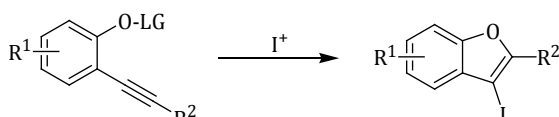


Benzofuran synthesis through iodocyclization reactions: recent advances

Abstract

Recent advancements (2014-17) in the benzofuran synthesis through iodocyclization have been summarized. The successful use of various iodinating agents, bases, additives etc. make iodocyclization a versatile and efficient methodology. The methodology has been applied for the synthesis of more complex benzofuran derivatives, and may open interesting avenues in the area of heterocyclic chemistry (Figure 1).



LG = H, Me or other Protecting group

R¹ = H, Me, OMe, I, CO₂Me, etc.

R² = H, aryl, alkyl, alkenyl, etc.

Figure 1

Keywords: annulations, alkyne, benzofuran, iodocyclization, heterocycle

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Introduction

Benzo[*b*]furan is a privileged heterocyclic scaffold. Several compounds containing this scaffold have interesting biological activities, such as anti-cancer, anti-viral, anti-inflammatory, etc.¹ Few derivatives are even used as commercial drugs, such as Amiodarone,² or investigational drugs, such as Bufuralol,³ etc. (Figure 2).

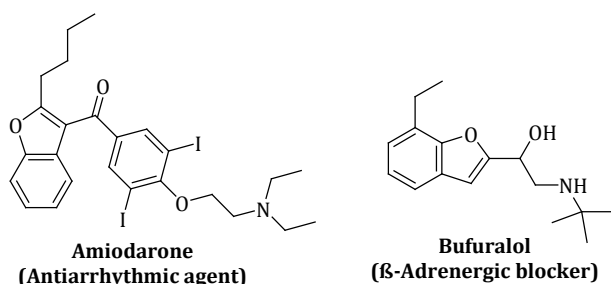


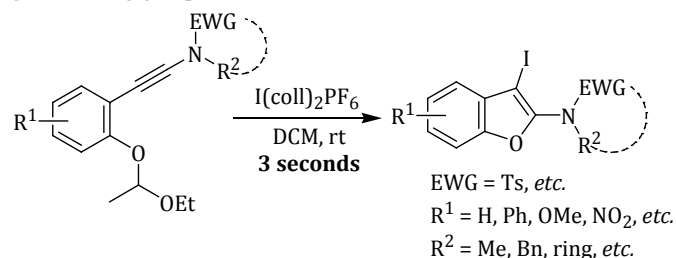
Figure 2 Examples of Benzo[*b*]furan scaffold containing drugs.

Over the years many synthetic routes have been reported for the preparation of benzofurans.^{1,4,5} Iodocyclization of functionalized alkynes is one of the most important and efficient synthetic methodologies for the synthesis of important heterocyclic compounds, including benzofurans.^{6,7} Due to our continuous interest in the synthesis and biological evaluation of important heterocycles,⁸⁻¹⁰ we became interested in Benzofuran synthesis. Here the recent advances (2014-17) in this powerful strategy for making benzofurans are reported.

Discussion

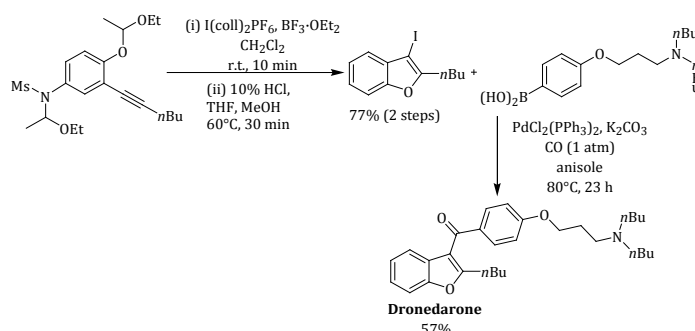
Okitsu et al.¹¹ recently reported a versatile synthesis of benzo[*b*]furans through iodocyclization of the ethoxyethyl ether-substituted alkynes (Scheme 1).¹¹ The reactions get completed within three seconds at room temperature and the corresponding benzofuran

derivatives were obtained in high yields (84%–100%) under mild conditions. The authors demonstrated that the choice of bis(2,4,6-collidine)iodonium hexafluorophosphate [I(coll)₂PF₆] as the iodinating agent was necessary for the success of the reaction. Also, the ethoxyethyl ether group acted as a protecting group as well as a good leaving group.



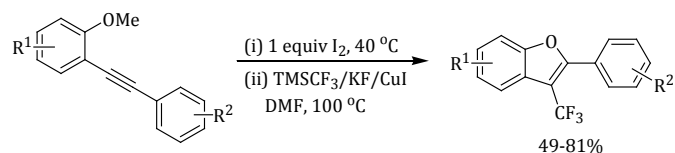
Scheme 1

The authors used a similar and previously reported methodology¹² for the synthesis (Scheme 2) of an antiarrhythmic agent Dronedarone (marketed as Multaq[®] from Sanofi-Aventis).¹³



Scheme 2

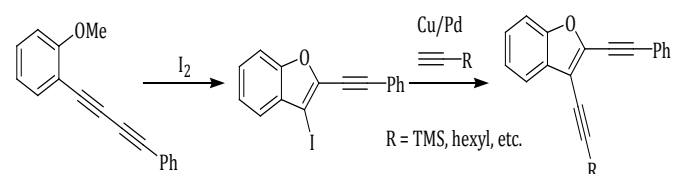
Wang et al.¹⁴ developed a novel and straightforward way for the preparation of 3-trifluoromethylbenzofurans.¹⁴ The methodology involves a two-step, one-pot tandem iodocyclization and trifluoromethylation reaction and affords the 3-trifluoromethylbenzofurans in moderate to excellent yields (Scheme 3).



