Recognition of Thiols in Coupling Reactions to Organic and Carbohydrate Acceptors

Zbigniew J. Witczak and Roman Bielski

Abstract Reactions of thiols in thio-click coupling processes with various reactive systems (including carbohydrates) are compiled. A selection of simple and complex thiols in stereoselective and non-stereoselective approaches recognizing their reactivity is also reviewed. Solvents, employed in the discussed processes including water, are briefly discussed as well.

1 Introduction

The coupling reaction forming C–S, C–C, or C–N bonds usually requires an activation of the existing functional group. To control the steric outcome of the coupling reaction, the reactive functionalities forming the new asymmetric center should be easily accessible and kinetically favor the formation of only one stereoisomer.

The addition of thiols to conjugated or nonconjugated multiple bonds belongs to a few processes applicable to our coupling and decoupling (CAD) methodology [1]. The practical utility of our CAD methodology to many strategic targets is outstanding. The strategy can be easily adopted for many complex reactive systems provided that the activation step is strictly followed and the intermediate adducts will be actively involved and be compatible with a specific protocol of activation.

The click reactions involving the addition of thiols have been reviewed. Thiol-ene click chemistry, particularly applicable to polymer chemistry, was reviewed by Hoyle and Bowman [2]. The Bowman team [3] also reviewed the thio-Michael addition click reaction as another powerful tool in material chemistry.

Our laboratory reviewed [4] the synthesis of carbohydrate thiols as universal coupling agents applicable in our CAD [1] methodology. The synthetic procedures explored the versatility, stereochemical outcome of thio-click coupling reactions,

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Z.J. Witczak and R. Bielski (eds.), *Coupling and Decoupling of Diverse Molecular Units in Glycosciences*, https://doi.org/10.1007/978-3-319-65587-1_7

and synthetic aspects of thiols as universal starting materials. Additionally, the thiol activation under alkaline pH (8–9.5), polarity of the reaction solvent, and thiol/acceptor ratio were discussed.

Two other review articles [5, 6] explore the sensitivity and specificity of organic thiols recognition and detection in biological systems.

2 Thiol Recognition in Synthetic Approaches in Thio-Click Addition Reactions

The thiol recognition in biological systems is a primary factor of efficacy of many biologically important molecules containing –SH functionality. A rapidly developing area of synthetic organic and carbohydrate chemistry is exploring many specific tools for biological ligation of natural thiols and their peptide and protein systems.

It also utilizes a variety of other tools such as metalo-organic catalysts, effects of polar solvents, and enzymatic systems to form stereoselectively non-hydrolyzable C–S bonds. These sulfur bonds often are resistant to multiple enzymatic systems widely present in living organisms. Consequently, the sulfur-linked derivatives may escape any enzymatic intervention by scavenging the –SH group.

As already mentioned, Yoon and co-workers reviewed [6] fluorescent and colorimetric probes to detect three important thiols present in living organisms—cysteine, (Cys) homocysteine (Hcy), and glutathione (GSH). Their similar chemical character and structural composition derive from the presence of three reactive functional groups, –SH, –COOH, and $–NH_2$ capable of forming specifically labeled molecules.

All these three biomolecules (Fig. 1) equipped with the mercapto group play a crucial role in maintaining functionality of biological systems. Their low cellular levels are linked or implicated in many diseases. Therefore, the development of fluorescent and colorimetric probes for their detection is of utmost importance. Shiu and co-workers reported [7] a highly selective FRET-based fluorescent probe to detect cysteine (Cys) and homocysteine (Hcy).

