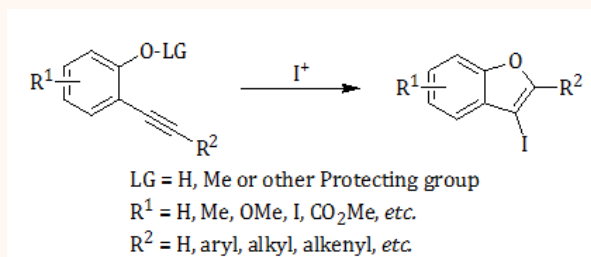


Benzofuran Synthesis through Iodocyclization Reactions: Recent Advances

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.



Keywords: Annulations; Alkyne; Benzofuran; Iodocyclization; Heterocycle

Mini Review

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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 1).

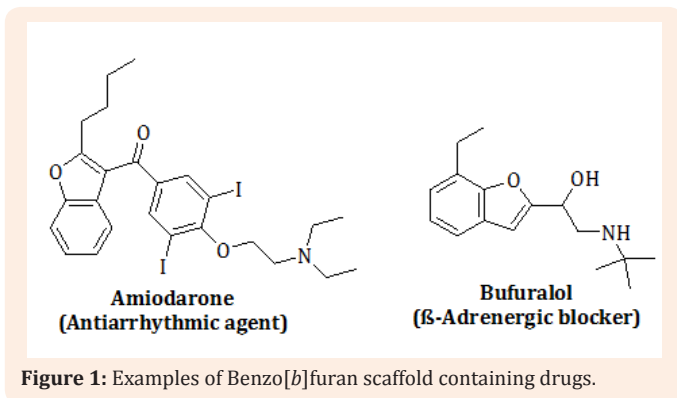


Figure 1: Examples of Benzo[*b*]furan scaffold containing drugs.

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

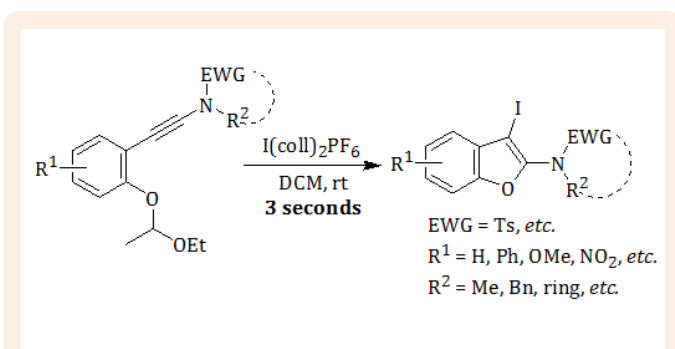
continuous interest in the synthesis and biological evaluation of important heterocycles, [8-10] we became interested in Benzofuran synthesis. Here the recent advances (2014-17) in this powerful strategy for making benzofurans are reported.

Discussion

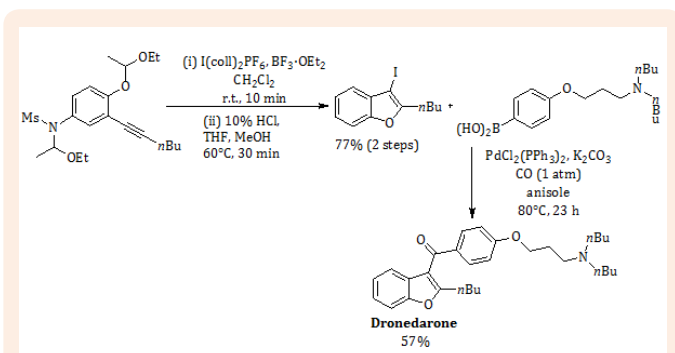
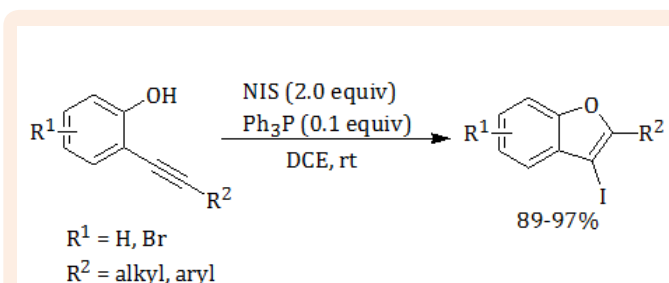
Okitsu et al. [11] recently reported a versatile synthesis of benzo[*b*]furans through iodocyclization of the ethoxyethyl ether-substituted alkynes (Scheme 1) [11]. The reactions get completed within three seconds at room temperature and the corresponding benzofuran derivatives were obtained in high yields (84%–100%) under mild conditions. The authors demonstrated that the choice of bis(2,4,6-collidine)iodonium hexafluorophosphate [$I(coll)_2PF_6$] 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.

