

PROTECTING-GROUP-FREE CARBOHYDRATE SYNTHESIS USING BENCH-STABLE HETEROARYL GLYCOSYL SULFIDES AS DONORS

FIELD OF THE INVENTION

[0001] The present invention generally relates to a method of chemical glycosylation. In particular, the present invention relates to a method for protecting-group-free chemical glycosylation.

BACKGROUND

[0002] Carbohydrates are an indispensable class of organic compounds that play pivotal roles in a myriad of biological processes. Because of their importance, significant efforts have been devoted to accessing these saccharides in order to better understand their properties, functions and potential disease-related implications, which are vital towards the development of sugar-based therapeutics. The difficulty of extracting meaningful quantities of pure samples from nature has prompted chemists to access most saccharides via synthetic means. To this end, non-enzymatic chemical glycosylation represents the cornerstone of carbohydrate chemistry as a reliable and versatile approach to assemble a vast array of natural and non-natural glycoside entities.

[0003] However, unlike enzymatic systems which are capable of mediating glycosylation of polyhydroxylated glycosyl donors with exquisite regiocontrol, established non-enzymatic or chemical glycosylation methodologies are less precise and typically require arduous protecting-group strategies to overcome the problem of site selectivity. These shortcomings are explicitly highlighted in the chemical synthesis of *C*-glycosides [1], which are increasingly gaining prominence as robust and often more biologically potent surrogates of *O*-glycosides. Over the last few decades, advances in *C*-glycosylation (Figure 1a) entail multi-step reaction sequences (hydroxyl group protection, functionalization, deprotection) involving delicate or harsh reaction conditions to transform fully unprotected native sugars into tailored glycosyl precursors containing anomeric leaving groups such as halides, esters, sulfoxides or sulfones, setting the stage for the ensuing carbon-carbon bond-forming reaction to deliver the desired unprotected *C*-glycoside. The current multi-step strategies for the chemical synthesis of unprotected *C*-glycoside involves lengthy sequence, excessive waste generation, strong oxidants, and late-stage deprotection which cause complications. In light of the practical drawbacks and inefficiencies of these approaches, developing a protecting-

group-free regime for broad-scope chemical glycosylation remains a longstanding goal in glycoscience.

[0004] Thus, there is a need for a novel method of chemical glycosylation which does not involve multi-step reaction sequences (hydroxyl group protection, functionalization, deprotection) with delicate or harsh reaction conditions. In this invention, a protecting-group-free regime for broad-scope chemical glycosylation is developed. The method achieves direct chemical glycosylation of native sugars through a transient thioglycosyl donor, and achieves site- and diastereoselective anomeric functionalization of unprotected native sugars.

SUMMARY

[0005] In one aspect, the present disclosure refers to a method of synthesizing a compound selected from the group consisting of *C*-alkyl glycoside, *C*-Alkenyl glycoside, *C*-heteroaryl glycoside, *Se*-glycoside, and *S*-glycoside, comprising:

- a. reacting a natural unprotected sugar with a mixture of 2-chloro-1,3-dimethylimidazolinium chloride (DMC), heteroaryl thiol and trimethylamine (Et₃N) in a mixture of water and dioxane to produce a heteroaryl glycosyl sulfide;
- b. photoinduced cross-coupling of the heteroaryl glycosyl sulfide with a reagent in the presence of Hantzsch ester (HE), 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMSO under blue LED irradiation to produce the compound.

[0006] Advantageously, the present disclosure solves a longstanding challenge in carbohydrate chemistry by providing a general strategy to achieve site- and stereoselective chemical glycosylation from fully unprotected native sugar building blocks, bypassing unnecessary hydroxyl group masking and manipulation. As a result, this offers significant savings in cost, reduces waste generation and represents a greener and more sustainable solution to carbohydrate synthesis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0008] **Figure 1** is a schematic drawing illustrating the prior art and the development of a protecting-group-free approach for the chemical glycosylation of native sugars. (a) Challenges in the multi-step chemical synthesis of unprotected saccharides using *C*-

glycosides as examples. (b) Design of a traceless activation strategy to achieve site- and diastereoselective anomeric functionalization of unprotected native sugars.

[0009] **Figure 2** is a schematic drawing illustrating the reaction development. **a**, Selection of an appropriate activator for site-selective nucleophilic substitution. **b**, Identification of the most effective thioglycosyl donor for photoinduced cross-coupling. Yields were determined by ^1H NMR analysis of the crude reaction mixture; yields in parentheses denote isolated yields. $\alpha:\beta$ Anomeric ratios were determined by ^1H NMR and LC-MS analysis. DMC, 2-chloro-1,3-dimethylimidazolinium chloride; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; NMM, N-methylmorpholine; HE, Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate); DABCO, 1,4-diazabicyclo[2.2.2]octane; DMSO, dimethyl sulfoxide; LED, light-emitting diode; RT, room temperature; C_6F_4 , 2,3,5,6-tetrafluorophenyl.

[0010] **Figure 3** is a schematic drawing illustrating the mechanistic studies. **a**, Different anomers of the thioglycoside intermediate eventually converge to a stereoisomerically pure C-glycosyl product. **b**, Radical trap experiment supports the intermediacy of a glycosyl radical species. **c**, Ultraviolet/visible absorption spectra of reaction components in DMSO. **d**, Plausible mechanisms for native sugar activation and photoinduced cross-coupling. Yields were determined by ^1H NMR analysis of the crude reaction mixture; yields in parentheses denote isolated yields. $\alpha:\beta$ Anomeric ratios were determined by ^1H NMR and LC-MS analysis. TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; DMI, 1,3-dimethylimidazolidin-2-one; PET, photoinduced electron transfer; HRMS, high-resolution mass spectrometry; ESI, electrospray ionization; E, electrophile; calcd, calculated.

