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Review: One-pot synthesis protocol for highly functionalized benzofuran scaffold

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Abstract

Benzofuran scaffold appears frequently in natural products, commercial libraries, biologically and pharmaceutically relevant compounds. The presence of substituent handles help to diversify the structure further. Various classes of reactions such as enzyme-catalyzed, transition metal-catalyzed, base, acid and photochemical-induced cyclization were reported in the last few decades. Several modified protocols such as microwave-based and solid-phase reactions are recently reported with improved yield and scope of the reaction. This review provides an insight into one-pot transformation reactions for synthesis of functionalized benzofuran scaffold.

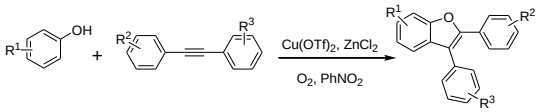
Introduction

Heterocyclic scaffold containing compounds have high pharmaceutical and biological importance due their diverse pharmacological and pharmacokinetic profiles. Fused heterocyclic rings such as benzofuran and indole are extensively found in natural products, biologically and pharmaceutically relevant compounds with diverse set of clinical conditions, and various commercial chemical libraries. Heterocyclic structures not only introduce diversity in chemical space but also in term of electronic properties. Heterocyclic scaffold containing compounds display diverse physiochemical and physiological profile. Presence of heterocyclic ring in a molecule generally improves its aqueous solubility and permeability profiles thereby, improving the overall pharmacokinetics. Improved aqueous solubility is commonly associated with lesser toxicity and tissue disposition due to increased renal clearance.

Benzofuran scaffold have been extensively studied due to its numerous biological and pharmaceutical relevance. Benzofuran containing scaffold possess several biological properties such as anti-inflammatory,[1] anti-vasoconstriction,[2] anti-microbial,[3] antifungal,[3-5] anti-coagulant,[6-12] and many more. Such a wide range of biological properties inherent by benzofuran scaffold justifies the extensive interest in its synthesis. Besides its diverse biological importance, it has also been used as building blocks for heterocyclic and acyclic compounds. Chemical synthesis of heterocyclic ring in one-step helps in quickly developing diverse and large libraries of these compounds. Great attention is being paid recently in search of chemical reactions to form highly substituted heterocyclic scaffold in one step with high yield. In this review, a literature survey is done on new and modified one-step synthesis protocol for synthesis of highly functionalized benzofuran scaffold. These reactions are classified based on reaction-type. This review doesn't cover reactions involving multiple steps required for ring formation.

Oxidative cyclization by metal-catalyzed reaction

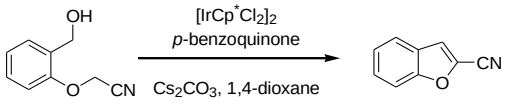
Copper as catalyst: Catalytic oxidation process with molecular oxygen is an economical and environment-friendly process applicable for industrial use. There are various copper-catalyzed oxidative C-H functionalization or nucleophilic/cyclization processes for synthesis of heterocycles. In this method, phenol and di-substituted alkyne are oxidatively cyclized using copper as a catalyst. The optimal reaction condition includes cu(OTf)2 as a catalyst, zinc chloride as a Lewis base in nitrobenzene as a solvent at 120°C (Scheme 1). The reaction proceeds with moderate yield. This reaction can tolerate various substitutions at both phenol and alkyne. The electron rich substitutions on phenol favor the transformation. Low to moderate yields were observed in reaction carrying sulfide, fluoro, chloro and iodo groups on phenol as well as alkyne. Differently substituted alkyne selectively formed one product which describes the region-selectivity of this reaction.[13]



Scheme 1

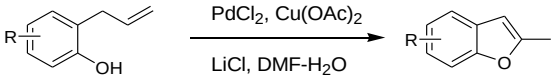
Copper catalyzed oxidative coupling of phenol and inactivated alkyne was further optimized by adding Rh-catalyst. The Rh(III)/Cu(II) system has been widely used before. The simple one-pot synthesis of benzofuran scaffold from commercially available phenol and alkyne advocate high utility and ease to develop diverse libraries.[13]

Iridium as Catalyst: Iridium complexes offer advantage of better thermal stability over cobalt and rhodium complexes. This makes iridium complexes a good choice for hydrogen transfer processes. In this method, benzofuran is synthesized from benzylic alcohols using p-benzoquinone as co-oxidant and Iridium complex as a catalyst. The reaction was performed at 110°C under microwave radiation (Scheme 2) and proceeds with moderate to excellent yield. Both electron withdrawing and donating substitutions at aromatic ring favor the reaction. Both primary and secondary benzylic alcohol lead to moderate to good yields.[14]



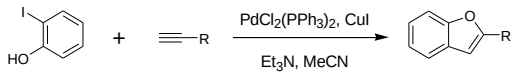
Scheme 2

Palladium as Catalyst: Pd-catalysts have extensively changed the field of organic chemistry by improving the C-C bond formation. Pd-catalysts are extensively used today and have been reported in many literatures. First pd-catalyzed oxidative cyclization to form benzofuran ring was reported in 1973. However, its synthetic utility was not explored due to the cost related issues involved in using stoichiometric amount of palladium catalyst.[15] Also, this method has drawback of Glaser coupling leading to the dimerization products. This reaction was optimized by avoiding Glaser coupling side reaction. Benzofuran ring formation can be achieved by intramolecular coupling of 2-allyl phenol using palladium (II) chloride as a catalyst and $Cu(OAc)_2$-LiCl system as a re-oxidant (Scheme 3).