The authors used a similar and previously reported methodology [12] for the synthesis (Scheme 2) of an antiarrhythmic agent Dronedarone (marketed as Multaq® from Sanofi-Aventis) [13].

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).

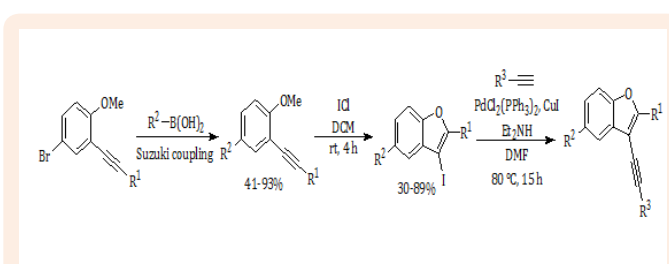
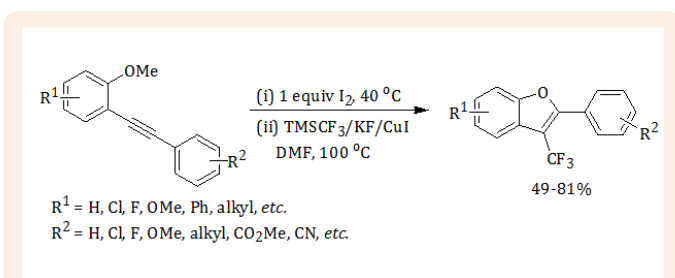


Li et al. [16] demonstrated that a variety of 3-iodobenzofuran derivatives can be conveniently prepared from the corresponding 2-alkynylphenols through Ph_3P -catalyzed iodocyclization in the presence of N-iodosuccinimide (NIS) [16]. This protocol provides a quick access to and 3-iodobenzofurans in good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



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).

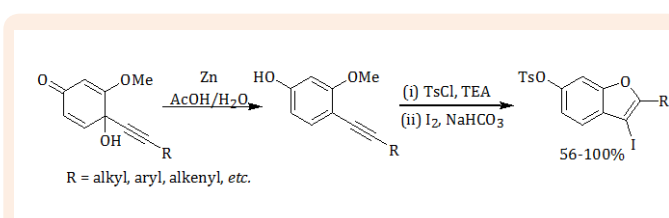
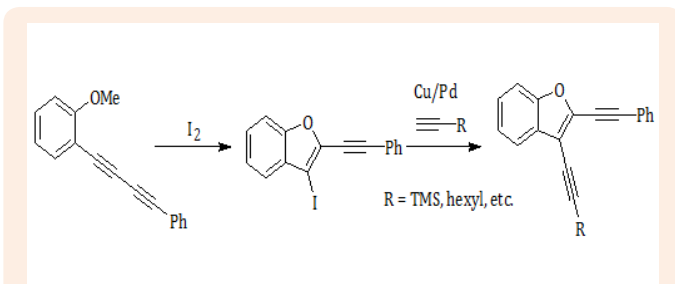


Scheme 3

Scheme 6

Danilkina et al. [15] reported an efficient strategy for the synthesis of asymmetrically substituted enediynes 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.

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].

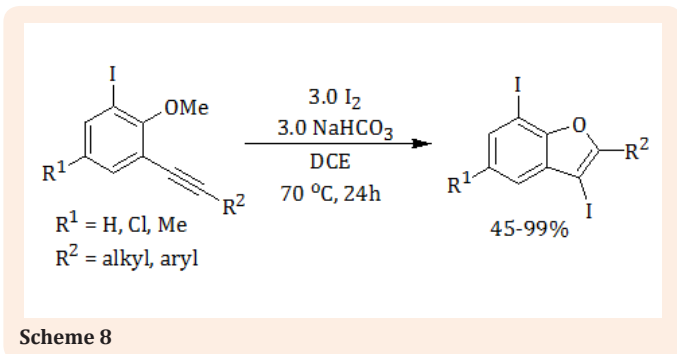


Scheme 4

Scheme 7

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.



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.

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Conflict of Interest

There is no conflict of interest.

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