

Halogen-Mediated Electrophilic Cyclization Reactions

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Medicines have been an integral part of human life, whether they are traditional remedies or modern drugs. The search for newer and more efficient drugs has led researchers to transit from classical phenotypic drug discovery to target-based drug discovery. Phenotypic drug discovery involves the identification of active ingredients from traditional medicines, followed by screening of natural products or chemical libraries of small molecules in cells or animals to identify substances that have an anticipated medicinal properties [1]. In target-based drug discovery, isolated biological targets, which are hypothesized to cause a disease, are first identified. High-throughput screening of several small molecule libraries are subsequently performed on these selected targets [1]. Target-based drug discovery has become more widely used since the sequencing of the human genome, which has allowed scientists to clone and synthesize large quantities of purified proteins.

Reverse pharmacology or target-based drug discovery has created a need for an efficient synthetic process that can generate a library of small molecules, particularly heterocycles containing diverse chemical functionalities and structures. More than 80% of the top drugs produced by US retailers contain at least one heterocyclic unit. Heterocycles can improve pharmacological, toxicological and physicochemical properties of a drug candidate by altering its lipophilicity, polarity, solubility and hydrogen bonding capability [2].

Among known synthetic methodologies transition-metal-catalyzed annulation reactions are a direct way of synthesizing substituted heterocycles from acyclic precursors. However, the use of expensive transition metals and harsher reaction conditions, and intolerance to several functionalities limits the scope of these methodologies. In past decade there has been an impressive increase in the reports of heterocyclic synthesis, involving cyclization of an alkyne onto a tethered nucleophilic carbon or heteroatom with the help of an electrophile [3]. Cyclization involving C, O, N, S and Se nucleophiles are well studied, while a few examples involving P are also known. The most commonly used electrophiles for these cyclization reactions are I₂, ICl, IPyBF₄, Br₂, NBS, and PhSeBr [3]. However, reports of chlorocyclizations are rare [4,5]. These cyclization reactions are effected by nucleophilicity, polarizability of the C-C triple bond, geometrical orientation of the functional groups, and the nature of the electrophile. Depending on the chain length and substitution pattern, heterocyclic ring systems can be formed through *endo*-dig or *exo*-dig cyclization (Figure 1).

Heterocycles constructed by electrophilic cyclization have the advantage of undergoing further transformations due to the presence of a halogen moiety, in particular iodine and bromine, leading to diversification of the drug candidates. Heterocyclic rings structures having a halogen moiety allow late stage modifications via metal-catalyzed

cross-coupling reactions, such as Suzuki, Sonogashira, Heck, Negishi, Kumada, Hiyama, Fukuyama, Stille and Buchwald-Hartwig reactions.

Several heterocyclic ring systems, such as thiophene, furan, pyrrole, indole, benzo[*b*]furan, benzo[*b*]thiophene, benzo[*b*]selenophene, indolizine, furo[2,3-*d*]pyrimidin-2(3*H*)-one, azaspiro[4.5]trienones and alkylidene furanones, have been constructed via 5-*endo* and 5-*exo*-dig cyclizations (Figure 2) [3]. 6-*endo*-dig cyclization reactions have also been employed for the synthesis of various heterocyclic core structures. Synthesis of heterocycles, such as 2*H*-chromene, 2*H*-thiochromene, 1,2-dihydroquinoline, quinoline, isochromene, 4*H*-chromen-4-one, quinolin-4(1*H*)-one, 4*H*-thiochromen-4-one, 1*H*-2,1-benzoxaphosphinine-1-oxide, and isoquinoline, have recently been reported via 6-*exo*-dig cyclization (Figure 3) [3]. The resulting functionalized heterocycles have been shown to undergo useful subsequent transformations to give highly substituted heterocycles [6,7]. Along with iodine and bromine, organoselenium and organotellurium compounds have also been proved as effective electrophiles [3].

