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Surveying the Synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones and Related Analogs

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Abstract: ***This review presents a systematic and comprehensive survey of the methods of preparation of 2H-benzo[b][1,4]oxazin-3(4H)-one derivatives. Many research groups have synthesized and evaluated benzoxazinones against several biological agents. This review examines recent publications relating to the synthesis of benzoxazinones. Benzoxazinone derivatives have exhibited a broad spectrum of biological activities, and approved benzoxazinone containing drugs include Bisoxatin (laxative), Caroxazone SB-64,915 (antagonist), Paraxazone (antidepressant) and DIMBOA (antibiotic). Due to their selective transformations with different reagents they have been attracting increasing attention in view of their high reactivity as building blocks for the preparation of compounds of various classes towards biological and therapeutical perspective.***

Keywords: Synthetic strategies, reactions, heterocycles

Graphical Abstract

1. Introduction and Scope

Heterocyclic compounds are the interesting core structures for the development of new bioactivecompounds. These are the important class of organic compounds that have been used for many important medicinal and synthetic chemistry applications. Heterocycles are present in variety of drugs, vitamins, natural products, biomolecules and biologically active compounds, including antibacterial,[1,2] antifungal,[3] antiinflammatory,[4] and antitumor drugs,[5-7] Also, they have been frequently found as a key structural motif in pharmaceuticals and agrochemicals.[8] Heterocyclic structures having the ability to synthesize various compounds based on core structure and screen against a variety of biological activities which provide several active compound leads. Therefore, more combinations of heterocyclic structures can be designed, resulting in new structures with expected biological properties. Heterocycles having heteroatoms at 1,4 positions and fused to a benzene ring are considered as important targets in medicinal chemistry due to their wide range of biological and therapeutic potentials. Notably, nitrogen bearing fused heterocycles[9] have gained a substantial attention and occur in a variety of bioactive natural products, pharmaceuticals, organic materials, dyes and agrochemicals.[10a-b]Among these *N*-fused heterocycles, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**Figure1**), a fused heterocycle bearing benzene and morpholin-3-one portions has gained a significant attention in the field of bioorganic and medicinal chemistry. It is one of the attractive fused heterocyclic moiety owing to its synthesis and immense pharmacological importance.[11a-d]The most eye catching features of these compounds are their greatest utility resides in pharmaceuticals (antiproliferative, antimicrobial, antifungal, inhibitors and antagonists).[12]Benzoxazinone derivatives are considered to be important chemical synthons of various physiological significances and pharmaceutical utilities. Therefore, we speculate the detailed investigations into thesynthetic and pharmacological diversity with special emphasis on structural variations around 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one scaffold. This endeavour has thus uncovered the medicinal worthiness of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one framework. The aim of the present investigation is to study in some details thesynthesis, reports of somederivatives of these classes of compounds since 2005. It is hoped that this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic benzoxazinone medicinal drugs. Although, a detailed description of the synthesis of benzoxazinones would be far beyond this review, some aspects that have already reviewed elsewhere[12]are indispensable to impart a better understanding and will be therefore recapitulated shortly.

1. Synthetic methodologies for 2*H*benzo[*b*][1,4]oxazin-3(4*H*)-one scaffold

Classic synthetic strategies towards benzoxazinones have been reviewed. The following section gives an overview of highlights in the field of benzoxazinone synthesis since

2005, as an extensive progress in methodology has been made. Established synthetic strategies towards benzoxazinones will be touched shortly in order to convey an integral overview.

According to AGIOS PHARMACEUTICALS, [13]2*H*-Benzo[*b*][1,4]oxazin-3(4*H*)-one has been prepared (**Scheme 1)** by the reaction of of 2-amino phenol **2** (3.0 gm, 27.5 mmoles) in chloroform, TEBA (3.1 gm, 13.7 mmol) and $NaHCO_3$ was added at 0°C. Then a solution of chloro acetyl chloride**3** (4.6 gm, 41.2 m moles) in chloroform was added over 20 minutes at the same temperature and the resulting mixture was allowed to stir at 60 °C for 16 h gave 2*H*-Benzo[*b*][1,4]oxazin-3(4*H*)-one with 78.04% yield.