Huo and co-workers reported [8] the chemistry of the functionalized chromene moiety as a “lock”, the thiol as a “key”, and a mercury (II) ion as a “hand”, a single

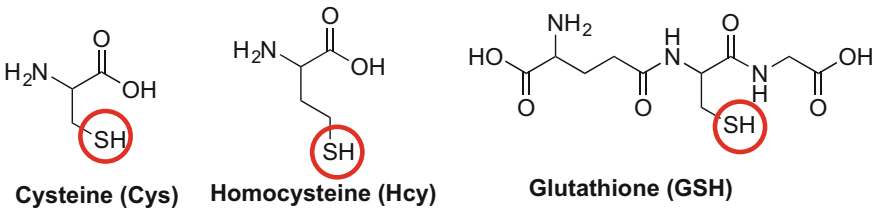
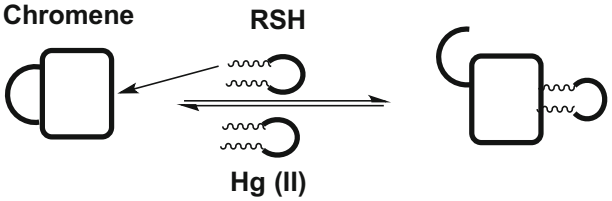


Fig. 1 Natural Thiols; Cysteine (Cys), Homocysteine (Hcy) and Glutathione (GSH)



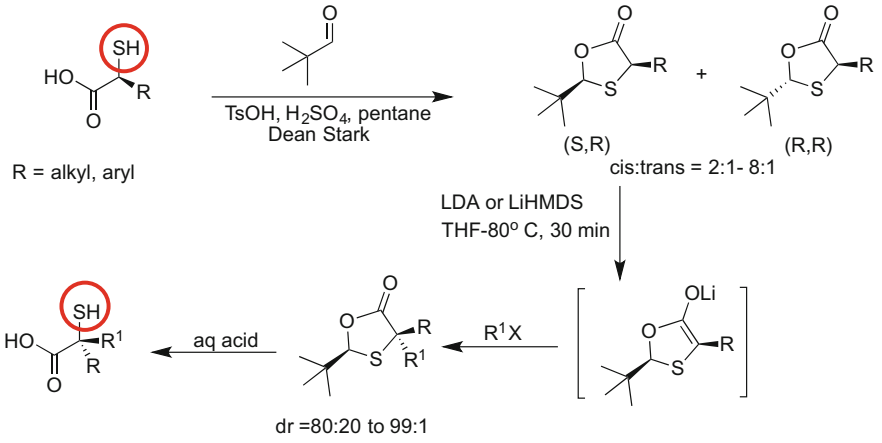
Scheme 1 A single molecular machine thiol recognition system

molecular automated recognition system. The simplified aspect of the thiols recognition mechanism is shown in Scheme 1.

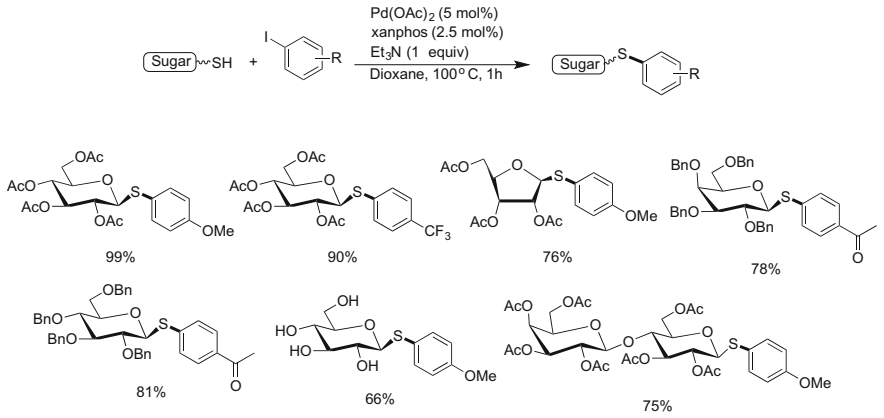
Clayden and MacLellan [9] reported the asymmetric synthesis of specifically designated tertiary thiols and their functionalized thioethers. Selected strategic coupling approaches are shown in Scheme 2.

