Exploration of Diaryliodonium Salts for *N*- and *S*-Arylations of Biologically Significant Heterocyclic Scaffolds

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Chapter 6

Conclusion & Future Scope

6.1 General Conclusion

6.1.1 Concluding remarks on each chapter

Overall, diaryliodonium salts, versatile aryl-transferring reagent are utilized in this thesis to accomplish arylations of heteroatoms of some synthetically and biologically useful heterocycles. The utility and scope of this reagent on arylation reactions are remarkable and many research groups have been working on this reagent in search of arylation reactions under metal-free, transition-metal catalyzed, and photoredox conditions. The thesis is divided into six chapters: Introduction (chapter 1), four experimental works (chapters 2-5) and conclusion (chapter 6). The significant outcomes of each chapter are highlighted below:

Chapter 1:

i. Different synthetic routes and their reactivity of the diaryliodonium salts are discussed,
ii. The scopes and limitations symmetrical and unsymmetrical iodonium salts are underlined,
iii. Applications of diaryliodonium salts with various nucleophiles (N, O, and S) are addressed.

Chapter 2:

i. Regioselective N^2-arylation of 1*H*-tetrazoles under metal-free conditions is described,
ii. 41 examples of N^2-arylated tetrazoles in moderate to good yields (56-88%) are demonstrated,
iii. 8 examples of 2,5-diaryl-tetrazoles are synthesized under one-pot multi-component reactions,
iv. The methodology is applicable towards bio-active 1*H*-tetrazoles, e.g., Valsartan.

Chapter 3:

i. *S*-arylation of N^1-substituted-5-mercaptotetrazole are explored with unsymmetrical diaryliodonium salt, aryl(TMP)iodonium trifluoroacetate,
ii. Broad scope of aryl moieties from TMP-iodonium salts is discussed,
iii. The methodology with aryl(TMP)iodonium salts is applicable to other mercaptoazoles except 2-mercaptopyridine,
iv. *S*-arylation of 2-mercaptopyridine has been accomplished.

