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Review Article

A mini review: recent developments of heterocyclic chemistry in some drug discovery scaffolds synthesis

Ritu Sapra*, Dhara Patel, Dhananjay Meshram

Department of Pharmaceutical Chemistry and Quality Assurance, Pioneer Pharmacy Degree College, Vadodara, India

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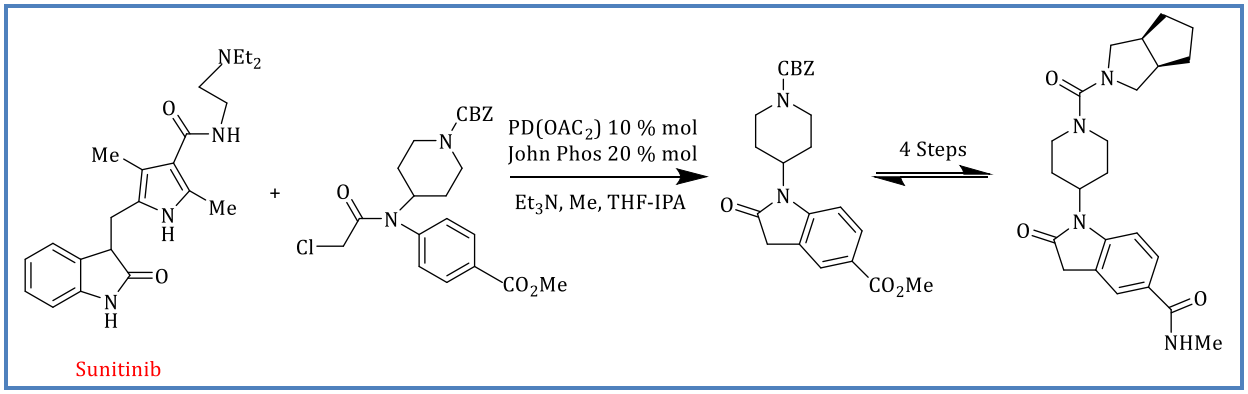
ABSTRACT

Novel developments in the synthetic techniques that facilitate rapid access to various functionalized heterocyclic compounds are essential in medicinal chemistry. They enable an expansion of the available drug-associated chemical space and enhance the efficiency of drug delivery. In addition, the creation of more robust synthetic techniques that can increase the drug yield can enhance the drug production rate. While researchers and manufacturers utilize established synthetic techniques during a program aimed at drug discovery, the innovation of heterocyclic synthesis processes that permit varied bond formation strategies is influencing the pharmaceutical industry in the most significant way. This review focuses on the utilization of some novel methods of activation of the C-H bonds, hydrogen borrowing catalysis, photoredox chemistry, regio- and stereo-selective synthesis, and multi component reactions for the functionalization and creation of heterocycles that aided in driving project delivery.