[0011] **Figure 4** is a schematic drawing illustrating the scope of the reaction with various native sugars. Cross-coupling of mono- and oligosaccharides via unprotected glycosyl donors to directly afford unprotected C-alkyl glycosyl compounds. Yields were determined by ^1H NMR analysis of the crude reaction mixture; yields in parentheses denote isolated yields. $\alpha:\beta$ Anomeric ratios were determined by ^1H NMR and LC-MS analysis. Bn, benzyl.

[0012] **Figure 5** is a schematic drawing illustrating the synthesis of diverse classes of robust glycosides and glycoconjugates. **a**, C-Alkyl glycosyl compounds via reaction with **I**. **b**, C-Alkenyl and C-heteroaryl glycosyl compounds via reaction with **II** (for **44**) and **III** (for **45-47**). **c**, *Se*-Glycosides via reaction with **IV**. **d**, *S*-Glycosides via reaction with **V**. Yields were determined by ^1H NMR analysis of the crude reaction mixture; yields in parentheses denote isolated yields. $\alpha:\beta$ Anomeric ratios, diastereomeric ratios (dr) and *E:Z* ratios were

determined by ^1H NMR and LC-MS analysis. *Obtained as a 77:23 *E:Z* mixture. †D-galactose was used. Ar, aryl; X, halide; Ac, acetyl; Boc, *tert*-butoxycarbonyl.

DETAILED DESCRIPTION

[0013] The present disclosure describes a protecting-group-free carbohydrate synthesis method using bench-stable heteroaryl glycosyl sulfides as donors.

[0014] In one aspect, the present disclosure refers to a method of synthesizing a compound selected from the group consisting of *C*-alkyl glycoside, *C*-Alkenyl glycoside, *C*-heteroaryl glycoside, *Se*-glycoside, and *S*-glycoside, comprising:

- a. reacting a natural unprotected sugar with a mixture of 2-chloro-1,3-dimethylimidazolium chloride (DMC), heteroaryl thiol and trimethylamine (Et_3N) in a mixture of water and dioxane to produce a heteroaryl glycosyl sulfide;
- b. photoinduced cross-coupling of the heteroaryl glycosyl sulfide with a reagent in the presence of Hantzsch ester (HE), 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMSO under blue LED irradiation to produce the compound.

[0015] Inspired by reports of biological *S*-glycosylation [2] in which *S*-glycosyltransferases catalyze the formation of metabolically stable *S*-glycosidic linkages with unprotected nucleotide sugars (generated from their native variants through site-selective phosphorylation of the hemiacetal), the present invention aims to adopt a biomimetic approach to preferentially activate and substitute the anomeric hydroxyl group (hemiacetal) within a native sugar, affording a reactive thioglycoside intermediate that is sufficiently long-living to undergo desulfurative cross-coupling with an appropriate reagent in a single operation. Through this process, the *S*-glycosyl donor (heteroaryl glycosyl sulfide) that was temporarily introduced remains traceless. In this invention, the heteroaryl glycosyl sulfides, 2,3,5,6-tetrafluoro-4-pyridyl glycosyl sulfides, are disclosed as air- and moisture-stable glycosyl donors of a wide range of carbohydrate units (Figure 1b). These compounds are readily accessed in one step from sugars in their native form (fully unprotected), and can be either isolated in pure form or directly subjected (without isolation) to photoinduced cross-coupling to construct *C*-alkyl glycosides. This invention thus solves a longstanding challenge in carbohydrate chemistry by providing a general strategy to achieve site- and stereoselective chemical glycosylation from fully unprotected native sugar building blocks, bypassing unnecessary hydroxyl group masking and manipulation. As a result, this offers significant savings in cost, reduces waste generation and represents a greener and more sustainable

solution to carbohydrate synthesis. This invention paves the way for the future development of protecting-group-free strategies that will inspire widespread utility in glycoscience.

[0016] The natural unprotected sugar can be any type of sugar. In one example, the natural unprotected sugar is a monosaccharide. In another example, the monosaccharide is selected from the group consisting of a triose, a tetrose, a pentose, a hexose, a heptose, an octose and a nonose. In another example, the triose is selected from the group consisting of glyceraldehyde and dihydroxyacetone. In another example, the tetrose is selected from the group consisting of erythrose, threose and erythrulose. In another example, the pentose is selected from the group consisting of arabinose, lyxose, ribose, xylose, ribulose, xylulose, and deoxyribose. In another example, the hexose is selected from the group consisting of allose, altrose, galactose, glucose, gulose, idose, mannose, talose, fructose, psicose, sorbose, tagatose, fucose and rhamnose. In another example, the heptose is selected from the group consisting of mannoheptulose and sedoheptulose. In another example, the octose is selected from the group consisting of octulose and 2-keto-3-deoxy-manno-octonate. In another example, the nonose is sialose.

[0017] In another example, the natural unprotected sugar is a disaccharide. In another example, the disaccharide is sucrose. In another example, the disaccharide is lactose. In another example, the disaccharide is trehalose. In another example, the disaccharide is maltose. In another example, the disaccharide is cellobiose. In another example, the disaccharide is gentiobiose. In another example, the disaccharide is isomaltose. In another example, the disaccharide is kojibiose. In another example, the disaccharide is laminaribiose. In another example, the disaccharide is mannobiose. In another example, the disaccharide is melibiose. In another example, the disaccharide is nigroscose. In another example, the disaccharide is rutinose. In another example, the disaccharide is xylobiose.