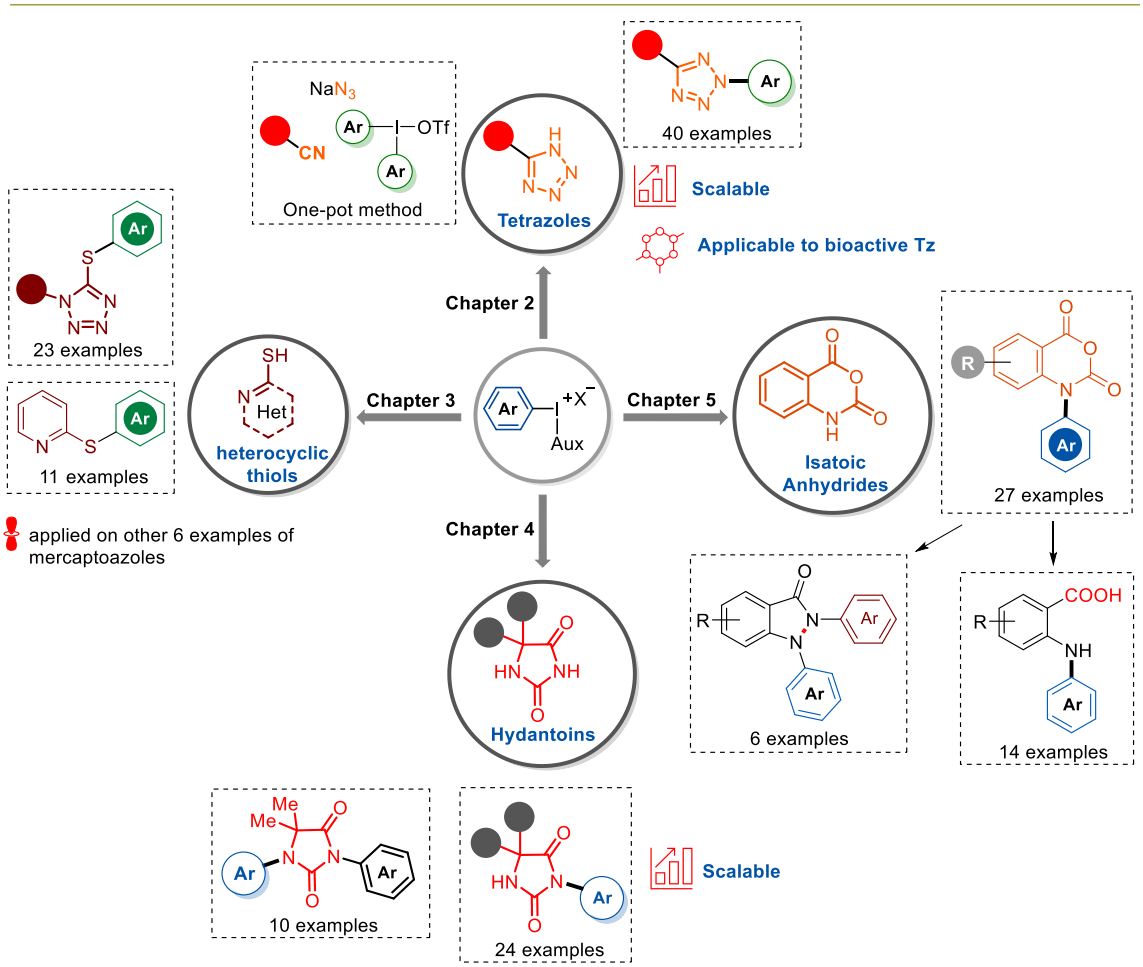


Figure 6.1 Summary of performed experimental works with diaryliodonium salts

<u>Chapter 4</u>:

i. Copper-catalyzed version of N^3-arylation of hydantoin moiety is disclosed,
ii. The protocol is highly regioselective and scope of diverse hydantoins are discussed,
iii. Wide range of functionalized aryl moieties are explored,
iv. The same methodology is further implemented successfully on N^1-arylation of N^3-arylated hydantoins.

<u>Chapter 5</u>:

i. Highly versatile aryl(TMP)iodonium trifluoroacetates are utilized for *N*-arylation of isatoic anhydride under copper-catalysis condition,
ii. 27 examples of *N*-arylated isatoic anhydrides are presented in moderated to good yields where broad scope of aryl moieties (22 examples) are discussed,

iii. Synthetic utilities of *N*-arylated isatoic anhydrides are explored with alternative one pot-economical method for the synthesis two important scaffolds: fenamic acid derivatives and *N,N'*-diarylindazol-3-ones.

The schematic representation of the overall experimental works is shown in Figure 6.1.

6.1.2 Remarks on diaryliodonium salts as arylating precursor

In this thesis, diaryliodonium salts were explored under both metal-free conditions and copper-catalyzed reactions. In each chapter, identification of the metal-free arylation route with diaryliodonium salts was the initial objective, however hydantoins and isatoic anhydrides were not compatible under metal-free arylation conditions. During arylation studies with diaryliodonium salts, symmetrical iodonium salts and unsymmetrical iodonium salts with auxiliary such as anisyl (An), mesityl (Mes) and 2,4,6-trimethoxyphenyl (TMP) were synthesized and the same were tested for arylation. Although each reaction condition is specific for a particular type of iodonium salt, it is seen that the substrate scope varies (with respect to aryl moiety) with each type of iodonium salts. In our study, it was realized that aryl(TMP)iodonium salts were more suitable to obtain broad scope of aryl groups, and the synthetic procedure was comparatively easier than other types of iodonium salts. Another important concern experienced with unsymmetrical iodonium salts was chemoselectivity of the iodonium salt. The chemoselectivity pattern observed in case of metal-free reactions (chapter 2 & 3) were easier to follow in comparison to copper-catalyzed reactions.