Graphical Abstract



Corresponding author, email: ritu.mehndi@gmail.com (R. Sapra).
Tel.: 9657671482

Introduction

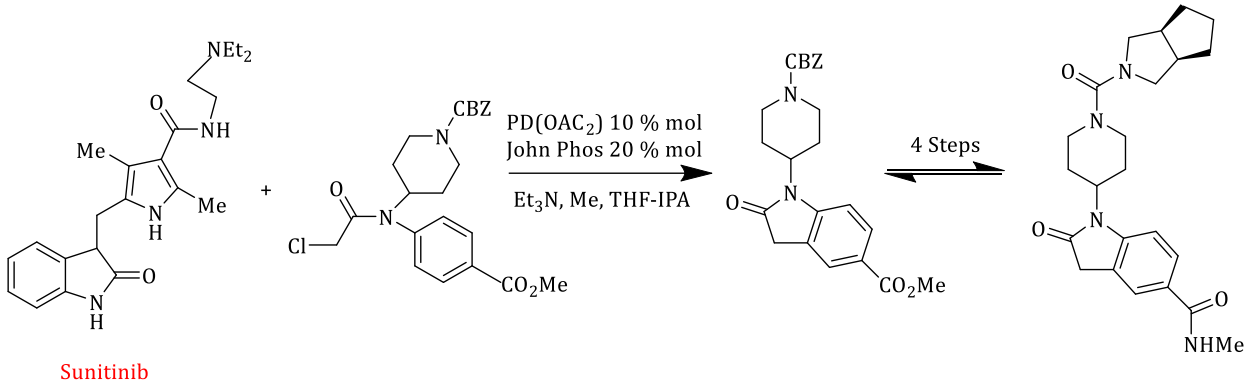
Functionalized heterocyclic compounds are critical in drug discovery. Even though research focused on synthesis and functionalization of the heterocyclic compounds, it remains quite necessary to further advance in these tasks. The medicinal chemistry requires a novel set of heterocycles and the substitution patterns that can meet strict physicochemical needs to generate new vectors in the structure-based designing of drugs and it can access the new intellectual properties. From responding to a biological hypothesis to the preparation of an Active Pharmaceutical Ingredient (API) for clinical trials, several opportunities emerge for new technique development in the heterocycle chemistry [1]. Firstly, the opportunities emerge for the stereo-, regio- and chemo-selective production of new heterocycles to enhance the flexibility of the substitution patterns and the substituents. Secondly, opportunities emerge for regio-, chemo-, and stereo-selective functionalization of the already developed heterocycles to facilitate the flexibility of the substitution patterns and the substituents [1]. Thirdly, opportunities can emerge for the reaction conditions optimization for the functionalization and the manufacture of the heterocycles to facilitate the enhancement of tolerance of the different functional groups of aiding the late-stage modification of the multifaceted intermediates. The development in heterocycle chemistry will also streamline the synthesis processes by eliminating the steps or merging the steps into the one-pot procedures. Fourthly, the heterocycle chemical processes also aid in the removal of the toxic and costly reagents, vigorous reaction conditions, and the tedious product separations [1].

Heterocyclic synthesis of Drug Discovery Scaffolds

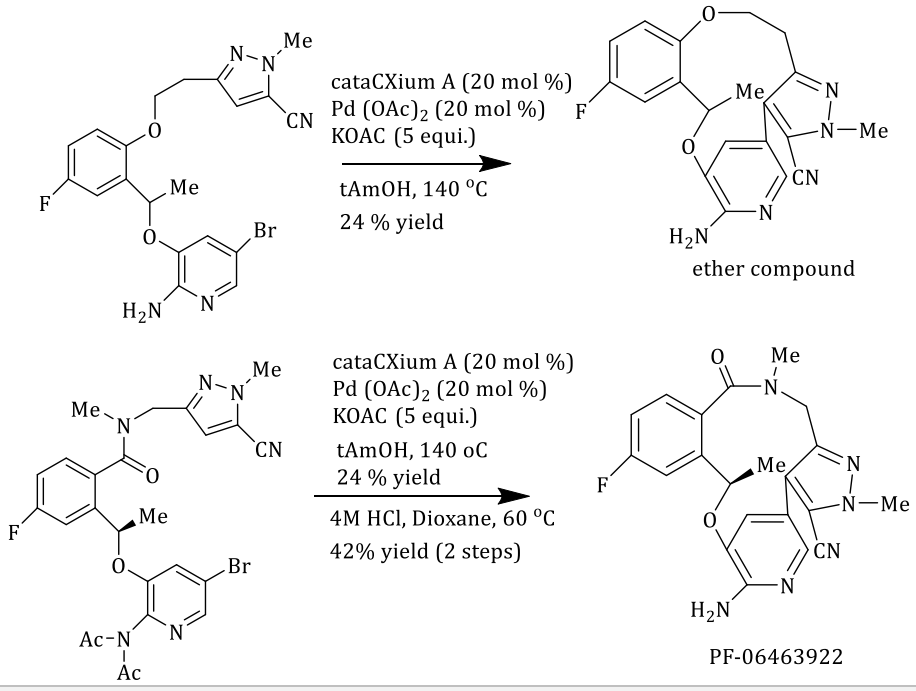
Via C–H functionalization:

