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Catalyst free synthesis of 2-Aryl-2*H*-benzo[*b*][1,4]oxazines and 3-Aryl-2H-benzo[*b*][1,4]thiazin-2-ones: An ultrasonication-assisted strategy

Bisma Teli[1,2] | **Malik Abdul Waseem**[1] | **Showkat Rashid**[1] | **Bilal Ahmad Ganaie**[1] | **Bilal A. Bhat**[1,2]

[1]Natural Products and Medicinal Chemistry, CSIR-Indian Institute of Integrative Medicine, Jammu & Kashmir, India

[2]Academy of Scientific & Innovative Research (AcSIR), Ghaziabad, India

Correspondence
Bilal A. Bhat, Natural Products and Medicinal Chemistry, CSIR-Indian Institute of Integrative Medicine, Jammu & Kashmir 190005, India.
Email: bilal@iiim.res.in

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Abstract

An ultrasonication-assisted synthesis of 2-Aryl-2*H*-benzo[*b*][1,4]oxazines and 3-aryl-2*H*-benzo[*b*][1,4]thiazin-2-ones has been established by reacting phenacyl bromides with 2-aminophenol and 2-aminothiophenol, respectively. This approach fosters flexibility in generating a diverse range of 1,4-benzoxazines and 1,4-benzothiazinones under catalyst-free reaction conditions. Further scope toward the synthesis of rarely occurring *bis*-benzoxazine adduct has also been explored, which enabled us to propose the reaction mechanism.

1 | INTRODUCTION

1,4-Benzoxazine motif constitutes an intrinsic part of a large class of heterocyclic constructs with a cosmopolitan distribution in drugs, bioactive agents, and a wide range of natural products.[1–4] Antibiotic drug, levofloxacin,[5] serotonin 3 receptor antagonist, azasetron,[6] neuroprotective synthetic compound HSB-13[7] and natural products like pitucamycin and dandamycin[8] are some of the commonly encountered examples harboring this important structural construct. A rare tetracyclic natural product based on *bis*-benzoxazine motif was also recently isolated from a co-culture of sponge-associated actinomycetes.[9] Similarly, benzothiazinones also constitute an essential heterocyclic motif present in a large number of bioactive compounds. For example, a bacteriostatic agent exhibiting activity against *Staphylococcus aureus* P-209 and *Escherichia coli* M17 is based on a benzothiazinone scaffold[10] (Figure 1).

Keeping into consideration the ubiquitous nature of 1,4-benzoxazines and their wide range of biological activities,[1–9] an ample number of synthetic methods have been developed toward this end. Traditional synthesis of 1,4-benzoxazine derivatives involves multistep processes, using 2-nitrophenols or 2-aminophenols as the starting materials.[11] However, due to their growing canvas, 1,4-benzoxazine derivatives have prompted newer and more efficient methodologies that follow diverse one-pot strategies including metal-catalyzed reactions,[12–20] cascade reactions[21–25] or even microwave-assisted transformations.[26,27] Toward the synthesis of 2-aryl-1,4-benzoxazines, recently two general strategies emerged in the literature (Scheme 1). One involves the oxidative dearomatization of quinols with amino acid derivatives[28] and the another one is based on BF_3-mediated Friedel Crafts arylation

Bisma Teli and Malik Abdul Waseem equally contributed to this work.

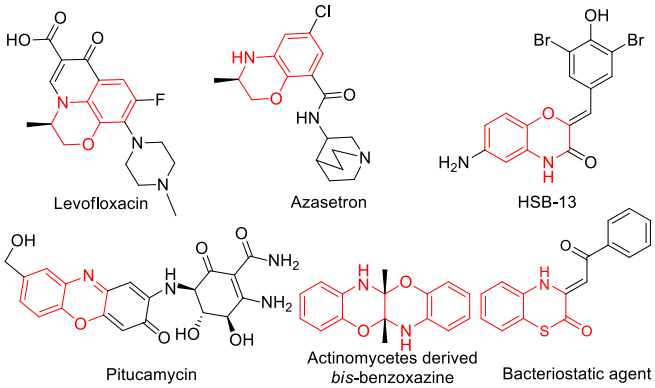
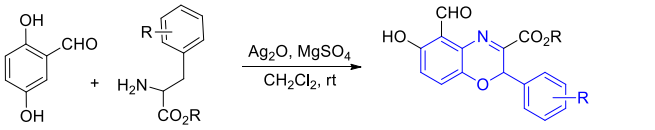
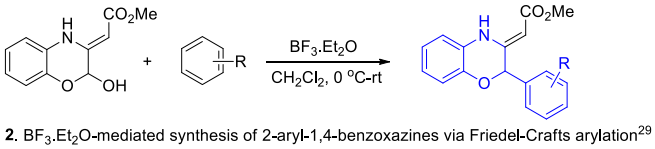


