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Towards click chemistry: Multicomponent reactions *via* combinations of name reactions

Majid M. Heravi*, Vahideh Zadsirjan, Mahzad Dehghani, Tahereh Ahmadi

Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran

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ABSTRACT

In this report, we try to show the importance of incorporation of name reactions in the sequential cascade reaction in which significantly decreasing the number of steps towards an ideal and practical multi-step synthesis of natural products as well showing virtually all the advantages already mentioned for "Click Chemistry". In addition, since the chiral inductions are desired for most of these sequential name reactions, their asymmetric catalyzed reactions were also described.

Contents

* Corresponding author.
E-mail addresses: mmheravi@alzahra.ac.ir, mmh1331@yahoo.com (M.M. Heravi).

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1. Introduction

The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole'.

Sir John Cornforth.[1,2]

Molecular diversity, modularity and efficiency are intrinsic in organic synthesis, and expected being involved in the synthesis of complex and multifunctional compounds. Generally speaking, "Click Chemistry" is the class of biocompatible reactions anticipated principally to link substrates of choice with specific biomolecules. Natural products are generated by joining small modular units *via* biosynthesis as well as photosynthesis. Thus, the first criteria required for "Click Chemistry" is well met by reactions occur in nature and their mimic in laboratory is the closest and most desirable to the brain and heart of most synthetic organic chemists. Two classic modern total synthesis are the quinine total synthesis[3–11] and total synthesis if Taxol.[12]

On the other hand "Click Chemistry" is a term that was initially devised by K. B. Sharpless in 1998 and fully described in 2001.[13,14] According to Sharpless et al. a click reactions should be proceeded to completion in one-pot reaction fashion, they are high yielding, wide in scope, generate minimal offensive by-products that can be easily eliminated. Where appropriate, they are stereo and region-selective and specific, simple to conduct in conventional safe organic solvents, less toxic solvents or even better done in either water or under solvent-free conditions thus, meaningfully more benign from environmental point of view They are "spring-loaded"-characterized by a high thermodynamic driving force resulting in a single reaction product in high yield and with high reaction specificity. These salient features represent a part of the field of chemical biology. Thus, click chemistry is expected to plays a key role in the total synthesis of natural products.[13] Huisegn 1,3-dipolar azide/alkyne cycloaddtion reaction[15] was a precious phenomenon which the broad scope and molecular diversity of this reaction was first realized and reported by German chemist, Rolf Huisgen in 1961. Generally speaking, Huisegn 1, 3-dipolar cycloaddition is a reaction between an azide and a terminal or internal alkyne, resulting in 1, 2, 3-triazoles.[16]

It was particularly stirred up the courtesy of the American chemist K. Barry Sharpless (Nobel prize laureate in chemistry, 2001) who referred, to this 1,3-dipolar cycloaddition as "*the cream of the crop*" of "Click Chemistry".[17] Although, several reactions may show such perfection as far as synthetic organic chemistry concerns nowadays, the Cu(I)-catalyzed Huisgen cycloaddtion reaction is recognized as one of the best transformations out of the complete collection of those reactions which are in agreement with the "Click Chemistry" criteria.[18,19]

1,2,3-Traizoles are biologically important class of compounds[20,21] and are present as framework in several natural products.[22] Thus, triazoles as a safe and mild connecting framework can be assembled in several circumstances during total synthesis of natural products *via* "Click Reaction". In addition, the extremely stable and aromatic nature of the triazole ring with large dipole moment along with hydrogen bonding aptitude, make it a moiety of great impending usefulness. Above all, the term "Click Chemistry" may has been influenced and coined by the giant organic chemist of 20th Century, K. Barry. Sharpless.[17,23,24]

There are several important name reactions in organic chemistry. Among the tens of thousands of organic reactions that are known, hundreds of such reactions have reached such status to be named after its discoverers or developer. Well-known examples include the Grignard reaction, the Sabatier reaction, the Wittig reaction, the Claisen condensation, the Friedel-Crafts acylation, and the Diels-Alder reaction. Some cases of reactions that were not actually discovered by their names discovers are also known. Examples include the Pummerer rearrangement,[25] the Pinnick oxidation[26] and the Birch reduction.[27]

Shall we contemplate that the click chemistry is not attributed to a single specific reaction, but defines a route of forming molecules that follows the biosynthesis of naturally occurring compounds. In nature, substances are generated by joining small modular units. Nowadays, Click Chemistry" is not considered being limited to biological conditions.

One of the most challenging aspects of designing a route to total synthesis is devising sequences of reactions that will lead from a designated starting materials to a desired target. Generally speaking, an ideal design of synthetic pathway for any total synthesis is the one which lead to the desired target with lowest possible steps. This route then should be studied from different points of view and being found reasonable and operational. Thus, the designers should try to decrease the number of steps as many as possible. One of the most appropriate ways to make a total synthesis more concise is combining steps together. To do so, it is absolutely essential to become comfortable with each step, considering the sequential steps, and examine the possible combination of two or more steps together. On the other hand, the status of organic synthesis is hindered by costly and time-consuming protection-deprotection protocol.[28]

Each protection and deprotection steps also need purification procedures in a multistep synthesis. To avoid these draw backs, the synthetic potential of multicomponent, cascade, cascade and domino reactions should be considered in designing an ideal route for the total synthesis of natural products as well as efficient and stereoselective construction of complex molecules from simple precursors in a single process. In particular, domino reactions mediated by organocatalysts are in a way biomimetic[29,30] as this principle is used very efficiently in the biosynthesis of complex natural products starting from simple precursors.

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more commercially available or readily accessible starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. "MCRs convert more than two molecules straightly to the expected products". Remarkably, a name reaction is a chemical reaction, which has reached to such status from different points of view, being named after its discoverers or developers. Among the tens of thousands of organic reactions that are known, hundreds of such reactions are well-known enough to be named after people.

As organic chemistry developed during the 20th century, chemists started associating synthetically useful reactions with the names of the discoverers or developers; in many cases, the name is merely a mnemonic.

Since MCRs are one-pot reactions, expectedly, they can be conducted much easier than multistep reactions. Combined, with high-throughput library screening, this protocol can be considered as an important development in the rational drug design in the terms of rapid and unambiguous identification and optimization of biologically active lead compounds. Libraries of small-molecule organic compounds are perhaps the most desired class of potential drug candidates, because standard peptides and oligonucleotides have limitations as bioavailable therapeutics. In the last decade, with the introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and