During the process of devising the suitable techniques for the heterocycle formation, the C-H bond functionalization aids in new retrosynthetic disconnection. The transition metal-catalyzed activation of the C-H bonds developed as a relevant methodology for the formation of heterocycles [2]. Oxindoles (indolin-2-ones) are famous scaffolds in the discovery of drugs [3]. Oxindole derivative is a serine palmitoyl transferase inhibitor. It is a potential clinical candidate for large-scale synthesis [4]. The most suitable route for producing it on a large scale is one that employs the palladium-catalyzed C–H activation and cyclization of the *α*-chloroacetanilide [5].

Scheme 1 shows the activation of C-H bonds (Sunitinib) using the palladium-catalyzed process to generate oxindoles. Scheme 2 also shows the process of formation of the ether and clinical compound PF-06463922 through C-H bond activation through the intramolecular palladium-catalyzed pyrazole arylation [6–8]. Some traditional methods such as intramolecular S_N2 etherification, intramolecular amide bond formation, and intramolecular Suzuki coupling can also form the same product bonds. The manufacture of drug moieties relies on the alteration of the *functional groups* such as the C-N and the C-C bond creation through a *metal-catalyzed cross coupling* reaction and the aryl halides and the boronic acid moieties. C-H functionalization is a method that is altering the standard model concerning the synthesis of the pharmaceutically suitable agents. This process depends on the selective modification of the C-H bonds of the organic molecules.

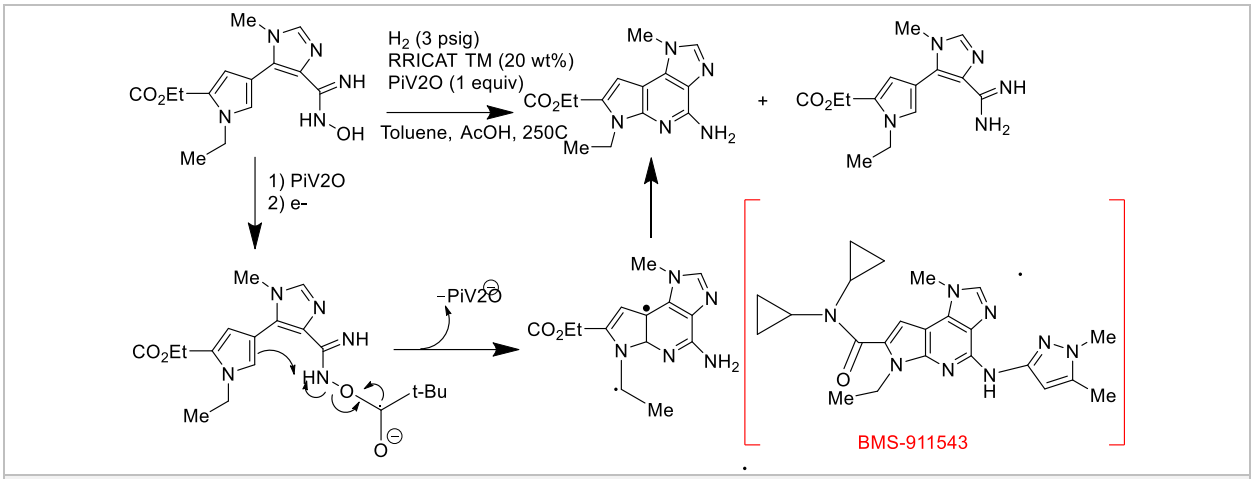


Scheme1: Synthesis of oxindoles using palladium catalysed C-H activation (Sunitinib)