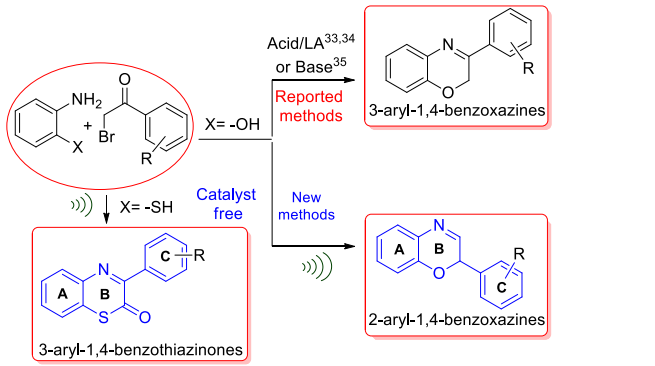
FIGURE 1 1,4-benzoxazine-based drugs, bioactive entities, natural products, and benzothiazinone agent



1. Synthesis of 2-aryl-1,4-benzoxazines via oxidative dearomatization[28]



2. $BF_3.Et_2O$-mediated synthesis of 2-aryl-1,4-benzoxazines via Friedel-Crafts arylation[29]



3. Acid or base-mediated synthesis of 3-aryl-1,4-benzoxazines and new catalyst free synthesis of 2-aryl-1,4-benzoxazines and 3-aryl-1,4-benzothiazinones

SCHEME 1 General approaches to access 2-aryl 1,4-benzoxazines

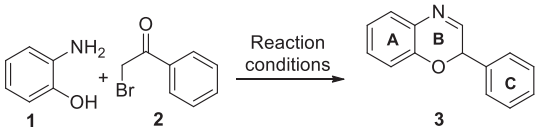
reaction of 1-hydroxy-1,4-benzoxazines.[29] Despite accounting for some interesting chemical reactions, both the strategies are not free from limitations in terms of substrate scope.

As a part of our ongoing medicinal chemistry research program on heterocyclic bioactive entities,[30–32] a research endeavor was initiated to establish a flexible protocol for synthesizing 1,4-benzoxazine derivatives. Keeping in mind the acidic and basic functional groups attached to 2-aminophenol, we subjected it to react with phenacyl bromide under ultrasonication condition, 2-aryl-1,4-benzoxazine was obtained as an exclusive product. This protocol was further elaborated on a range of substrates and also modified to demonstrate its application toward bis-benzoxazine derivatives. It is pertinent to mention that under acidic or basic conditions, the reaction between 2-aminophenol and phenacyl bromide or chloride is reported to change its path completely and furnish 3-aryl,1-4-benzoxazine as the main product[24,33,34] (Scheme 1).

Initially, we began our study with the reaction of 2-aminophenol (**1**) and phenacyl bromide (**2**) under various reaction conditions at variable temperatures in different organic solvents (Table 1). Our results indicated that this reaction was sluggishly working in various protic and aprotic solvents (entry 1–4). However, in a polar solvent like DMSO, and non-polar solvent like hexane, this reaction was not working at all (entry 5 and 8). Therefore, we sought to attempt it in chlorinated solvents like dichloromethane and chloroform, but the reaction was highly sluggish (entry 6 & 7). However, it was encouraging to see a decent conversion of the reaction in THF at rt or 60°C (entry 9 & 10). By switching over to ultrasonic conditions (40 kHz) at 60°C in THF as a solvent, we were delighted to see the complete conversion of reactants within an interval of 2 h and the product was obtained in a decent yield (entry 11). Based on these results, the reaction was further attempted in 1,4-dioxane at rt, but under these conditions, it was not effective like in most other solvents (entry 12). Therefore, the reaction was found comparatively suitable in THF at 60°C under sonication conditions (Table 1).

To examine the generality and scope of this method, several phenacyl bromide derivatives having electron-donating and withdrawing groups, halogenated, heterocycle, and biphenyl compounds were used in this study to increase the substrate scope. We initially tested this reaction on compounds having electron donating groups. It was observed that the reaction proceeded smoothly to furnish the products **4** and **5** as in case of product **3** (Table 2). In case of compounds having halogen substitution, the reaction was slightly better than compounds with electron donating groups. However, in case of compounds with electron-withdrawing group attached to the ring-B, the reaction was somewhat efficient than the earlier two cases. We next sought to further broaden its canvas on ring-A substituted compounds and 2-aminothiophenol compounds. Due to their limited commercial availability, we used the 3-nitro-aminophenol and phenacyl bromide initially. It was interesting to observe that the reaction between 3-nitro-2-aminophenol and phenacyl bromide furnished 3-aryl-benzoxazine as an exclusive product instead of 2-aryl-benzoxazine. The reason could be attributed to the possible electronic effects,