Daniel Spinks et al.[14] have synthesized 2*H*-1,4-benzoxazin-3-(4*H*)-ones**4** on reaction of chloroacetyl chloride with the appropriately substituted 2-aminophenol to give the NH benzomorpholinone intermediate (**Scheme 2**). This was then alkylated with potassium carbonate as the base, with heatinginDMF.Workup and purification yieldedcompounds with 30-70% yield.

As shown in **Scheme 3**Rajitha C et al.[15a-b]have reported a novel synthesis in two steps via formation of ethyl 2-(2-nitrophenoxy) acetate (**6**) from 2-nitrophenol (**5**) by using ethyl bromoacetate, potassium carbonate in acetone followed byreduction with Fe powder in acetic acid and in situ cyclization of the resulting ether derivative (**5**) provided the desired 2*H*benzo[*b*][1,4] oxazin-3(4*H*)-one (**1**).

In **Scheme 4**Hanumant B. Borateet al.[16] have reported two step synthesis of 2*H*benzo[*b*][1,4]oxazin-3(4*H*)-one(**1**) via formation of 2-chloro-*N*-(2-hydroxyphenyl) acetamide (**7**) as an intermediate with readily available starting materials.

Mark Armitage and associates[17]have explained an existing route to formation of SB-649915 (**13**) which is depicted in **Scheme 5a.** The existing route to **12** involved coupling quinoline**12** with piperidine**11** and was considered lengthy as a consequence of the nine synthetic steps required to prepare **12**. Therefore, they had synthesized a new route to formation of SB-649915, for that they had first synthesized6-bromobenzoxazinone **18**, involves the bromination of 2-nitrophenol **5**, followed by alkylation of the phenol **15** with methyl chloroacetate to give ester **16** and subsequent reduction to give **18**. Alternatively reduction of nitrophenol**15**to aminophenol **17** followed by acylation with chloroacetyl chloride and subsequent cyclisation leads to **18** (**Scheme 5b**).

For this work, however, an alternative approach to **18** was successfully evaluated, exploiting the cheap and readily available2-hydroxyacetanilide **19** using a classical approach to selective bromination. Phenol **19** is converted to aniline **17** via the acetamide**20** following bromination and hydrolysis, and subsequent acylation of **17** with chloroacetyl chloride and "in situ" cyclisation delivers benzoxazinone**18**. This chemistryproved to be remarkably facile and high yielding, and was easilyscaled to deliver multiple gram quantities of the target 6-bromobenzoxazinone**18** (**Scheme 5c**).This approach avoided a dissolved metal reduction and therefore minimized any risk of reductive dehalogenation pathways.

Enguang Feng et al.[18] have developed an efficient and convenient method for preparing *N*-substituted 2*H*-1,4-benzoxazin-3-(4*H*)-ones (**23**) via a cascade reaction with a nucleophilic substitution of 2-halophenols (**21**) with 2-chloroacetamides (**22**) followed by a CuI/DBU-catalyzed coupling cyclization (**Scheme 6a**).Sincethis method involves simple reaction conditions, a shortreaction time, and a broad substrate scope, it is particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

Ali Sharifiet al.[19]reported an efficient procedure for the one-pot synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives (**27**) from their corresponding o-aminophenols (**25**) with 2-bromoalkanoates(**26**) is developed using DBU in the ionic liquid [omim][BF_4]. The reactions are chemoselective and give high yields (73-95%) of products in short times (**Scheme 7**).Various bases such as Na_2CO_3, K_2CO_3, CsF, KF, DBU, Et_3N and DABCO were also studied for this reaction. However, they are not efficient as compared to Cs_2CO_3. Here, the [omim][BF_4] could be recovered and reused several times without significant loss of their activity.

Chen et al.[20] demonstrated various 2*H*-1,4-benzoxazin-3-(4*H*)-ones through copper-catalyzed coupling of o-halophenols (**28**) and 2-halo-amides (**29**)various 2*H*-1,4-benzoxazin-3-(4*H*)-one (**30**) scaffolds have been synthesized under N_2 at 90 ^oC for 24 h conveniently in good to excellent yields (**Scheme 8).**Various catalysts, ligands, bases and solvents were examined for this synthesis. However, the isolated yield increased greatly (95%) when the combination of *o*-iodo phenol, 2-chloroacetamide, CuI and 1,10-phenanthroline in the presence of Cs_2CO_3as base in dioxane.