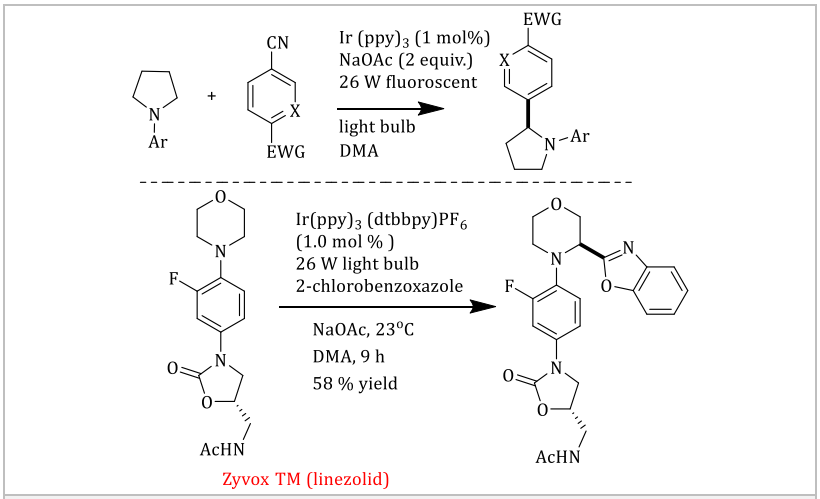
Scheme 2: Synthesis of macrocyclic heterocycles using palladium catalyzed C-H activation to access ACK inhibitor

Researchers can also achieve a low reaction rate through unselective activation of the C-H bonds at the C_4 and C_2 positions, which generates the mixtures of regio-isomeric 2, 7-naphthyridin-1(2H)-one and 1, 6-naphthyridin-5(6H)-one products [9, 10]. This concerns the initial actions to extend the techniques of annulation of the derivatives of nicotinamide, which ended up suffering low reaction rate. Alternatively, as evidenced by the process in scheme 3, a nickel-catalyzed C-H functionalization can be a crucial phase in a small, convergent scale-up means to the *BMS-911543*, which is a strong inhibitor of the Janus kinase 2 (JAK_2) [11]. The Hoffman–Löffler–Freytag (HLF) reaction, which is one of the effective techniques of the C-H functionalization, the authors employed this technique during the production of diazatricyclodecane agonists of the G-protein receptor 119 (GPCR119) [12].



Scheme 3: Synthesis of BMS-911545 using a key nickel catalysed C-H functionalization

It is always imperative in drug discovery to create efficient, convenient, rapid, and environmentally benevolent synthetic techniques for the functionalization and manufacture of heterocycles. Visible light photoredox catalysis is one of the most suitable approaches utilized today [13]. Following the photo excitation with visible light, metal complexes and the organic dyes tend to engage in single-electron transfer (SET) process entailing carbon-based molecules to attain the chemical transformation processes [14]. Scheme 4 portrays photoredox catalyzed amine C–H arylation reaction in the construction of α-aryl amines[15].

