscovered functionalized cellulose derivatives are explored combining with other area studies like Biology, Materials, Medical, Energy Sciences. However, the following works are suggested in future work of regioselective substituting celluloses: (1) The intelligentized embedding reagents are desired, and can be introduced regioselectively onto direct C2, C3 and C6 locations of cellulose respectively without the protecting process; An important result in

this regard is that the objective groups can be directly introduced onto the intelligentized embedding reagents. This avoids the reduplicative protecting-deprotecting process from the previous protecting groups like trityl chlorine, trimethylsilyl group during regioselective substituting cellulose process; (2) The reaction medium like DMAc/LiCl, ILs, N-menthylpyrrolidone ammonia are considered their influence on the accuracy and efficiency of regioselectively substitutions of cellulose. ILs was reported their superiority on regioselective substituting the primary hydroxyl group at C6 by tritylation compared to the typical cellulose solvents like DMAc/LiCl. It is assumed that functionalized ILs combining with catalytic actions probably prompt the efficient modification of celluloses. Further study is suggested to develop functionalized ILs dedicated to regioselective substituting celluloses; (3) More functionalized biomacromolecules based on regioselective substituting celluloses are expected due to their biodegradable and renewable nature. For instance, most functionalized green polymers are required for industrial products like green resins, filters, organic pesticides, films and biomedicines. In combining with celluloses, it is possible to achieve green multifunctional products by introducing two or more functionalized groups onto C2, C3 and C6 of celluloses under mild conditions.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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