Whereas tertiary thiols are important synthetic templates, their dominant reactive character must be recognized during coupling reactions, including thiol-yne. In the presence of metal catalysts, their reactivity increases and the reaction time is significantly shortened as, compared to catalyst-free methodologies [10]. Among many metal catalysts, the following primary catalysts were employed for construction of C–S bonds during synthesis of *S*-thioglycosides: nano indium oxide [11], iridium complex ($Ir(COD)_2BF_4$), [12], and palladium diacetate [$Pd(OAc)_2$] phosphine ligand system [13, 14]. The highly efficient palladium diacetate catalyzed synthesis of thioglycosides is depicted in Scheme 3.

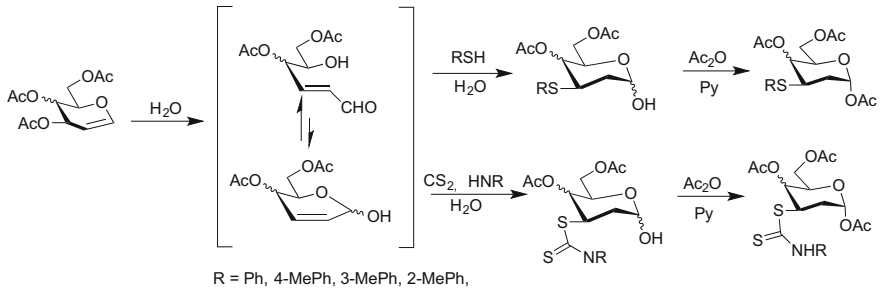
Misra and co-workers [15] reported a green chemistry approach toward synthesis of 3-thio-2-deoxy and 3-dithiocarbamate sugar derivatives. This efficient methodology uses no catalyst and is performed in water as a polar solvent. The products high yields and purities are impressive as compared to other methods. Examples are shown in Scheme 4.



Scheme 2 Asymmetric synthesis of tertiary thiols

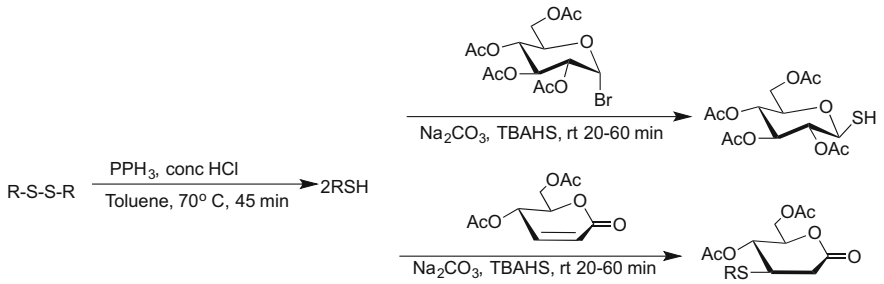


Scheme 3 Synthesis of thioglycosides catalyzed by $Pd(OAc)_2$/Xanphos system

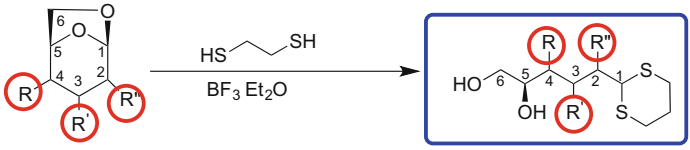


Scheme 4 Catalyst-free green chemistry synthetic approach to 3-thio-2-deoxy, and 3-dithiocarbamate sugar derivatives

Misra and co-workers [16] developed also an odorless methodology of preparing 1-thio-sugars and thio-Michael adducts of carbohydrate derivatives as intermediates for the advanced syntheses of thio-sugars. Selected synthetic routes to these intermediates are shown in Scheme 5.



Scheme 5 Synthesis of carbohydrate thiols and 3-Thio-Michael adducts



Scheme 6 Lewis acid-catalyzed Opening of 1,6-Anhydrosugars with 1,3-propanethiol

Krohn and co-workers [17] developed a successful methodology of Lewis acid-catalyzed opening of 1,6-anhydro sugars with 1,3-propanedithiol to produce open chain aldehydes protected as 1,3-dithianes. The methodology constitutes a simple route to the complex macrolide building blocks, which are difficult to synthesize. The primary example of this strategy is illustrated in Scheme 6.