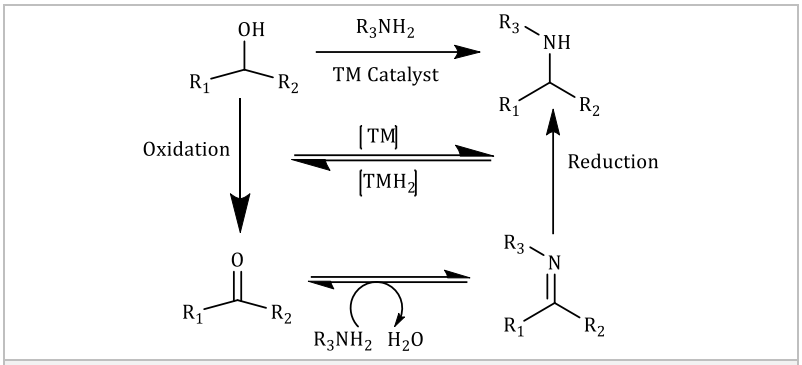


Scheme 4: Photoredox α-arylation of amines

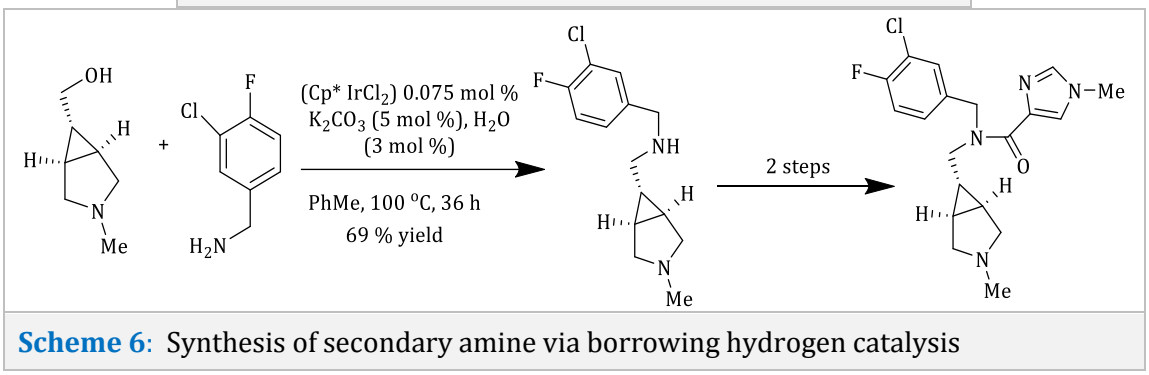
Via Hydrogen transfer Catalysis

Hydrogen auto transfer reactions involve the aid of a catalyst to enable the relocation of a hydride from the raw material to a product as defined in scheme 5 [16]. This process can involve the oxidation of alcohol through a mechanistic procedure to generate a corresponding carbonyl compound via a metal-catalyzed withdrawal of hydrogen. Atom economy is one of the benefits of the hydrogen auto-transfer system alongside other benefits such as minimal generation of waste and the net redox-neutral nature of the reaction. A

significant example of its utility in the production system is the kilogram manufacture of *PF-03463275* which is a Pfizer GlyT1inhibitor indicated by scheme 6 [16].



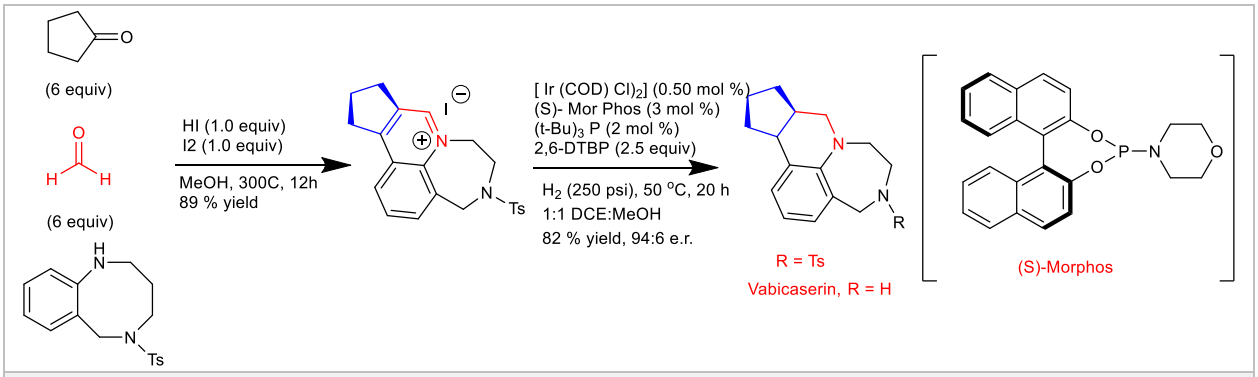
Scheme 5: Mechanism of borrowing hydrogen catalysis to generate amines



Scheme 6: Synthesis of secondary amine via borrowing hydrogen catalysis

Via multicomponent coupling

These reactions entail convergent reactions comprising of at least three components. These reactions allow the generation of complex compounds from simple raw materials in one-step. Scheme 7 always portrays a multicomponent coupling process for the synthesis of vabicaserin [17–20]. The synthesis of azoindole is also a multicomponent reaction that involves simple ketones and the haloaminpyridines.