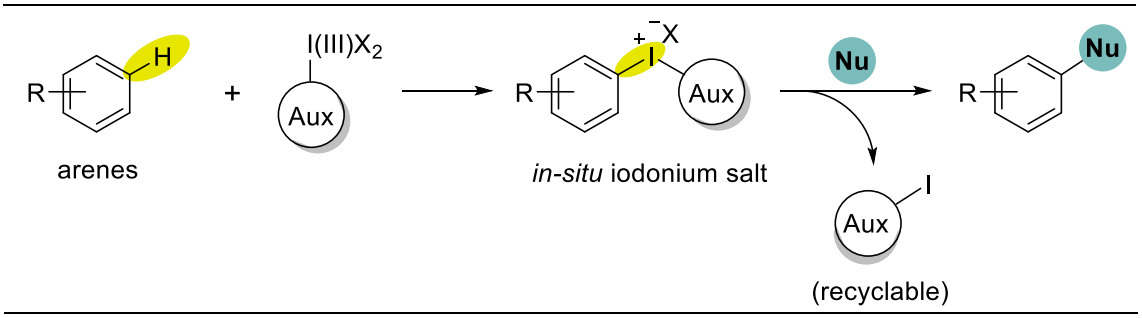
In conclusion, arylation technique with diaryliodonium salts under metal-free conditions (by avoiding the dependence of any toxic and costly transition-metal catalyst) is always for pharmaceutical drug development and sustainable chemistry. Alternatively, arylation reactions with diaryliodonium salts under copper-catalysis are operationally simple, ligand-free, and milder in comparison to those with available conventional arylating sources.

6.2 Future scope of the work

As the mentioned work in this thesis mainly focuses on synthesis of different diaryliodonium salts and their applications, many potential areas in diaryliodonium

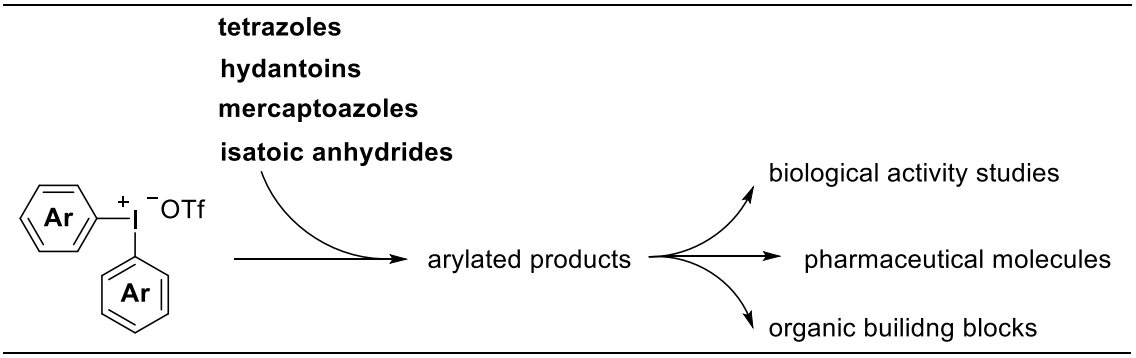
salt chemistry can be investigated for other useful organic transformations. The future scope of this work is discussed below:

i) Direct C-H functionalization of arene moieties: In general, an aryl(Auxiliary)iodonium salt requires aryl iodide and electron-rich arene (auxiliary) for its synthesis and after the arylation reaction, the auxiliary-iodide group is eliminated as side product (waste). In this conventional strategy, aryl iodide is the actual arylating source. However, by reversing this synthesis technique with appropriate choice of auxiliary-iodine(III) reagents and by synthesizing *in-situ* iodonium salts, many functionalized arenes can be utilized as arylating sources and the eliminated auxiliary-iodide can be recycled (Scheme 6.1). The recyclability of the wasted auxiliary-iodide is a highly beneficial approach.



Scheme 6.1 C-H functionalization of arenes

ii) As discussed in the experimental chapters, the investigated heterocyclic molecules in our studies are biologically privileged molecules, therefore it is most likely that their *N*-arylated products can also be promising candidates with some biological activities (Scheme 6.2). Moreover, the *N*-arylated products can be utilized as organic building blocks or important intermediates for other important synthetic organic scaffolds or pharmaceutical drug frameworks.



Scheme 6.2 Future scope of synthesized *N*-arylated compounds