J. Wu et al.[21] reported potentially bioactive heterocycles starting from 2- aminophenols (**2**)were converted into the *N*-(2-bromobenzyl)-substituted derivatives (**31**)in excellent yields through reductive N-alkylation with (**32**)by using $NaBH(OAc)_3$ as the reductant. The acyclic aryl bromides(**34**)are readily available from microwave-assisted one-pot annulation of *N*-(2-bromobenzyl)-2-aminophenols (**32**)and ethyl 2-bromoalkanoates (**33**)**(Scheme 9**).

Kang et al.[22]reported a novel and effective synthesis of substituted 1,4-benzoxazinones (**37**) *via* Smiles rearrangement (**Scheme10a**). Treatment of *N*-substituted 2-chloroacetamide, substituted 2-chlorophenols (**35**) and cesium carbonate in refluxing DMF afforded the corresponding substituted 1,4-benzoxazinones in excellent yield (**37**) and also investigated the base and solvent effects on the synthesis of **37a** and found that K_2CO_3in CH_3CN was the most effective system (90% yield) in step-1 and on the other hand, CS_2CO_3 in DMF was found to be more effective for the cyclization of **36a**when compared with other bases such as Li_2CO_3, Na_2CO_3, K_2CO_3 and Ag_2CO_3.

The formation of **37** was confirmed by the reaction of 5-methyl-2-amino phenol (**38**) with 2-chloroacetyl chloride using known methods (**Scheme10b**). Thus 2-chloroacetyl

chloride was reacted with **38** to afford the intermediate **39** which was further cyclized (to give **40**) followed by treatment with benzyl chloride furnished the compound **37a**. The two compounds obtained by different synthetic routes were compared using physical and spectral data which was found to be same.

M. Von Wantoch Rekowski et al.[23]have described a straightforward and efficient synthesis of 6-bromo-2*H*-1,4-benzoxazin-3(4*H*)-one (**18**) started with the reduction of 4-bromo-2-nitrophenol (**14**) with tin(II)chloride dihydrate in concentrated hydrochloric acid. Ring closure with chloroacetyl chloride under basic conditions gave rise to 6-bromo-2*H*-1,4-benzoxazin-3(4*H*)-one (**18**) (**Scheme11**).

Ramesh et al.[24] reported a simple and facile route for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones (**44**) *via* reductive cyclization of 2-(2-nitrophenoxy)acetonitrile adducts (**43**) in the presence of Fe/acetic acid afforded excellent yields. This system was compatible with various other functional groups (**Scheme12**).The desired products possessing alkyl, ester and halogen group(s) were well tolerated in this method.

Xiao Tianet al.[25] synthesized novel 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives (**52a-g**) by condensation, reduction, *O*-alkylation and Smiles rearrangement using 3-bromo-4-hydroxy benzaldehyde (**48**), anilines (**45**), and chloroacetyl chloride (**3**) as starting materials (**Scheme13**).

Qunxian Hu et al.[26]developed a facile and an efficient one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives (**56**) by condensation between 2-(*o*-haloaryloxy)acyl chlorides (**53**) and primary amines (**54**) followed by Cu(I)-catalyzed intramolecular C-N bond coupling afforded a variety of 2*H*-1,4-benzoxazin-3 (4*H*)-ones in good to excellent yields (**Scheme14**) and also optimized with the ligands, bases and solvents effects on the synthesis of **56** and found that 1,10-Phen, CS_2CO_3in dioxane was the most effective system (96% yield). Diversified substitutents on the 4-position could be conveniently introduced.

Maciaaset al.[27]reported an isolation and synthesis ofmodified methodology to access DIBOA and DIMBOA which were first isolated from *Zea mays*and *Secalecereale* respectively (**Scheme15**).New synthetic methodology was employed for the obtention of the lactams2-hydroxy-(2*H*)-1,4-benzoxazin-3(4*H*)-one (**57**) and 2-hydroxy-7-methoxy-(2*H*)-1,4-benzoxazin-3(4*H*)-one (**58**). This methodology employed allowed the desired compounds to be obtained in high yield andin an easy-to-scale manner.