Starting alkyne precursors required for these reactions are either commercially available or easy to synthesize. These methodologies tolerate a wide variety of functionality, thereby avoiding the need of protection group chemistry. Electrophilic cyclization not only proceeds regioselectively, but also requires relatively mild reaction conditions. In fact, these cyclization reactions have transformed heterocyclic

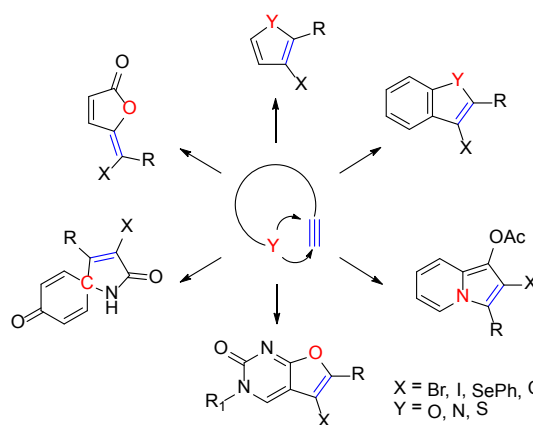


Figure 2: Examples of heterocycles formed via 5-*endo*- and 5-*exo*-dig cyclizations.

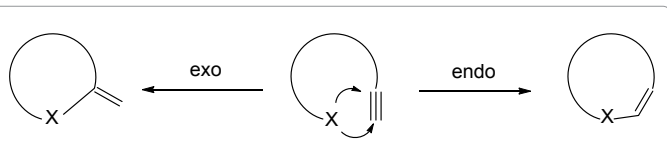


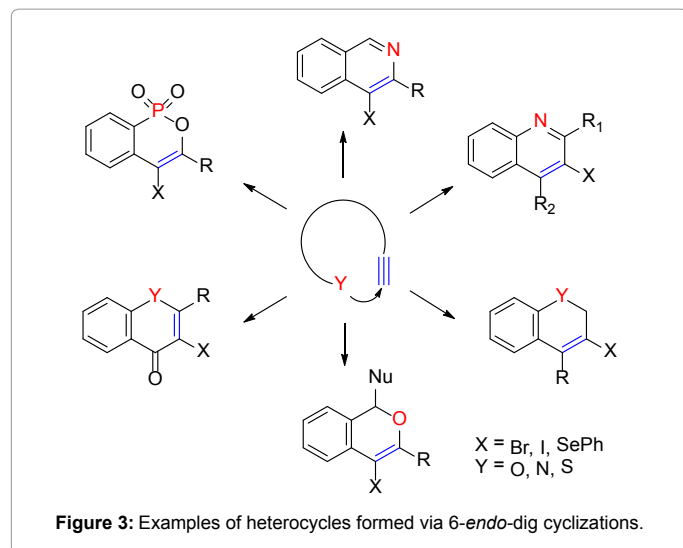
Figure 1: *endo*- and *exo*-dig mode in electrophilic cyclization reactions.

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Received May 15, 2013; Accepted June 14, 2013; Published June 18, 2013

Citation: Kesharwani T (2013) Halogen-Mediated Electrophilic Cyclization Reactions. Organic Chem Curr Res 2: e122. doi:10.4172/2161-0401.1000e122

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chemistry into an exciting field with many opportunities for target-based drug development.

There is definitely a need to unearth many more systems, which can undergo electrophilic cyclization. In the next few years, we anticipate to see many new exciting findings. We also hope to see more work in the area of finding better electrophiles for chloro- and fluorocyclization. Fluorocyclization could be an interesting way to introduce fluorine in heterocycles. Fluoride is very useful in pharmaceuticals, since steric demand of active site of an enzyme does not change when hydrogen is replaced with fluorine in a drug candidate. In addition, fluorine can

alter adsorption, metabolism, distribution, and excretion properties of a drug candidate. In the future, newer studies on toxicological and pharmacological aspects of heterocycles would be an area of interest. We hope that "Organic Chemistry: Current Research" will motivate more chemists to pursue innovative methods for heterocyclic synthesis. This journal is open access, which allows universal access of novel scientific findings to all, regardless of their affiliation, and gives authors opportunities to be more acknowledged; therefore we encourage the scientific community to publish their high quality work to this journal.

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