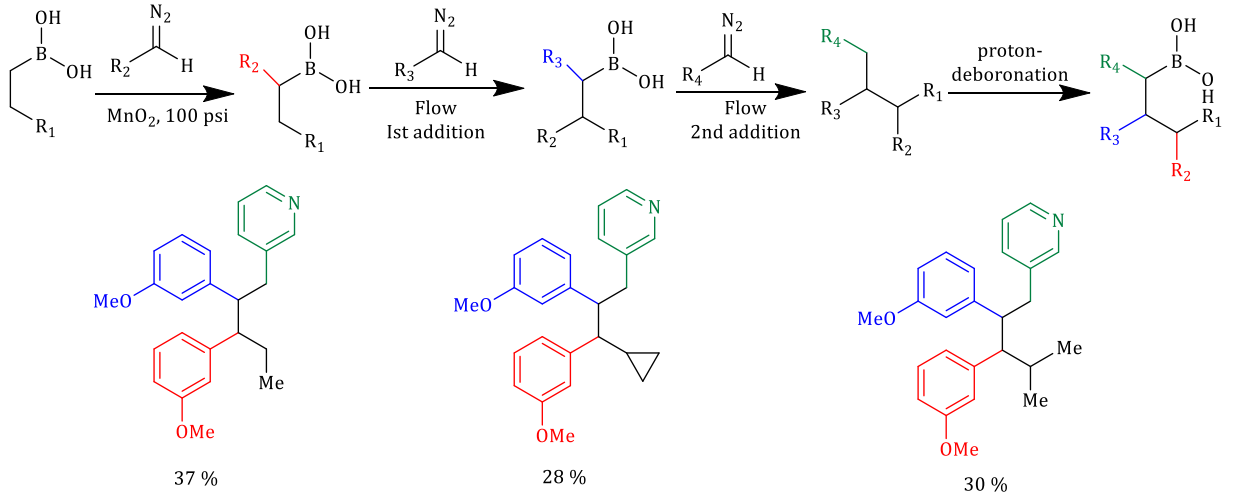


Scheme 7: Multicomponent coupling for the synthesis of vabicaserin

via C-C bond formation

Drugs-discovery necessitates the controlled access to the cores that display different patterns of substitution. In most occasions, the

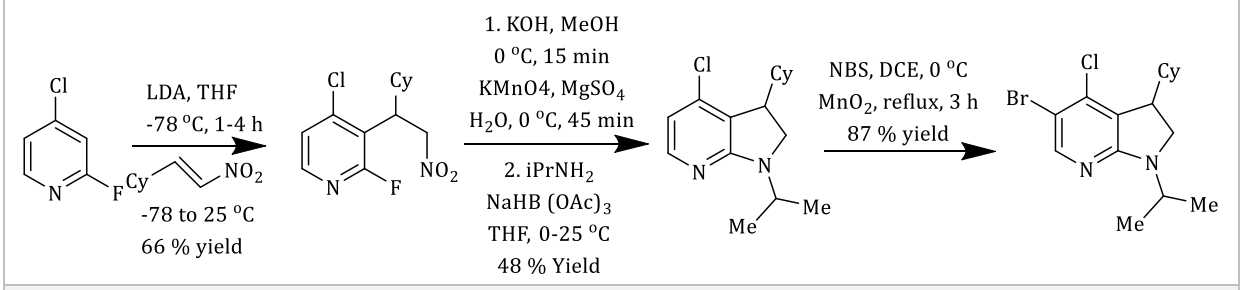
heterocycle core tends to be accessible though there is no suitable technique through which medical researchers can access the derivatives with substituents in different segments. Medical researchers, therefore, are seeking new methods through which they can elaborate the available cores. As evidenced in scheme 8, the boronic acids tend to undergo a controlled iterative C-C bond formation process up to about three bonds in a sequence that includes final proto deboronation [21, 22].