[0018] In another example, the natural unprotected sugar is an oligosaccharide. An oligosaccharide is a saccharide polymer containing a small number (typically three to ten) of monosaccharides. In one example, the oligosaccharide is a trisaccharide comprised of three monosaccharides. The trisaccharide is selected from the group consisting of nigerotriose (3 glucose units joined by $\alpha(1-3)$ glycosidic linkage), maltotriose (3 glucose units joined by (1-4) glycosidic linkage), melezitose (glucose-fructose-glucose), maltotriulose (glucose-glucose-fructose), raffinose (galactose-glucose-fructose), kestose (glucose-fructose-fructose). In another example, the oligosaccharide is a tetrasaccharide comprised of four monosaccharides. The tetrasaccharide is selected from the group consisting of nigerotetraose

(4 glucose units joined by α (1-3) glycosidic linkage), maltotetraose (4 glucose units joined by (1-4) glycosidic linkage), lychnose (galactose-glucose-fructose-galactose), nystose (glucose-fructose-fructose-fructose), sesamose (galactose-galactose-fructose-glucose), and stachyose (galactose-galactose-glucose-fructose). In another example, the oligosaccharide is a pentasaccharide comprised of five sugar units. N-linked oligosaccharides are mostly pentasaccharide. In another example, the oligosaccharide is a hexasaccharide comprised of six sugar units. α -Cyclodextrin is an example, which consists of six glucose units linked via α -1,4 linkages. In another example, the oligosaccharide is a heptasaccharide containing seven sugar units. In another example, the oligosaccharide is an octasaccharide containing eight sugar units. In another example, the oligosaccharide is a nonasaccharide containing nine sugar units. In another example, the oligosaccharide is a deecasaccharide containing ten sugar units.

[0019] In another example, the natural unprotected sugar is a polysaccharide which is a saccharide polymer containing more than 10 monosaccharide units. In another example, the polysaccharide is a linear polysaccharide. In another example, the polysaccharide is a branched polysaccharide.

[0020] In another example, the natural unprotected sugar is selected from the group consisting of glucose, mannose, melibiose, lactose and cellobiose. In another example, the natural unprotected sugar is glucose. In another example, the natural unprotected sugar is mannose. In another example, the natural unprotected sugar is melibiose. In another example, the natural unprotected sugar is lactose. In another example, the natural unprotected sugar is cellobiose.

[0021] For the natural unprotected sugar disclosed herein, they can either be in L-configuration or D-configuration.

[0022] The heteroaryl glycosyl sulfide is synthesized by reacting a natural unprotected sugar with a mixture of 2-chloro-1,3-dimethylimidazolinium chloride (DMC), heteroaryl thiol and trimethylamine (Et_3N) in a mixture of water and dioxane (step a of the method as disclosed herein). In one example, the molar ratio of DMC, heteroaryl thiol and Et_3N is within the range of 1-20 : 1-20 : 1-20. In another example, the molar ratio of DMC, heteroaryl thiol and Et_3N is 4:5:17. In another example, the synthesis of heteroaryl glycosyl sulfide is carried out in a solvent of H_2O and dioxane with any volume ratio of 1-20 : 1-20. In another example, the synthesis of heteroaryl glycosyl sulfide is carried out in a solvent of H_2O and dioxane with any volume ratio of 1:20 to 20:1. In another example, the synthesis of heteroaryl glycosyl

sulfide is carried out in a solvent of H₂O and dioxane with a volume ratio of 1:1. In another example, the synthesis of heteroaryl glycosyl sulfide is carried out at 0-100 °C. In another example, the synthesis of heteroaryl glycosyl sulfide is carried out for 1-24 h. In another example, the synthesis of heteroaryl glycosyl sulfide is carried out at 0°C for 2 h.

[0023] In one example, the heteroaryl thiol is 2,3,5,6-tetrafluoro-4-pyridinethiol (C₅F₄N-SH); and the heteroaryl glycosyl sulfide is 2,3,5,6-tetrafluoro-4-pyridiyl glycosyl sulfide.

[0024] Compared to the existing technologies, wherein synthesis of glycosyl donors involved multiple steps and harsh reaction conditions, in step a of the method as disclosed herein, a wide range of air- and moisture-stable 2,3,5,6-tetrafluoro-4-pyridiyl glycosyl sulfides (fully unprotected) can be synthesized and isolated in one step from native sugars under mild conditions.

[0025] In one example, the heteroaryl glycosyl sulfide such as 2,3,5,6-tetrafluoro-4-pyridiyl glycosyl sulfide is isolated before step b.

[0026] In another example, the heteroaryl glycosyl sulfide such as 2,3,5,6-tetrafluoro-4-pyridiyl glycosyl sulfide is not isolated before step b. The heteroaryl glycosyl sulfide such as 2,3,5,6-Tetrafluoro-4-pyridiyl glycosyl sulfide can be generated in situ from native sugars and used as transient donors (without isolation) to undergo photoinduced cross-coupling with electrophiles to form glycosides. In this way, glycoside products can be secured directly from native sugars in one operation without the need to isolate the glycosyl donor, providing significant savings in terms of cost and time.

[0027] The heteroaryl glycosyl sulfide synthesized using step a of the method as disclosed herein will then be subjected to photoinduced cross-coupling with a reagent in the presence of Hantzsch ester (HE), 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMSO under blue LED irradiation to produce the compound as disclosed herein (step b of the method as disclosed herein).