Wolferet al.[28]presented the first catalytic, asymmetric synthesis of 1, 4-benzoxazinones that relies on the highly enantioselective [4+2] cycloaddition of *o*-benzoquinoneimides (**60**) with chiral ketene enolates (derived from acid chlorides (**59**) and cinchona alkaloid [**a**] catalysts; **Scheme 16**). These cycloadducts can be functionalized in situ to provide 1,4-benzoxazines (**61**) in good-to-excellent yields and with virtual enantiopurity, only rivaled by that of enzymatic amino acid synthesis and also theyspeculated that chiral 1,4-benzoxazinone intermediates could also serve as flexible precursors for the efficient synthesis of highly enantiomerically enriched α-amino acids and related derivatives.

Zhou Xuet al.[29]have investigated an efficient approach for C-N cross-coupling reactions via intramolecularamidation of aryl chlorides catalyzed by a Buchwald–Hartwig second generation Pd catalyst (XphosPd G2) (**Scheme 17**). This catalyst system allows the primary amides (**62**) which have only modest nucleophilicity could couple successfully even with electron rich aryl chlorides whichcan afford valuable benzene-fused 6-membered amides (**44**) withhigh yield in short reaction time. The catalyst system also hasgood chemoselectivity and excellent functional group compatibilitywhich supplies an important alternative way to the synthesis of benzene-fused 6 as well as 7-membered amides (**44**).

Ji Min Lee et al.[30] have devisedan efficient method for the solid phase parallel synthesis of drug-like 7-aryl-benzo[*b*][1,4]oxazin-3(4*H*)ones derivatives **68**. The preparative sequence employs a microwave promoted Smiles rearrangement-cyclization reaction of BOMBA resin bound α-(2-chloro-4-bromophenoxy) acetamide**65**. Suzuki coupling reactions on the resulting BOMBA resin **66** with arylboronic acids followed by acid cleavage from the resin led to the formation of a series of 7-aryl-benzo[b][1,4]oxazin-3(4H)-ones **68** (**Scheme 18**).The target compounds, obtained by using this five-step sequence, are produced in high yields and purities.

Tingting Yanget al.[31] synthesized a new series of paeonol derivatives containing the 1,4-benzoxazinone moieties were synthesized in four steps and the synthetic routine is shown in **Scheme 19**. Paeonol (**69**) was first selectively introduced nitro group by reacting with HNO_3/H_2SO_4 at the C-3 position to form compound **70**, which could be further converted to intermediate **71** by reduction with zinc powder in acetic acid. After successfully synthesizing compound **71** via amidation and cyclization reaction, compound**72** containing the 1, 4-benzoxazinone moiety was obtained.

2. Conclusion

Overall, this review summarises numerous methods and reports for synthesizing variously substituted 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one heterocyclics since 2005 through conventional, multicomponent and microwave-assisted reaction methods.These observations may be useful in developing novel and therapeutically potent hybrids of heterocyclic-benzoxazinones.

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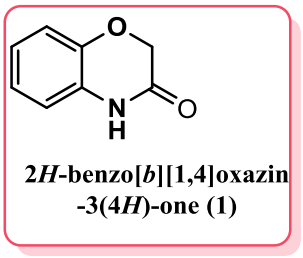
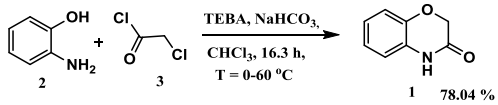
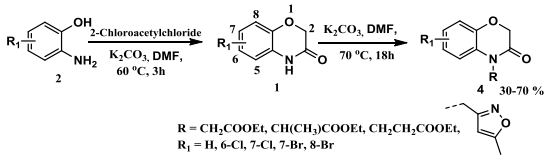


Figure 1: Structure of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one

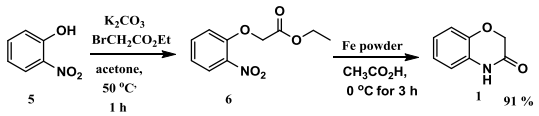
Scheme 1:



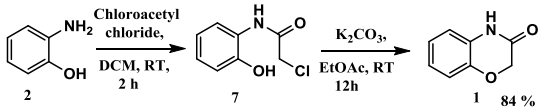
Scheme2: Synthetic route to the benzomorpholinone series



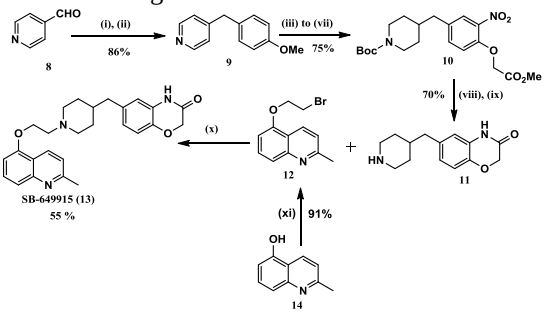
Scheme 3: Synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**1**) via formation of ethyl 2-(2-nitrophenoxy)acetate (**6**) as an intermediate



Scheme 4: Preparation of Preparation of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**1**) via 2-chloro-N-(2-hydroxyphenyl)acetamide (**6**) as an intermediate

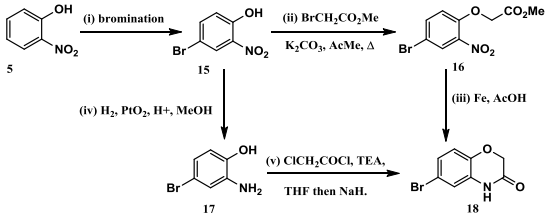


Scheme5a: Existing route to formation of SB-649915[a]



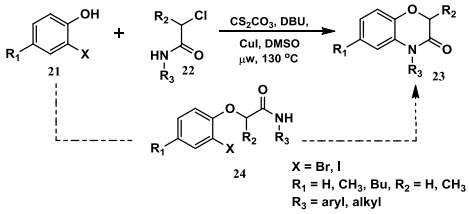
[a]Reagents and conditions: (i) 4-bromoanisole, Mg; (ii) Zn, HCO_2H; (iii) 48% aqHBr, Δ; (iv) H_2, PtO_2, H_2SO_4, MeOH; (v) HNO_3, AcOH; (vi) $(Boc)_2O$, NEt_3, H_2O, THF; (vii) $BrCH_2CO_2Me$, K_2CO_3, acetone, Δ; (viii) H_2, Pd/C; (ix) HCl, Et_2O, IPA, Δ; (x) DIPEA, IPA, Δ; (xi) $BrCH_2CH_2Br$, K_2CO_3, MEK, 80 °C.

Scheme 5b: Literature Routes to 6-Bromobenzoxazinone

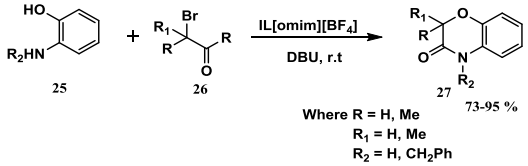


Scheme 5c : Efficient Route to 6-Bromo-2*H*-1,4-benzoxazin- 3(4*H*)-one

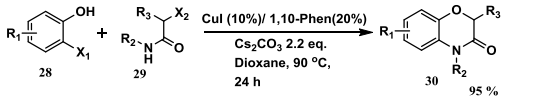
Scheme6: Synthesis of *N*-Substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones via Intermolecular Nucleophilic Substitution/ Intramolecular C-N Coupling



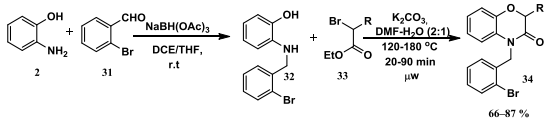
Scheme 7: [omim][BF_4] mediated synthesis of benzoxazinones



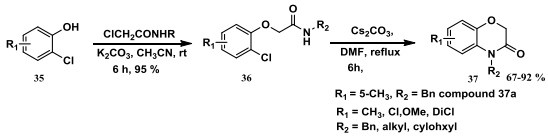
Scheme 8: CuI-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones from 2-halophenol and 2-halo-acetamides