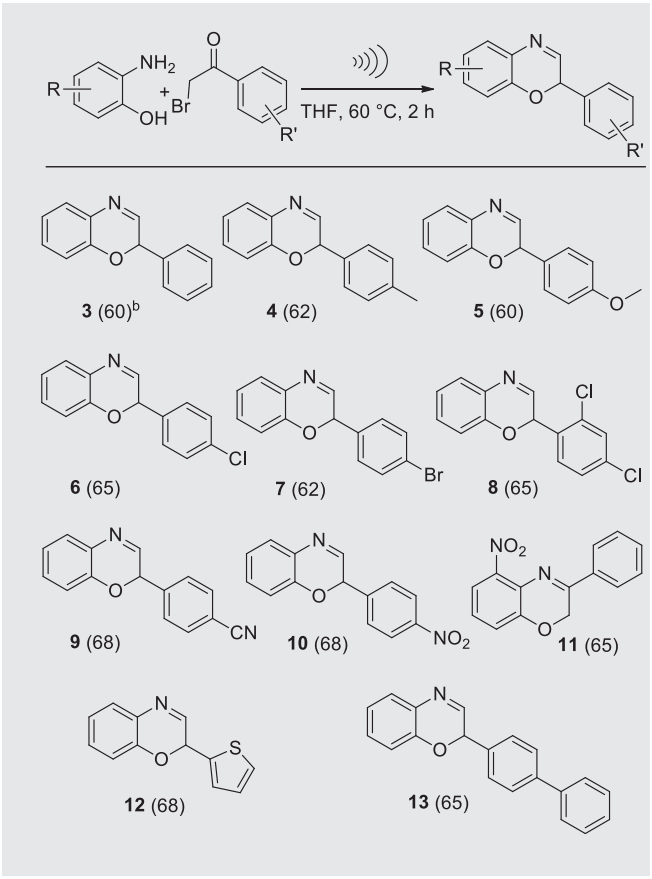
TABLE 1 Optimization of reaction conditions for the synthesis of 2-aryl-1,4-benzoxazines



Entry	Solvent[a]	Condition	Time, h	%Yield 3[b]
1	MeOH	rt	6	32
2	EtOH	rt	6	30
3	EtOH: H_2O	rt	6	35
4	MeCN	rt	6	20
5	DMSO	rt	6	0
6	CH_2Cl_2	rt	6	20
7	$CHCl_3$	rt	6	20
8	Hexane	rt	6	0
9	THF	rt	6	50
10	THF	60	5	45
11	THF	sonication (60°C, 40 kHz)	2	60
12	1,4-Dioxane	rt	6	15

[a]All the reactions were attempted at 1 mmol scale in 10 ml of solvents.
[b]Isolated yield.

TABLE 2 Access to substituted 2-aryl-1,4-benzoxazines[a]