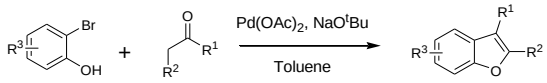
Scheme 3

The combinations of Pd-Cu are frequently used for intermolecular cyclization of terminal alkyne and 2-halophenol to yield benzofuran ring formation. It proceeds via formation of alkynyl phenol followed by intramolecular nucleophilic attack by neighboring OH group (Scheme 4). With improved conditions, benzofuran ring formation can be achieved using Sonagashira coupling of 2-iodophenol and acetylene derivative. The reaction proceeds through formation of the intramolecular oxypalladation cyclized product followed by β-elimination.[16-19]



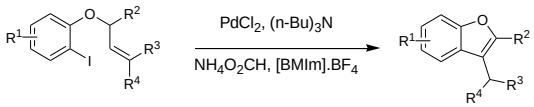
Scheme 4

This reaction is adapted to microwave condition at 100°C. It significantly reduces the reaction time from 20 hours to 25 minutes and improved the yield.[20] One-pot synthesis of benzofuran ring can be readily achieved from ketone and 2-halophenol using palladium-catalyzed enolate arylation reaction (Scheme 5). The cyclization of aryl ketones proceeds through an acid-catalyzed process. The reaction has wide scope with variety of substitution on ketones and 2-halophenol such as alkyl, aryl, cyclic, electron-donating and withdrawing.[21]



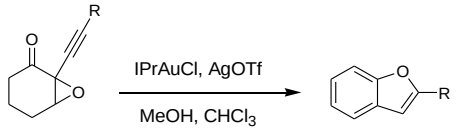
Scheme 5

A Pd-catalyzed intramolecular Heck reaction of 2-iodo aryl allyl ether to form benzofuran ring was reported in 1988.[22] But this reaction suffered from major drawback of low yield, need catalyst activation, and high temperature. The modified heck reaction using ionic liquid [BMIm] BF_4 improved the yield and the selectivity (Scheme 6).[23] Further improvement in reactivity was observed with use of oxidant.[24]



Scheme 6

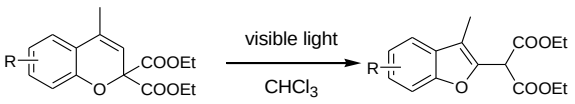
<u>*Gold as Catalyst:*</u> In fast few decades, enormous progress has been made in the field of gold-catalyzed transformation making it useful tool in organic synthesis. Benzofuran scaffold can be synthesized by gold-catalyst cyclo-isomerization of bicylco-[4.1.0] heptanes (Scheme 7). Based on the type of gold-complex, two types of products can be formed. The reaction offers wider scope and performs well with variety of substitutions with moderate to excellent yields. The aryl substituted alkyne groups showed high selectivity and excellent yields. However, reaction yield decrease significantly with alkyl substitutions and gave mixture of reduced products. This reaction proceeds by forming the coordination between gold and epoxide, then followed by attack of MeOH, cyclization and subsequent elimination steps. Various ligands were examined to improve the process efficiency. Electron-donating ligands and C-coordinated gold catalysts favor the epoxide coordination.[25]



Scheme 7

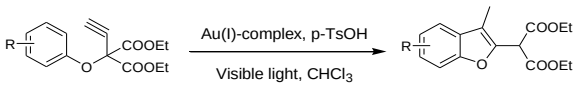
Photochemical rearrangement

The photochemical rearrangement of chromene can be achieved by visible light irradiation using sun-lamp to afford benzofuran scaffold. The reaction proceeds with excellent yield and has wider scope. The aromatic ring can tolerate various substitutions ranging from electron donating and withdrawing groups. However, this transformation suffers from disadvantage of long reaction time of 10 hours. Irradiation with visible light induces photochemical ring opening of the pyran ring, followed by 5-exo addition to form benzofuran ring (Scheme 8).[26]



Scheme 8

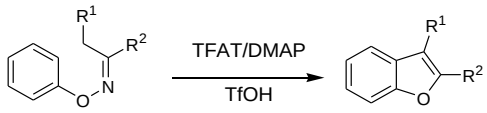
One-pot transformation of aryloxy propargyl malonates to benzofuran was achieved by mixing the substrates with gold-catalyst in the presence of p-TsOH under visible light irradiation in chloroform as a solvent at 60°C. This procedure is advantageous in terms of one-pot process and high yield. However, this process is limited by narrow substrate scope and cannot tolerate the strong electron-withdrawing groups such as cyano and nitro groups (scheme 9).[26]