Scheme 8: Iterative strategy for the sequential addition of three diazo species via flow chemistry

Miscellaneous

In therapeutic chemistry, researchers and manufacturers use the aza-variants of the common heterocycles to decrease lipophilicity, improve metabolic stability, and other physicochemical properties. These templates, however, require novel methodologies for their formation. Scheme 9 exemplified the process of formation of the 7-azaindoles using the 2-fluoropyridines. This technique involves the conjugate addition of the 2-fluoro-3-lithiopyridine into nitro-olefin followed by a subsequent Nef reaction, cyclization, reductive amination, and oxidation [23].

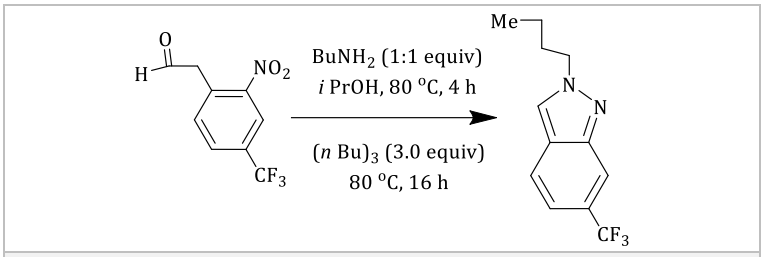


Scheme 9: Synthesis of 7-azaindoles from 2-fluoropyridines

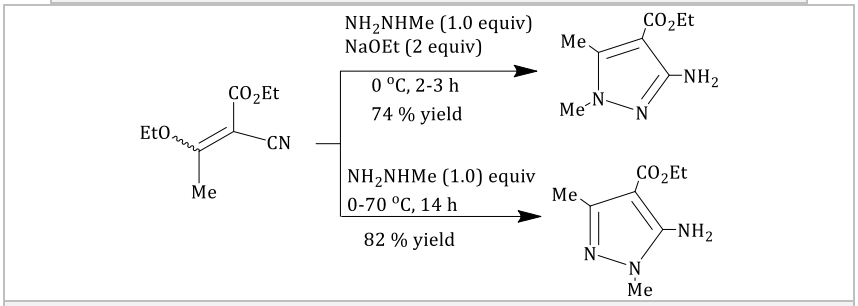
Regio-selectivity in Heterocyclic synthesis of Drug Discovery Scaffolds

In the previous years of drug innovation, the reactions that had no regio- and enantio-selectivity had advantages of generating at least two compounds for profiling. As a result, they helped to explore the structure-activity relationships (SAR) more efficiently [1]. However, after establishing the required configuration and reaching a point at which scaling up the production of the compound becomes necessary, the ability to manage the

regio- and enantio-selectivity can enhance the programs by saving time and money through efficient purification and limiting the waste of raw materials. Scheme 10 and 11 show the regio-selective production of 2H-indazoles [24], 3- and 5-aminopyrazoles [25] (using azomethine ylide chemistry) respectively.



Scheme 10: Regio selective synthesis of 2H-indazoles



Scheme 11: Regio selective synthesis of 3- and 5-aminopyroazoles

Conclusion

The synthetic creativity in the heterocycle preparation systems provides suitable opportunities to explore new drug-pertinent chemical scope. It is possible to enhance the diversity of the molecules that medical researchers in paralleled medicinal chemistry can prepare through robust heterocycle syntheses and functionalizations. This can also enhance the design-synthesis-screen sequence times in the pre-clinical research and the productivity of drug discovery. This study focused on the worth of academic-industrial collaboration during the development of new synthetic methodologies about the medicinally suitable heterocycles. In addition, the advancements in small chemistry that occur before the preparation of 1, 2, 3-triazoles to discover diverse heterocyclic scaffolds will discover significant value by refining the chemical- medicinal chemistry toolkit.

Disclosure statement

No potential conflict of interest was reported by the authors.

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