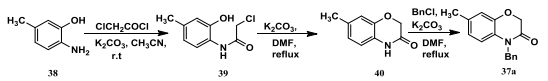
Scheme 9: Synthesis of *N*-(2-Bromobenzyl)-2-aminophenols **32** and Synthesis of 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazines **34**



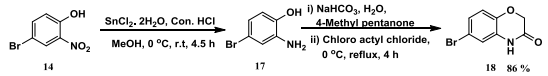
Scheme 10a: Synthesis of 2*H*-benzo[*b*][1,4]oxazin-3-ones from 2-chlorophenols



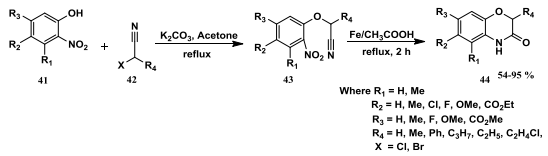
Scheme 10b: Synthesis of benzo[*b*][1,4]oxazin-3-ones from 5-methyl-2-amino phenol



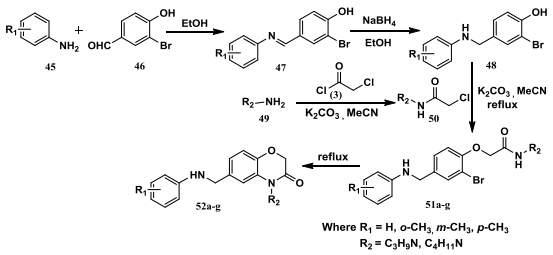
Scheme 11: Synthesis of 6-bromo-2*H*-1,4-benzoxazin-3(4*H*)-one (**41**)



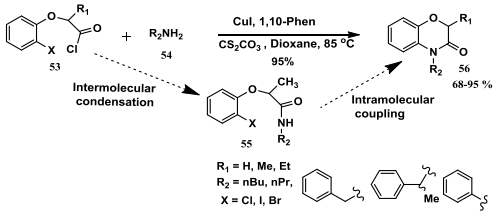
Scheme12: Route to the synthesis of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives (**44**)



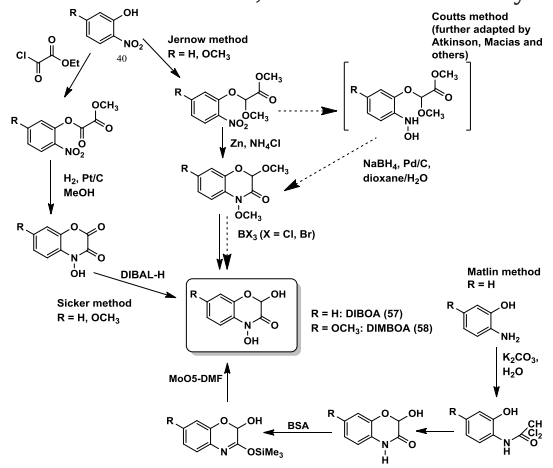
Scheme13: Synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones.



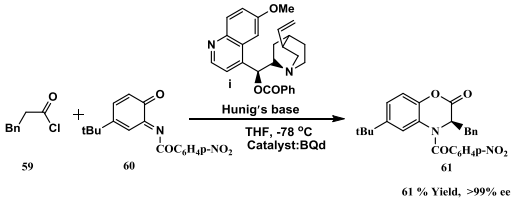
Scheme14: The proposed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones *via* Cu-catalyzed condensation/coupling process.



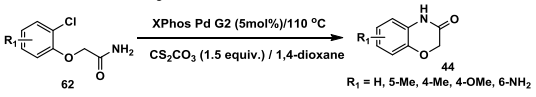
Scheme15: Overview of Benzoxazinone Synthetic Methods Based on Oxidation of 1,4-Benzoxazine Heterocycle



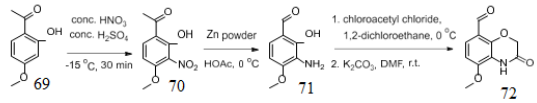
Scheme 16: Chiral 1,4-benzoxazinone product



Scheme 17: Synthesis of Benzene-fused amides:



Scheme 18: 7-aryl-benzo[b][1,4]oxazin-3(4*H*)-ones



Scheme19: Synthesis of paeonol derivatives containing the 1,4-benzoxazinone moieties