Scheme 9

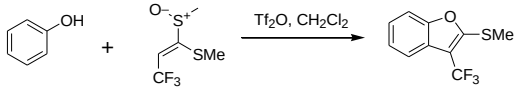
Acid and Base Catalyzed Cyclization

Cyclization of O-aryloximes by acid catalysis: Acid-catalyzed cyclization is a well-known synthetic process for synthesis of various heterocyclic rings. O-aryloximes can undergo acid-catalyzed cyclization to form benzofuran ring. This reaction proceeds through a [3,3]-sigmatropic rearrangement followed by condensation step (Scheme 10). This reaction suffers from drawback of harsh conditions such as high temperature and acidic conditions limiting the use of acid-liable groups.[27] Improvement in this process was achieved by first trifluoroacetylation of O-phenyloxime at low temperature, which lead to concomitant cyclization to form benzofuran.[28] This process works efficiently in mild conditions with excellent yield. Synthetic utility of this process is shown in short synthesis of various natural products such as Stemofuran A and Eupomatenoid.[29]



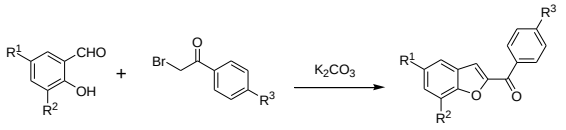
Scheme 10

Cyclization of phenol and Vinyl-CF3-derivatives: CF_3-substituted benzofuran can be obtained by Pummerer reaction of phenol and CF_3-vinyl derivatives with trifluoro-methanesulfonic anhydride in DCM at low temperature. Reaction proceeds through nucleophilic attack of phenoxy group at cationic sulfur followed by [3,3]-sigmatropic rearrangement (Scheme 11).[30]

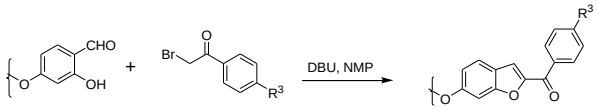


Scheme 11

Base-catalyzed cyclization: This is the oldest method for synthesis of benzofuran ring by condensation of salicylic aldehyde and chloroacetone in the presence of a base (Scheme 12).[31,32] Later, base-assisted condensation of salicyaldehyde with phenacyl bromide was reported to form benzofuran ring, also known as Rap-Stoermer reaction.[31] This reaction was modified to solvent free conditions to give quantitative yield by mixing salicaldehyde, phenacyl bromide and potassium carbonate at 80°C. This modified procedure yielded 98% of benzofuran product (Scheme 13).[33] The solid phase synthesis was reported using similar reaction conditions. Cyclization of aryloxyketone was utilized to build a library of benzofurans using solid-phase synthesis. The 4-hydroxy group of phenyl ketone was attached to DHP resin, followed by cyclization to form the benzofuran scaffold.[34]

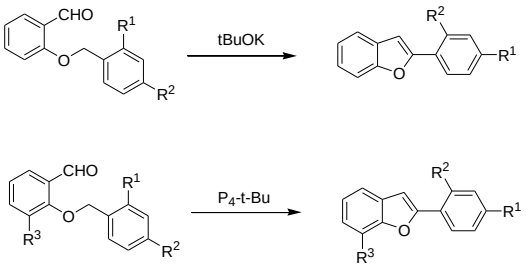


Scheme 12



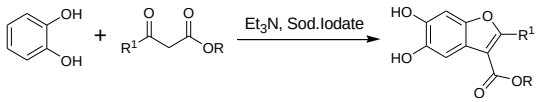
Scheme 13

Another strategy for base catalyzed cyclization of 2-arylmethoxy benzaldehyde proceeds through dehydrative cyclization. The reaction proceeds effectively with electron-withdrawing group as a substituent.[35] It was modified to perform reaction at ketone without electron withdrawing group with the help of a strong base such as LDA, LTMP and KH in an anhydrous solvent (see Scheme 15).[36] The superbase such as hindered phosphazene P4-t-Bu effectively directed the formation of benzofuran from o-arylmethoxy benzaldehyde (Scheme 14).



Scheme 14

Another approach for formation of benzofuran was reported utilizing Oxidative-Michael's reaction. The cyclization of catechol with ethylacetoacetate in the presence of base leads to formation of highly substituted benzofuran in moderate yield (Scheme 15). However, this process has limited scope in terms of substitution at both coupling partners.



Scheme 15

In conclusion, benzofuran scaffold is known for its importance in biological and pharmaceutically relevant compounds. A lot of work is currently being done on developing newer and/or modified protocols to improve yield and to provide a wider scope in terms of substitutions on the benzofuran scaffold. This review contains one-pot synthesis process for formation of substituted benzofuran building. The reactions are categorized according to type of reaction such as the transition-metal catalyst, the acid and base catalyzed ring formation. Benzofuran scaffolds are also commonly used as building blocks to develop libraries of compounds. Based on current trend, more improved processes will appear in literature in future. The transition metal catalyzed reactions offer higher yield, wider scope of substitutions and green chemistry as compared to photochemical, acid and base catalyzed reactions, which are limited in terms of stability and scope of reaction.

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