[0028] In one example, the reagent is alkene and the produced compound is C-alkyl glycoside. The alkene is any monosubstituted alkene CH₂=CH-R or 1,1-disubstituted alkene CH₂=CR-R'. R and R' can be any organic substituent, including but not limited to an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group. In another example, -R or R' is selected from the group consisting of aryl, alkyl, SO₂R, P(O)(OR)₂, SiR₃, and BR₂. In another example, -R is -CO₂/Bu. In another

example, -R is -NHPh. In another example, -R is -CO₂Bn. In another example, -R is -CO-NMePh.

[0029] In another example, the reagent is alkenyl halide (X-CH=CH-R) and the produced compound is C-Alkenyl glycoside. The halide group X of the alkenyl halide (X-CH=CH-R) is selected from the group consisting of fluoride (F), chloride (Cl), bromide (Br), and iodide (I). In one example, X is F. In another example, X is Cl. In another example, X is Br. In another example, X is I.

[0030] R in the alkenyl halide (X-CH=CH-R) can be any organic substituent, including but not limited to hydrogen, an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0031] In another example, the reagent is heteroarene (Ar-H) and the produced compound is C-heteroaryl glycoside. The heteroarene (Ar-H) is an aromatic molecule containing at least one heteroatom (an atom other than carbon or hydrogen) as part of the aromatic ring. The heteroarene includes but is not limited to a pyridine, a furan, a thiophene, a cytosine, an indole, a pyrrole, an imidazole, an oxazole, an isoxazole, a thiazole, a purine, an adenine, a guanine, a thymine, an uracil, a tetrahydrofuran, a pyrrolidine, a pyran, a pyrimidine, an oxirane, and an epoxide.

[0032] In another example, the reagent is diselenide (R-Se-Se-R) and the produced compound is Se-glycoside. R of the diselenide (R-Se-Se-R) can be any organic substituent, including but not limited to an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0033] In another example, the reagent is disulfide (R-S-S-R) and the produced compound is S-glycoside. R of the disulfide (R-S-S-R) can be any organic substituent, including but not limited to an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0034] As used herein, the alkyl group, refers to a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or

"cycloalkyl"), that has a single point of attachment to the rest of the molecule. An acyclic alkyl has the general formula of $-C_nH_{2n+1}$. A cycloalkyl group is derived from a cycloalkane by removal of a hydrogen atom from a ring and has the general formula $-C_nH_{2n-1}$. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some examples, aliphatic groups contain 8-20 aliphatic carbon atoms. In other examples, aliphatic groups contain 1-10 aliphatic carbon atoms. In other examples, aliphatic groups contain 1-8 aliphatic carbon atoms. In other examples, aliphatic groups contain 1-6 aliphatic carbon atoms. In other examples, aliphatic groups contain 1-5 aliphatic carbon atoms. In other examples, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other examples, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other examples, aliphatic groups contain 1-2 aliphatic carbon atoms. In some examples, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C3-C6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl. Exemplary alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0035] As used herein, the aryl group is any functional group or substituent derived from an aromatic ring, usually an aromatic hydrocarbon, such as phenyl and naphthyl. The term aryl refers to monocyclic and bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain examples of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. In one example, the aryl group is a tolyl, xylyl, phenyl, or naphthyl group. In another example, the aryl group is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0036] As used herein, the halide is selected from the group consisting of F, Cl, Br, I.

[0037] As used herein, the alkyl halide (also named haloalkanes) consists of an alkyl group disclosed herein attached to a halogen selected from the group consisting of F, Cl, Br, I.

[0038] As used herein, the alcohol group involves an oxygen atom that is bonded to one hydrogen atom and one carbon atom. The carbon atom will be part of a larger organic structure. One way to indicate a generic alcohol would be with the formula R-OH. R represents any organic fragment in which a carbon atom is directly bonded to the explicitly indicated functional group (in this case, OH). The R group is typically a chain of carbon atoms. In one example, the alcohol is a primary alcohol having an -OH function attached to an R-CH₂- group, shown as RCH₂OH. In another example, the alcohol is a secondary alcohol having an -OH function attached to a R₂CH- group, shown as R₂CHOH. In another example, the alcohol is a tertiary alcohol having an -OH function attached to a R₃C- group, shown as R₃COH.

[0039] As used herein, the aldehyde group has a hydrogen and an alkyl (or aromatic) group attached to a carbonyl function. Aldehydes can be shown as: RCHO.

[0040] As used herein, the ketone group has a pair of alkyl or aromatic groups attached to a carbonyl function. Ketones can be shown as: RCOR.

[0041] As used herein, the carboxylic acid group has an alkyl or aromatic groups attached to a hydroxy-carbonyl function. Carboxylic acids can be shown as: RCOOH.

[0042] As used herein, the ester group has a pair of alkyl or aromatic groups attached to a carbonyl plus linking oxygen function. Esters can be shown as: RCOOR.

[0043] As used herein, the amide group is a carbonyl in which the carbon is attached to one nitrogen atom and one carbon or hydrogen atom. Primary amides have an alkyl or aromatic group attached to an amino-carbonyl function. Primary amides can be shown as: RCONH₂. Secondary amides have an alkyl or aryl group attached to the nitrogen: RCONHR. Tertiary amides have two alkyl or aryl group attached to the nitrogen: RCONR₂.