Joshi and Anslyn [18] developed a novel approach to dynamic library of thiol exchange with β-sulfido-α,β-unsaturated carbonyl compounds.

The equilibrium between thiols and β-sulfido a,β-unsaturated carbonyls is observed within a few hours. These particular time scales make this system ideal for creation of dynamic combinatorial library.

The team cleverly utilizes the previously well-established thio addition to β-sulfido-conjugated system, as shown in Scheme 7.

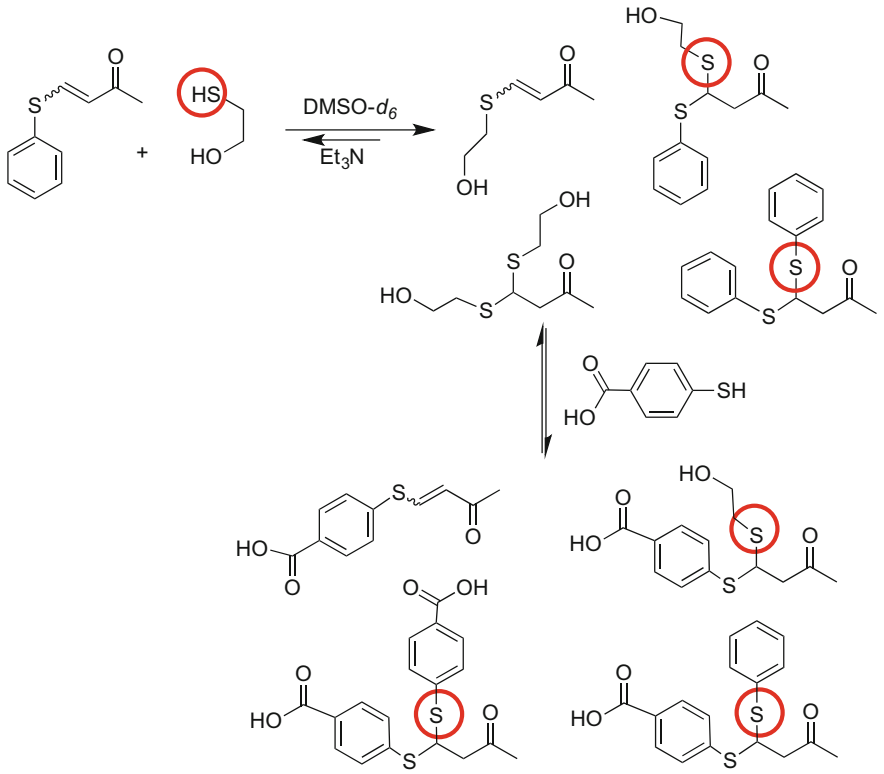
Anslyn and co-workers [19] also recently developed a unique thio-click coupling and decoupling approach, which utilizes a reversible amino and thiol coupling via a conjugate acceptor. Scheme 8 illustrates this elegant methodology.

Interestingly, Shi and Greaney [20] reported earlier (in 2005) a similar reversible Michael addition approach. The authors developed specific reaction conditions for subsequent decoupling. The synthetic approach is shown in Scheme 9.

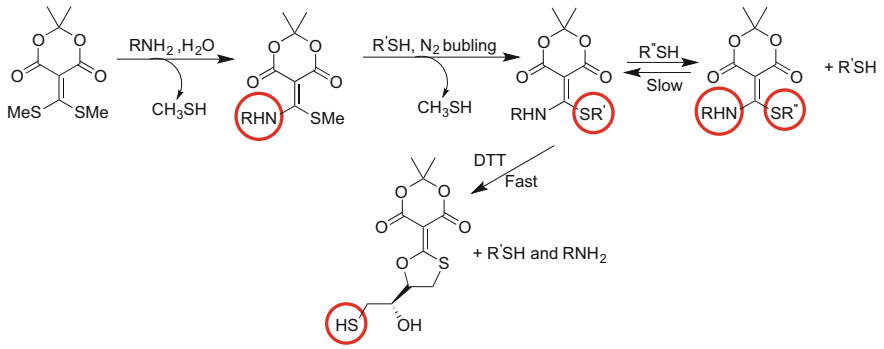
Among approaches used for the synthesis of macrolide thiols and disulfides, Otto and co-workers [21] constructed a dynamic combinatorial library. Dynamic libraries of macrocyclic disulfides form spontaneously upon stirring a mixture of three selected dithiols at pH 7–9 in an open flask. Oxygen from the air is sufficient to effectively oxidize thiols to disulfides. The simplified aspect of these thio functionalization reactions is shown in Scheme 10.