$R^1 = \text{H, Cl, F, OMe, Ph, alkyl, etc.}$
 $R^2 = \text{H, Cl, F, OMe, alkyl, CO}_2\text{Me, CN, etc.}$

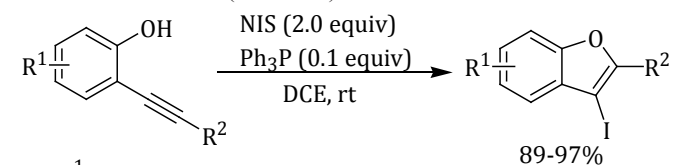
Scheme 3

Danilkina et al.¹⁵ reported an efficient strategy for the synthesis of asymmetrically substituted enediyne fused to benzofuran, and other important heterocycles (Scheme 4).¹⁵ The authors also demonstrated the extension of the methodology for the synthesis of fused macrocycles of indole derivatives.



Scheme 4

Li et al.¹⁶ demonstrated that a variety of 3-iodobenzo[*b*]furan derivatives can be conveniently prepared from the corresponding 2-alkynylphenols through Ph_3P -catalyzed iodocyclization in the presence of N-iodosuccinimide (NIS).¹⁶ This protocol provides a quick access to and 3-iodobenzo[*b*]furans in good to excellent yields under mild conditions (Scheme 5).



$R^1 = \text{H, Br}$
 $R^2 = \text{alkyl, aryl}$

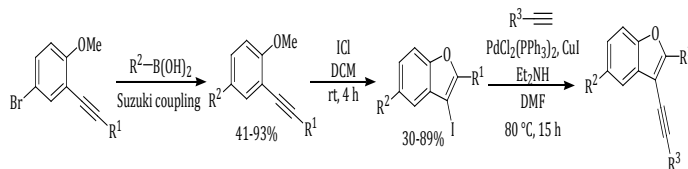
Scheme 5

Using the iodocyclization methodology (Scheme 6).^{17,18} He et al.¹⁹ designed and synthesized a 45-compound library of multi-substituted benzofurans, and using a high-throughput, cell-based HCV luciferase reporter assay studied its anti-hepatitis C virus (HCV) activity.¹⁹ The optimization of the scaffold resulted in the identification of several potent inhibitors ($\text{EC}_{50} < 100\text{nM}$) of HCV with low cytotoxicity ($\text{CC}_{50} > 25\mu\text{M}$), and good selectivity (selectivity index = $\text{CC}_{50}/\text{EC}_{50} > 371$ -fold).

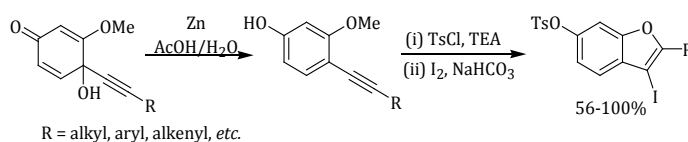
Jung et al.²⁰ recently reported an efficient synthetic approach to polysubstituted benzofurans where 2-methoxyquinone was used as a benzofuran backbone. The starting quinols were reduced to the phenols, the -OH group was protected and these substrates were further subjected to iodocyclization conditions affording the corresponding benzofurans (Scheme 7).²⁰

Raminelli et al.²¹ recently reported an interesting methodology for synthesizing diiodo-functionalized benzo[*b*]furans.²¹ The reaction

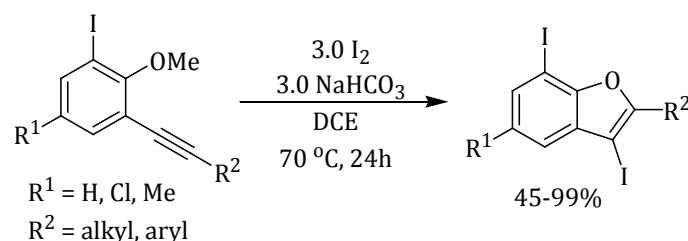
involves the iodocyclization of alkynylated 2-iodoanisoles using I_2 in the presence of sodium bicarbonate as base (Scheme 8). The resulting products containing two C-I bonds offer opportunities for further diversification of this important scaffold.



Scheme 6



Scheme 7



Scheme 8

Conclusion

Thus, the iodocyclization strategy presents an efficient approach for the synthesis of diverse benzo[*b*]furan derivatives. The choice of reagents, fast and high yielding reactions combined with the functional group tolerance make it a strategy of choice for many heterocyclic chemists. Further advances in this area of research are expected.

Acknowledgements

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Conflict of interest

The author declares no conflict of interest.

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