[0044] As used herein, the amine group consists of a nitrogen atom bonded to some combination of carbons and hydrogens. In one example, the amine is a primary amine having an alkyl or aromatic group and two hydrogens attached to a nitrogen atom. Primary amines can be shown as: RNH_2 . In another example, the amine is a secondary amine having a pair of alkyl or aromatic groups, and a hydrogen, attached to a nitrogen atom. Secondary amines can be shown as: R_2NH . In another example, the amine is a tertiary amine having three alkyl or aromatic groups attached to a nitrogen atom. Tertiary amines can be shown in text as: R_3N .

[0045] As used herein, the nitrile (or organo cyanide) group has an alkyl (or aromatic) group attached to a carbon-triple-bond-nitrogen function. Nitriles can be shown as: RCN .

[0046] As used herein, the carboxylate group is a conjugate base of a carboxylic acid, a carbonyl-containing functional group in which the carbon atom is bonded to an OH group on one side and either a carbon or hydrogen atom on the other.

[0047] As used herein, the amino acid can be any natural amino acid (encoded in the genome of organisms) or unnatural amino acid (also known as non-proteinogenic or non-canonical amino acids (ncAA), which is not genetically encoded by organisms and are not present in natural polypeptide chains, such as being chemical synthesized). In one example, the amino acid is Group I: nonpolar amino acid, selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, and tryptophan. In another example, the amino acid is Group II: polar, uncharged amino acid, selected from the group consisting of serine, cysteine, threonine, tyrosine, asparagine, and glutamine. In another example, the amino acid is Group III: acidic amino acid, selected from the group consisting of aspartic acid and glutamic acid. In another example, the amino acid is Group IV: basic amino acid, selected from the group consisting of arginine, histidine, and lysine. In another example, the amino acid is a selenocysteine. In another example, the amino acid is an unnatural amino acid synthetically prepared from their native analogs via modifications such as amine alkylation, side chain substitution, structural bond extension cyclization, and isosteric replacements within the amino acid backbone.

[0048] As used herein, the thiol group is any organosulfur compound of the form R-SH , where R represents an alkyl or other organic substituent.

[0049] The heteroaryl glycosyl sulfide synthesized from step (a) of the method as disclosed herein will then be subjected to photoinduced cross-coupling with a reagent in the presence of Hantzsch ester (HE), 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMSO under

blue LED irradiation to produce the compound as disclosed herein (step b of the method as disclosed herein).

[0050] In one example, in step b of the method as disclosed herein, the molar ratio of alkene, HE and DASCO is 1-20 : 1-20 : 1-20. In another example, in step b of the method as disclosed herein, the molar ratio of alkene, HE and DASCO is 1.5:2:2.5.

[0051] In another example, step b of the method as disclosed herein is carried out at 0-100 °C. In another example, step b of the method as disclosed herein is carried out for 1-24 h. In another example, step b of the method as disclosed herein is carried out at room temperature for 24 h.

[0052] In another example, step b of the method as disclosed herein uses blue LED with a wavelength of 400 - 450 nm. In another example, step b of the method as disclosed herein uses blue LED with a wavelength of 400 to 500 nm.

[0053] In another example, the resulted *C*-alkyl glycoside has an alkyl group which is an either linear or branched, saturated or unsaturated alkyl radical having from 8 to 20 carbon atoms. In another example, the alkyl group is selected from a group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, isopropyl, sec-butyl, isobutyl, and tert-butyl group. In another example, *C*-alkyl glycoside has a functional group which can be any organic substituent, including but not limited to an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0054] In another example, the resulted *C*-Alkenyl glycoside comprises a R group which can be any organic substituent, including but not limited to hydrogen, an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0055] In another example, the resulted *C*-heteroaryl glycoside comprises a heteroarene group including but not limited to a pyridine, a furan, a thiophene, a cytosine, an indole, a pyrrole, an imidazole, an oxazole, an isoxazole, a thiazole, a purine, an adenine, a guanine, a thymine, an uracil, a tetrahydrofuran, a pyrrolidine, a pyran, a pyrimidine, an oxirane, and an epoxide.

[0056] In another example, the resulted *Se*-glycoside comprises a R group which can be any organic substituent, including but not limited to an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0057] In another example, the resulted *S*-glycoside comprises a R group which can be any organic substituent, including but not limited to an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

[0058] The present invention harnesses redox-active 2,3,5,6-tetrafluoro-4-pyridyl glycosyl sulfides to undergo photoinduced cross-coupling with electrophiles to form glycosides, in the presence of a mild organic electron donor (e.g. Hantzsch ester) and an organic base under visible light irradiation at ambient temperature. 2,3,5,6-Tetrafluoro-4-pyridyl glycosyl sulfides are new donors that have not been reported to undergo radical-based cross-coupling. The direct transformation of native sugars, via these transiently formed glycosyl sulfide intermediates, into fully unprotected C-glycosides has not been demonstrated before.

[0059] As used in this application, the singular form “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a metal” includes a plurality of metals, including mixtures and combinations thereof.

[0060] As used herein, the term “comprising” means “including.” Variations of the word “comprising”, such as “comprise” and “comprises,” have correspondingly varied meanings. Thus, for example, a composition “comprising” X may consist exclusively of X or may include one or more additional unrecited components.

[0061] As used herein, the term “about” in the context of concentration of a substance, size of a substance, length of time, or other stated values means +/- 5% of the stated value, or +/- 4% of the stated value, or +/- 3% of the stated value, or +/- 2% of the stated value, or +/- 1% of the stated value, or +/- 0.5% of the stated value.