Rim and co-workers [22] discovered a 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) system for an ionic thiol-ene click reaction with the formation of functional tripodal thioethers. The authors continue to explore previously unknown chemistry of the TAT moiety and its potential biological importance and applications. According to the authors, thiol-ene reactions tolerate a wide range of functionalities including amino, hydroxyl, carboxylate, and trimethoxysilyl groups. Commercially available aliphatic and aromatic thiols efficiently reacted with TAT to produce thio adducts in high yields (63–96%) and high purity. Some of the aspects of thiol-ene click reactions are shown in Scheme 11.

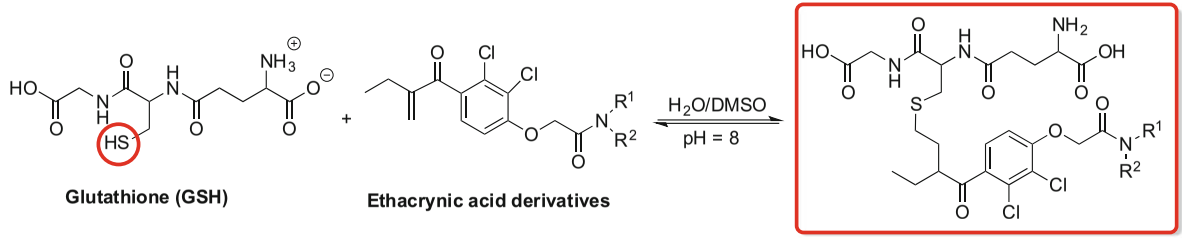
Gothelf and co-workers [23] developed a cleavable amino-thiol linker for reversible linking of amines to DNA. This discovery has a great practical potential for the exploration of various protection techniques of functionalized DNA derivatives. Some aspects of this new methodology are depicted in Scheme 12.



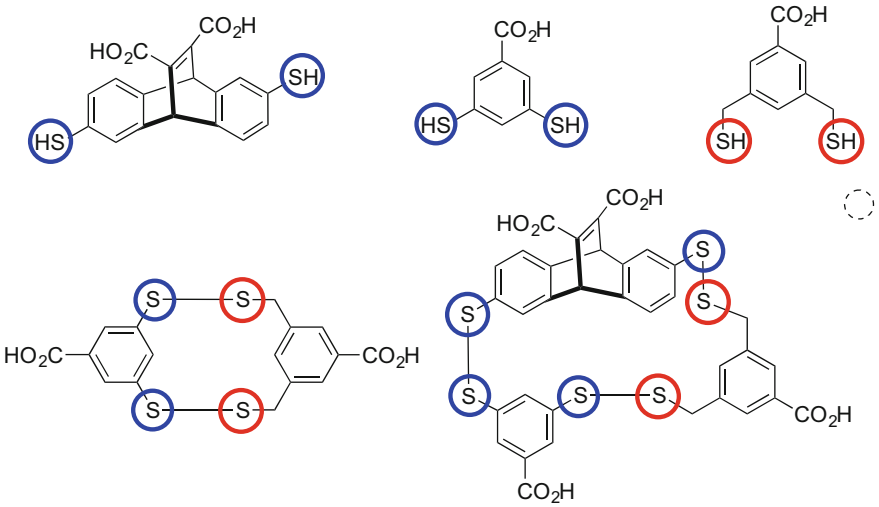
Scheme 7 Dynamic thiol exchange with β-sulfido-α,β-unsaturated carbonyl compounds



