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REVIEW

Progress on Click Chemistry and Its Application in Chemical Sensors

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Abstract: In recent years, in the field of chemical sensors, the sensors with high selectivity, stability and repeatability are becoming increasingly urgent. Click chemistry provides a new efficient and convenient way for these researches, which have become a hot field. In this review, the concept and classification of click chemistry and the working mechanisms in chemical sensors and biosensors, as well as some recent developments were introduced in detail. The prospect of this application was also discussed.

Key Words: Click chemistry; Chemical sensors; Application; Review

1 Introduction

Click chemistry, which is also known as linking chemistry, matching and joint combinatorial chemistry or dynamic combinatorial chemistry, was defined by Nobel laureate Sharpless and associates in 2001, and the aim of which is to synthesize various products from readily available starting materials and reagents by simple and fast procedures[1,2]. Most reactions involve the formation of carbon-heteroatom (mostly N, O, and S) bonds. The process has characteristics including simple operation, mild reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, high production yield, high selectivity, and simple product isolation procedure. Click chemistry has aroused so much interest recently and emerged to be one of the most powerful tools in drug discovery, chemical biology, etc[3].

In situ click chemistry is the mostly commonly used click chemistry method in synthesis and other applications. During the synthesis, the reactants are usually formed in the solvent. No further purification and dryness are needed before the addition of another substance to initiate the click chemical reaction. The procedure is simple, with higher efficiency and yield. For example, *in situ* click chemistry could be used in the synthesis of natural product. Sharpless *et al*[4–7] used reactants which are inert under physiological conditions to synthesize high-affinity enzyme inhibitors using irreversible target oriented synthesis method. Inhibitors like tacrine and phenanthridinium were connected by the cycloaddition reactions between azide and alkynyl groups[4]. Acetyl cholinesterase (AChE) was used as the microvessel to control the reaction to make sure that the product could fit optimally the active center of the enzyme, ensuring not only high affinity but also specificity of the interaction (Fig.1).

Up to now, click chemistry has been broadly used in the areas such as surface functionalization[8–12], synthesis of functional polymers[13–18] and dendrimers[19,20], labeling of cells[21,22] and DNAs[23–27] etc. But there are still many issues to be solved.

As for the functionalization of materials, the surface of the materials could be easily modified by click chemistry to improve the performance. Fabre *et al*[28] employed click chemistry to covalently modify ferrocene-terminated monolayers onto Si–H substrate. The obtained material showed good stability and electron-transfer/retention ability. Holst *et al*[29] prepared a series of tetrahedrally linked conjugated microporous polymer networks using various bond-forming methods including Sonogashira-Hagihara coupling, Yamamoto coupling, thermal alkyne condensation, and click

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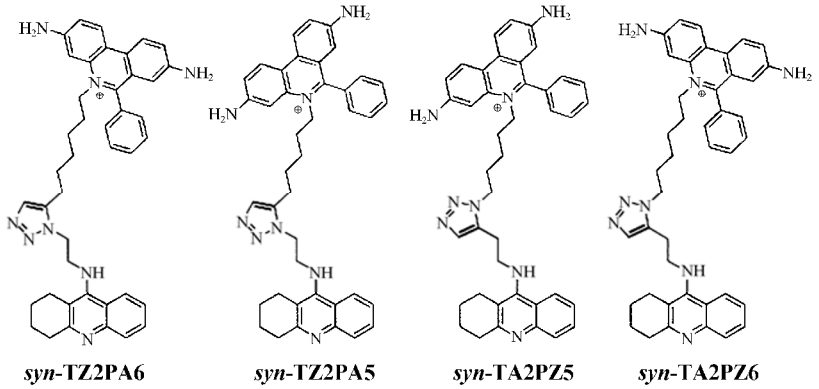

Fig.1 Four disubstituted 1,2,3-triazoles formed in situ, in the AChE molecule, from building blocks of the phenylphenanthridinium[4]

chemistry. The products had high surface area and good adsorbing ability towards H_2 and CO_2.

As in organic synthesis, according to the structure, shape, performance and other characteristics of the target substances, researchers have synthesized various kinds of products using click chemistry. Compared with traditional methods, click chemistry could not only simplify the procedure, but also improve the conditions and increase the yield of the reaction. Health *et al*[30] used click chemistry to synthesize a kind of antibody that could capture proteins. No information of agent affinity against the target protein was required prior to the synthesis of the capture agent. The *in situ* click synthesis rendered the antibody with a very large chemical space, and the process could be repeated. Camponovo *et al*[31] synthesized a new dendrimer from *tris*-alkynyl dendrons and azidomethylferrocene by click chemistry and investigated its electrochemical sensing for oxo-anions ($H_2PO_4^-$ and ATP^{2-}) and Pd^{2+} cation.

Click chemistry could also be used in bio-labeling for tracing biomolecules or even cells, which could be realized under relative moderate conditions. The signals could be enhanced during the process, and the background signals could also be reduced. For example, Kang *et al*[32] labeled cells by click chemistry and the results showed that compared with traditional methods, click chemistry could enhance the efficiency and reduce the interferences. Seo *et al*[33] labeled ssDNA with 6-carboxyfluorescein by click chemistry and then successfully used it as a primer to produce DNA sequencing products with single-base resolution in a capillary electrophoresis DNA sequencer with laser-induced fluorescence detection.

2 Classification of click chemistry

The advantages of click chemistry include modular design, high yield and reaction rate, as well as high stereo-selectivity, single product and wide applications. There are four kinds of click chemistry reactions, namely cycloaddition reaction, nucleophilic ring-opening reaction, non-aldol carbonylation reaction and carbon-carbon multiple bonds addition reaction.

2.1 Cycloaddition reaction

The mechanism of click chemistry could be fully reflected in the cycloaddition reaction, and the modular reaction procedure could combine two unsaturated compounds together, forming a five- or six-member heterocyclic ring. The functional groups are usually nonpolar (like in Diels-Alder reaction). At present, the 1,3-dipolar cycloaddition is the most common type, represented by the reaction between azide and terminal acetylene, which is called “the cream of the crop”. The reaction was firstly reported by Mechael in 1893[34], and studied in detail by Rolf Huisgen from 1960s to 1980s[35]. After that, Medal *et al*[36] and Sharpless *et al*[37] respectively reported that this kind of reactions could form 1,4-triazole specifically under the catalysis of Cu^+. The yield was as high as 91% and the reaction time could be reduced from 18 h to 8 h. The mechanism is shown in Fig.2.

2.2 Nucleophilic ring-opening reaction

Nucleophilic ring-opening reaction happens easily because the reaction could release the tensile energy of the three-membered heterocyclic ring. The possible reactants include epoxy derivatives, aziridines, cyclic sulfates, annular sulfamides, aziridine ions and sulfocarbenium ions, etc. Among these compounds, epoxy derivatives and aziridine ions are mostly often used as substrates in click chemistry. They could form products with highly stereo-selectivity in alcohol/water mixture, or without any solvents. Nucleophilic ring-opening reaction also includes the Michael addition of the α,β-unsaturated carbonyl compounds.

Taking the reaction between biepoxyethan and benzylamine as an example, Sharpless *et al*[1] reported the production of

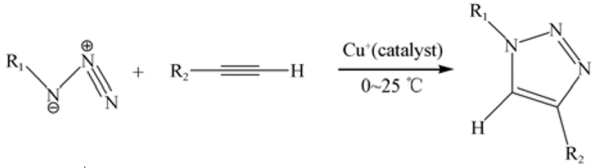

Fig.2 Cu^+-catalyzed terminal azide-alkyne coupling