[0062] Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0063] The disclosure illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[0064] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0065] Unless otherwise indicated, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

[0066] Other embodiments are within the following claims and non-limiting examples.

EXAMPLES

[0067] Non-limiting examples of the disclosure will be further described in greater detail by reference to specific Examples, which should not be construed as in any way limiting the scope of the disclosure.

[0068] Referring to Figure 1(a), over the last few decades, advances in *C*-glycosylation entail multi-step reaction sequences (hydroxyl group protection, functionalization, deprotection) involving delicate or harsh reaction conditions to transform fully unprotected native sugars into tailored glycosyl precursors containing anomeric leaving groups such as halides, esters, sulfoxides or sulfones, setting the stage for the ensuing carbon-carbon bond-forming reaction to deliver the desired unprotected *C*-glycoside. Challenges in the multi-step

chemical synthesis of unprotected saccharides include lengthy sequence, excessive waste generation, late-stage deprotection causing complications, and strong oxidants required.

[0069] As shown in Figure 2, reaction parameters that promote regioselective nucleophilic substitution (capping) was first evaluated using D-glucose **1** as the model substrate. Taking advantage of the greater acidity of the anomeric OH with respect to other hydroxyl units, various activating agents (R-LG) were examined to convert **1** to its bench-stable 2,3,5,6-tetrafluoro-4-pyridinethioglycoside derivative **2** under weakly basic conditions (Figure 2a). In the presence of commercially available 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as activator and triethylamine as base, **2** was obtained in 85% yield (72% isolated yield) and >95:5 β : α ratio at 0 °C within 2 hours. **2** (white solid) could be stored in air on the bench over months without noticeable decomposition. Other analogues of DMC (**3** and **4**) led to drastically diminished yields, whereas other commonly used reagents such as chlorophosphonium salt **5** and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)/N-methylmorpholine (NMM) failed to promote the reaction.

[0070] With DMC identified as the most effective activator, the nucleophilic substitution conditions were employed to synthesize not only **2** but also a range of unprotected (hetero)aryl thioglycosides (**6-9**) for comparison. To drive glycosylation, the thioglycosides was subjected to reaction with acrylate **10** under visible light illumination. After an extensive survey of conditions, it was discovered that **2** underwent desulfurative C-C coupling to deliver unprotected C-alkyl glucoside **11** in 96% yield (82% isolated yield) and >95% α selectivity via a combination of Hantzsch ester (HE) as reductant, 1,4-diazabicyclo[2.2.2]octane (DABCO) and dimethyl sulfoxide (DMSO) as solvent under blue LED irradiation at ambient temperature (Figure 2b).

[0071] In contrast, poor conversion was observed with the less redox-active S-glucosides derived from other less electron-withdrawing (hetero)aryl thiols (**6-9**), highlighting the importance of the fluorinated heteroaromatic moiety for photoinduced cross-coupling. On the other hand, excluding the light source, HE or DABCO was detrimental to reaction, and changing the base or solvent led to lower yields. To demonstrate the power of the “cap and glycosylate” approach via traceless activation, it was shown that α -**11** could be generated from **1** in a single sequence without the need for isolating the S-glycosyl intermediate **2** (Figure 2, inset). The overall step efficiency and yield (64% yield, 52% isolated yield) offer significant advantages over previous chemical C-glycosylation approaches that require multiple steps.

[0072] Experiments were conducted to gain insight into the individual processes for native sugar activation and cross-coupling. As disclosed in Figure 3a, nucleophilic substitution of D-glucose **1** afforded 2,3,5,6-tetrafluoro-4-pyridinethioglycoside **2** in 85% yield (72% isolated yield) and >95:5 β : α ratio. On the contrary, it was found that the corresponding thioglycoside **13** was secured in 44% yield (30% isolated yield) and >95:5 α : β ratio from D-maltose **12** under the same established conditions (Figure 3a). In solution, the α and β anomers of native sugars (**1**, **12**) likely interconvert and exist in equilibrium; each anomer individually reacts with DMC before undergoing stereoinvertive nucleophilic displacement by the thiol. Alternatively, the 2-OH group of the DMC-activated β anomeric intermediate may engage in neighboring group participation via intramolecular nucleophilic attack to generate a 1,2-anhydro species, which is susceptible to site-selective ring cleavage by the thiol nucleophile. This pathway is probably insignificant in the reaction leading to **13**, given that β -**13** was detected in minor amounts. For other saccharides (see Figure 4), the various pathways for nucleophilic substitution may be favored to different extents in the reaction system.

[0073] Subjecting **2** and **13** separately to standard cross-coupling conditions with an acrylate gave **11** and **15**, respectively, both of which possess the same sense of anomeric selectivity (Figure 3a). This notably implies that, unlike heterolytic glycosylations, the C1 stereochemistry of the *S*-glycosyl donor is inconsequential, highlighting the distinct advantage of the present strategy in transforming mixtures of unprotected native sugar isomers, via their thioglycoside derivatives, into stereoisomerically pure glycosides in a streamlined fashion. In a separate study, the addition of exogenous 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) inhibited the photoinduced transformation of **2** to **11** (Figure 3b). HRMS analysis revealed the formation of a complex that can be ascribed to a TEMPO-glycoside adduct **16**, providing evidence that a sufficiently long-lived glycosyl (anomeric) radical species is generated during the process. These processes are in contrast to heterolytic glycosylations that essentially lack the formation of a clear intermediate species (for example, glycosyl cation). The nature of the photoinduced reaction (using **2** as model substrate) was further explored through ultraviolet/visible absorption (UV/vis) spectroscopy (Figure 3c). Independent absorption spectra of **2** and DABCO revealed bands largely in the UV region, and a mixture of these two components only led to a small redshift that extends into the visible region (>400 nm). On the other hand, a DMSO solution of HE exhibited strong absorption in the visible region, but no noticeable changes were observed with a mixture of HE and DABCO. Interestingly, a mixture of **2** and HE showed a slight bathochromic shift, which was

appreciably amplified when **2**, HE and DABCO were combined together in solution. These results suggest the generation of a putative ternary complex between **2**, HE and DABCO, which is proposed to absorb visible light and undergo fragmentation to the glycosyl radical.