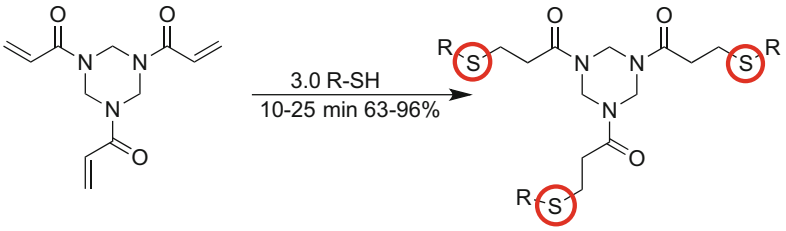
Scheme 8 Click and chemically triggered declick strategy by reversible amine and thiol coupling via a conjugate acceptor



Scheme 9 Reversible Thio-Michael addition of thiols to ethacrynic acid enone

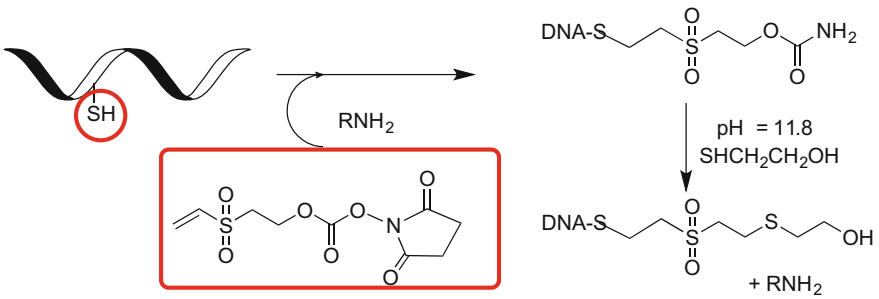


Scheme 10 Dynamic combinatorial library of macrocyclic disulfides

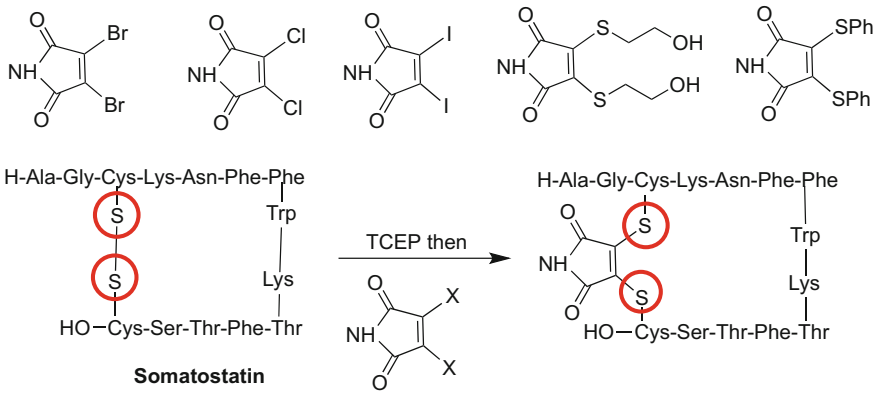


R = -CH_2CH_2OH, -$CH_2CH(OH)CH_2OH$, -$CH_2CO_2CH_3$, -$CH_2CH_2CH_2Si(OCH_3)_3$, -$CH_2CH_2NH_2$,-$CH_2CH_2CO_2H$, -$CH_2CH(NH_2)CO_2H$, -*o*-$C_6H_4NH_2$, -*o*-$C_6H_4CO_2H$

Scheme 11 Thiol-ene reactions of 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT)