[0074] The studies presented here support a mechanism as proposed in Figure 3d. Site-selective capping of the more acidic anomeric hydroxyl motif by DMC forms an activated leaving group that undergoes facile nucleophilic attack by 2,3,5,6-tetrafluoro-4-pyridinethiol under basic conditions, driven by concomitant generation of 1,3-dimethylimidazolidin-2-one (DMI) as a by-product. Formation of a 1,2-anhydro species prior to nucleophilic substitution could also occur and cannot be completely ruled out. The resulting thioglycoside intermediate is postulated to associate with HE and DABCO in solution, affording a ternary complex that can absorb visible light to trigger photoinduced electron transfer (PET). Consistent with previously documented reactions, the highly electrophilic nature of the fluorinated heteroaryl motif renders the thioglycoside sufficiently redox-active for PET. This delivers dihydropyridine radical **17** and a radical anion **18**, which is prone to desulfurative fragmentation to give a glycosyl radical species and 2,3,5,6-tetrafluoro-4-pyridinethiolate (the conjugate acid was detected in the reaction mixture). Subsequent reaction of the glycosyl radical with an electrophilic cross-coupling partner, facilitated by **17**, proceeds in a stereoselective manner under kinetic control to give the desired unprotected glycoside.

[0075] As a proof-of-concept, the feasibility of performing direct conversion of native sugars to C-alkyl glycosides without isolation of the glycosyl sulfide intermediate was shown. Through this operation, the S-glycosyl donor that was temporarily introduced remains traceless. The desired C-glycoside product was secured in good overall yield and diastereoselectivity via a single purification, which is comparable to the two-step procedure. This approach significantly simplifies chemical glycosylation and represents a more efficient and sustainable solution to carbohydrate synthesis.

[0076] The generality of the disclosed protecting-group-free protocol was highlighted by the wide spectrum of native mono- and oligosaccharides that could be reliably transformed into fully unprotected C-alkyl glycosides (Figure 4) via their 2,3,5,6-tetrafluoro-4-pyridinethioglycoside precursors, which were either isolated or generated in situ and used (without purification) for cross-coupling. Representative examples include pyranoside products constructed from biomass-derived monosaccharides (**19-21**, **24**), rare sugars (**22**, **23**) and non-natural L-glucose (**25**). More complex glycans from natural sources also served

as effective substrates to deliver the corresponding *C*-alkyl glycosides (**15**, **26-29**) in good efficiency. Across the board, good to excellent stereocontrol was observed.

[0077] Besides α,β -unsaturated carbonyl compounds, other alkenes were investigated as cross-coupling partners in Figure 5a. Densely functionalized acrylates and acrylamides conjugated to biologically active compounds (**30**, **31**), an aminosalicylate (**32**), an amino sugar (**33**) and oligopeptides (**34-36**) were compatible substrates, providing access to highly polar *C*-glycosylated conjugates bearing multiple acidic and basic sites. This offers a straightforward way to glycosylate complex molecules with native sugars for various applications, including the design of sugar-based peptidomimetics. Other Michael acceptors such as vinyl sulfone (**37**), vinylphosphonate (**38**) and vinylboronate (**40**) as well as less electrophilic vinyl silane (**39**) and allyl acetate (**41**) also underwent efficient reaction to furnish the desired *C*-alkyl glycoside adducts bearing functional groups which could serve as useful synthetic handles for further manipulations. Of particular note, cross-coupling was found to proceed even in the presence of a less-activated alkyl-substituted alkene (**42**). Importantly, metabolically stable pseudo-oligosaccharide building blocks such as *C*-glycosidic disaccharide **43** featuring two newly formed stereocenters could be expeditiously assembled with complete stereocontrol through reaction with an *exo*-glucal as radical acceptor.

[0078] To showcase the versatility of the present “cap and glycosylate” approach in securing other categories of unprotected saccharides, the alkene coupling partner was replaced with other electrophilic reagents that could participate as radical acceptors. Using a haloalkene reagent (Figure 5b), a *C*-alkenyl glycosyl compound (**44**) was successfully secured in high anomeric selectivity; this process is postulated to proceed through a glycosyl radical addition–reduction– β halide elimination pathway. *C*-Heteroaryl glycosylation could also be realized by direct coupling with heteroarenes under acid-free conditions, delivering unprotected **45-47** selectively at the most electron-deficient sites which is congruent with a previous report involving fully protected glycosyl radicals.

[0079] Beyond *C*-glycosylation, the protecting-group-free reaction was extended manifold to the preparation of other glycomimetics such as selenoglycosides (Figure 5c) and thioglycosides (Figure 5d). Along with *C*-glycosyl compounds, these entities have found many applications as robust substitutes of the naturally occurring *O*-saccharides, thus efficient ways to synthesize them in high stereochemical purity are highly desirable. Gratifyingly, both unprotected *Se*-glycosides (**48**, **49**) and *S*-glycosides (**50-54**) were

accessible through reaction with diselenide or disulfide reagents, respectively, comparing favorably with previous protocols that relied on laborious preparation of glycosyl precursors.

[0080] **Industrial Applicability**

[0081] The bench-stable heteroaryl glycosyl sulfides disclosed herein offer a straightforward way to access a diverse range of unprotected glycosides, bypassing the need for protecting groups. These sulfide donors can also be generated from native sugars (fully unprotected) and used in situ (without isolation) for photoinduced cross-coupling to furnish unprotected glycosides. For commercialization purposes, these sulfides will become the benchmark glycosyl donor reagents for use in all applications related to carbohydrate synthesis. The resulting glycosides are key building blocks used in the preparation of high-value chemicals such as sugar-based natural products, pharmaceuticals and therapeutic candidates.

[0082] It will be apparent that various other modifications and adaptations of the invention will be apparent to the person skilled in the art after reading the foregoing disclosure without departing from the spirit and scope of the invention and it is intended that all such modifications and adaptations come within the scope of the appended claims.

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Claims

1. A method of synthesizing a compound selected from the group consisting of *C*-alkyl glycoside, *C*-Alkenyl glycoside, *C*-heteroaryl glycoside, *Se*-glycoside, and *S*-glycoside, comprising:
 - a. reacting a natural unprotected sugar with a mixture of 2-chloro-1,3-dimethylimidazolinium chloride (DMC), heteroaryl thiol and trimethylamine (Et₃N) in a mixture of water and dioxane to produce a heteroaryl glycosyl sulfide;
 - b. photoinduced cross-coupling of the heteroaryl glycosyl sulfide with a reagent in the presence of Hantzsch ester (HE), 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMSO under blue LED irradiation to produce the compound.
2. The method of claim 1, wherein the heteroaryl glycosyl sulfide is not isolated before step b.
3. The method of claim 1, wherein the heteroaryl glycosyl sulfide is isolated before step b.
4. The method of any one of claims 1-3, wherein the natural unprotected sugar is selected from the group consisting of glucose, mannose, melibiose, lactose and cellobiose.
5. The method of any one of claims 1-4, wherein the heteroaryl thiol is 2,3,5,6-tetrafluoro-4-pyridinethiol (C₅F₄N-SH); and the heteroaryl glycosyl sulfide is 2,3,5,6-tetrafluoro-4-pyridyl glycosyl sulfide.
6. The method of claim 1, wherein the reagent is selected from the group consisting of an alkene, an alkenyl halide (X-CH=CH-R), a heteroarene (Ar-H), a diselenide (R-Se-Se-R), and a disulfide (R-S-S-R).
7. The method of claim 6, wherein the alkene is a monosubstituted alkene CH₂=CH-R, or a 1,1 disubstituted alkene CH₂=CR-R', wherein R- or R'- is selected from the group consisting of an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.
8. The method of claim 7, wherein -R is selected from a group consisting of -CO₂Bu, -NHPh, -CO₂Bn, and -CO-NMePh.
9. The method of claim 6, wherein X of the alkenyl halide (X-CH=CH-R) is selected from the group consisting of fluoride (F), chloride (Cl), bromide (Br), iodide (I), and wherein R- is selected from the group consisting of hydrogen, an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.

10. The method of claim 6, wherein the heteroarene (Ar-H) is selected from the group consisting of a pyridine, a furan, a thiophene, a cytosine, an indole, a pyrrole, an imidazole, an oxazole, an isoxazole, a thiazole, a purine, an adenine, a guanine, a thymine, an uracil, a tetrahydrofuran, a pyrrolidine, a pyran, a pyrimidine, an oxirane, and an epoxide.
11. The method of claim 6, wherein R- of the diselenide (R-Se-Se-R) is selected from the group consisting of an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.
12. The method of claim 6, wherein R- of the disulfide (R-S-S-R) is selected from the group consisting of an alkyl, an aryl, a halide, an alkyl halide, an alcohol, an aldehyde, a ketone, a carboxylic acid, a carbonyl group, an ester, an amide, an amine group, a nitrile, a carboxylate, an amino acid, and a thiol group.
13. The method of claim 7, wherein the alkyl group of the C-alkyl glycoside is an either linear or branched, saturated or unsaturated alkyl radical having from 8 to 20 carbon atoms.
14. The method of any one of claims 1-13, wherein the molar ratio of DMC, heteroaryl thiol and Et₃N is 1-20 : 1-20 : 1-20.
15. The method of claim 14, wherein the molar ratio of DMC, heteroaryl thiol and Et₃N is 4:5:17.
16. The method of any one of claims 1-15, wherein step a is carried out in a solvent of H₂O and dioxane with a volume ratio of 1-20 : 1-20, at 0-100 °C for 1-24 h.
17. The method of claim 16, wherein step a is carried out in a solvent of H₂O and dioxane with a volume ratio of 1:1, at 0 °C for 2 h.
18. The method of any one of claims 1-17, wherein the molar ratio of alkene, HE and DASCO is 1-20 : 1-20 : 1-20.
19. The method of claim 18, wherein the molar ratio of alkene, HE and DASCO is 1.5:2:2.5.
20. The method of any one of claims 1-19, wherein step b is carried out at 0-100 °C for 1-24 h.
21. The method of claim 20, wherein step b is carried out at room temperature for 24 h.
22. The method of any one of claims 1-21, wherein the blue LED has a wavelength of 400 - 500 nm.
23. The method of claim 22, wherein the blue LED has a wavelength of 400 - 450 nm.