Scheme 12 A cleavable amino-thiol linker for reversible linking of amines to DNA



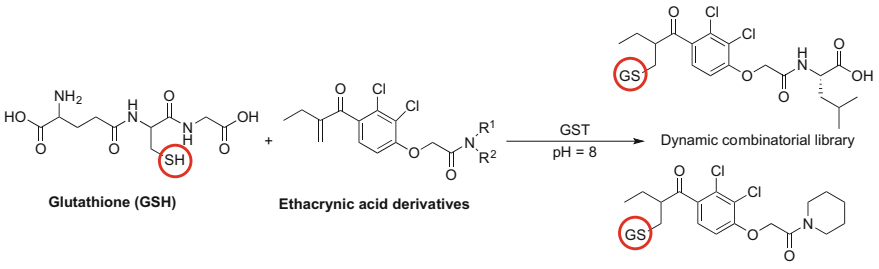
Scheme 13 Maleimides coupling with peptide disulfides

Schumacher and co-workers [24] created a new approach to the protein PEGylation utilizing maleimide bridging of disulfides. The highly reactive conjugate system of selected functionalized maleimides can be coupled with disulfides to form C–S functionalized derivatives as shown in Scheme 13.

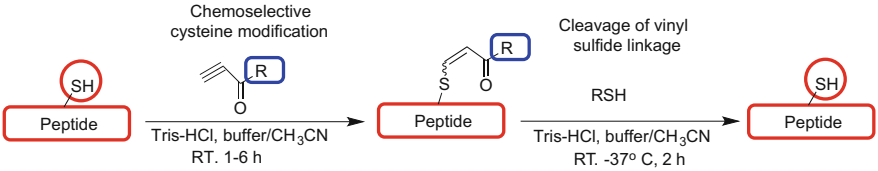
Campopiano and co-workers [25] discovered novel glutathione *S*-transferase (GST) inhibitors using a dynamic, combinatorial chemistry approach. The synthetic approach to this new class of inhibitors begins exploration of these fascinating and medicinally important molecules. Some of the examples are depicted in Scheme 14.

Shiu and co-workers [26] developed cleavable reagents to modify cysteine-containing peptides in an aqueous medium. Highly reactive alkynes were used as starting materials, as depicted in Scheme 15.

Finally, Dondoni and co-workers [27] highlighted a critically important approach in thio-click chemistry; thio-ene cluster formation, and thiol-yne click reaction [28, 29]. Dondoni [30] further developed a thiol-yne strategy applied to diagnostic aspects of serum albumin. Massi and Nani [31] reviewed previously reported methods of thiol-yne click chemistry, creating an up-to-date chronology.



Scheme 14 Glutathione S-transferase inhibitors synthesized via dynamic combinatorial chemistry



Scheme 15 Cleavable reagent for the modification of cysteine-containing peptides

3 Conclusion

The new strategical developments in the construction of protected diverse molecular targets of biological importance are growing steadily. Among the important areas, the glycoscience is one with particularly enormous growth. Other areas including biomolecular and macromolecular chemistry are developing as well. Among many strategic approaches, thiol directed functionalization and coupling reactions are of great importance and applicability.

When applied to thiols the CAD methodology will always utilize the convenience of four essential factors: the reacting system, catalysts, solvents, and thiol reactivity. We hope that the CAD strategy of creation of sacrificial unit will be further developed into conventionally applicable approach to many new targets of biological importance.

Additionally, other multiple approaches were developed for forming C–S bonds via methodologies utilizing thiol-ene and thiol-yne additions, providing the desired coupling C–S products in a highly stereoselective manner. Moreover, specific reaction conditions are compatible with the stability of the functionalized substrates and products, so yields of desired coupling products are not compromised. The demonstrated thiol-ene and thiol-yne sequences indicate the great potential of functionalized organic and carbohydrate thiols in the synthesis of highly functionalized biomimetic structure motifs by operationally simple protocols. It is worth adding that some of the discussed processes became competitive to the addition of thiols to conjugates multiple bonds such as the Michael addition. All of the new strategies currently available or under development constitute a significant milestone in the area of glycoscience. These new synthetic methodologies are of utmost importance and will be closely followed, as many new biological targets will constitute promising prospects for the future syntheses.

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