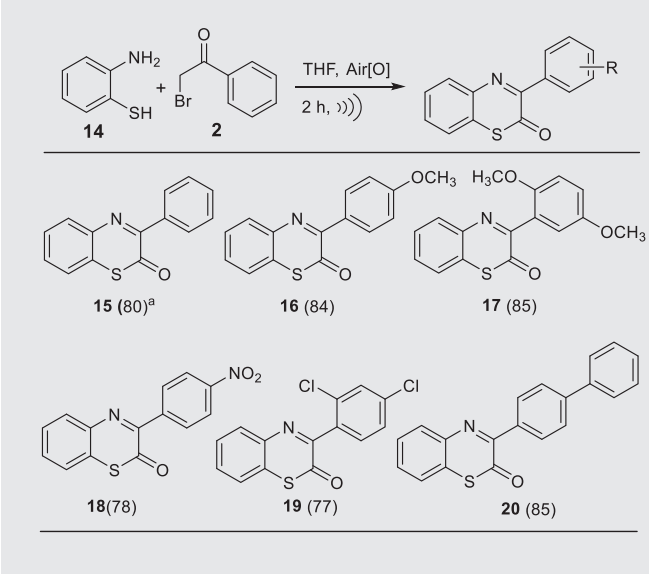


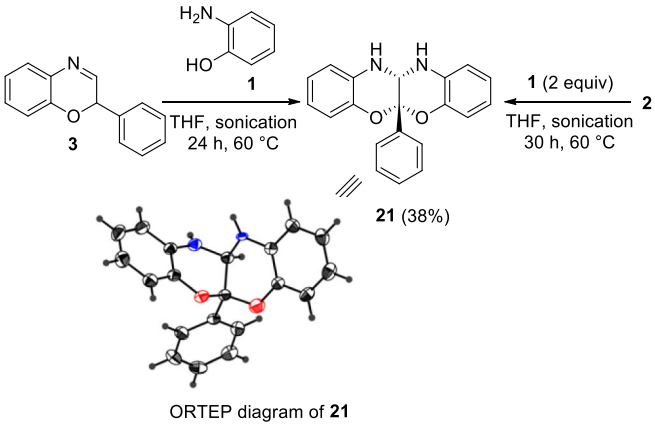
the powerful electron-withdrawing nitro group at position-3 in 3-nitro-aminophenol diminishes the electron density at 2-amino group and thereby the first attack takes place through -OH group (discussed vide infra in mechanism). Further, the reaction was also tried on thiophene and biphenyls substituted compounds (**12** and **13**). To our delight, this reaction also worked well in all these cases, irrespective of the position and substitutions (Table 2).

After the reaction was found successful on a range of 1,2-aminophenols, we next sought to broaden its canvas on 1,2-aminothiophenols under similar conditions. Interestingly, the reaction of 1,2-aminothiophenol with phenacyl bromide under sonication in the presence of air lead to the aromatic ring swapping and result in the formation of 3-phenyl-2*H*-benzo[*b*][1,4]thiazin-2-one as an exclusive product (Table 3). It is pertinent to mention that this product was earlier accessed in two steps involving one additional oxidation-step using similar starting materials.[35,36] Since our protocol leads an in-situ air oxidation therefore, we tested it on a range of different substrates having electron-donating, withdrawing groups and halogen substitutions. As is evident from Table 3 the compounds **15–20** were obtained in excellent yields.

Having addressed its generality and substrate scope, we next attempted to utilize this reaction further toward bis-benzoxazines. In this endeavor, we first reacted compound **3** with another mole of 2-aminophenol to establish

TABLE 3 Access to substituted 3-aryl-2*H*-benzo[*b*][1,4] thiazin-2-one

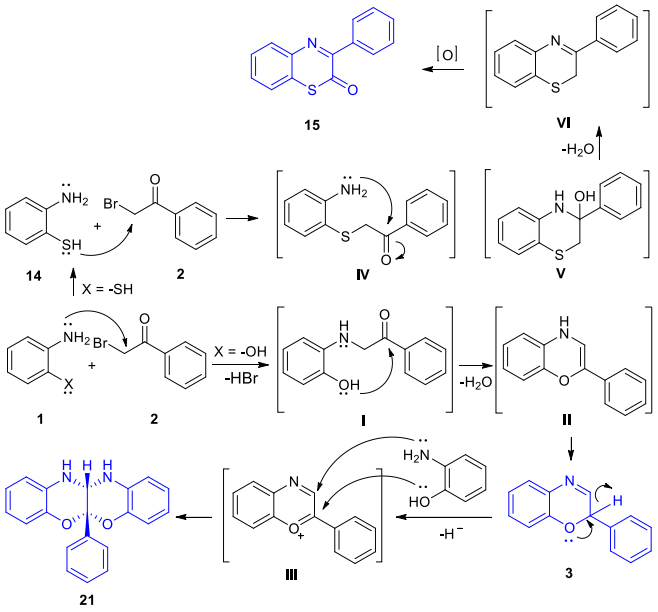




SCHEME 2 Applications toward the synthesis of bis-benzoxazines

its reactivity and mechanism. Under similar reaction conditions in 24 h, this compound was converted to bis-benzoxazine derivatives (**21**) albeit in compromised yield (Scheme 2). Later on, we concluded that when the reaction of phenacyl bromide (1 mole) was carried out with 2-moles of aminophenol, bis-benzoxazine derivative (**21**) was again obtained as one of the products (Scheme 2). The structure and stereochemistry of compound **21** were assigned unambiguously through a single X-ray crystal structure analysis. It is to note that these bis-benzoxazine regiomers are present in recently isolated and rarely occurring bioactive natural products isolated from the co-culture of sponge-associated actinomycetes.[9]

Based on these results, we tried to explain the plausible mechanism for the formation of 2-aryl-1,-4-benzoxazines, 3-aryl-2*H*-benzo[*b*][1,4]thiazin-2-one and bis-benzoxazine adducts. We propose that in the presence of acid or base as reported in earlier methods, the first attack of 2-aminophenol takes place through oxygen functionality due to the more nucleophilic character of phenoxide ion than ammonium ion. As a result, 3-aryl-1,-4-benzoxazines were the only products obtained in literature so far. However, under neutral conditions, as expected, —NH_2 group is more nucleophilic and therefore undergoes N-alkylation with phenacyl bromide to furnish the intermediate **I** (Scheme 3). Cyclization of the intermediate **I** takes place through phenol group addition on carbonyl group, followed by eliminating water to result in intermediate **II**. Double bond repositioning in intermediate **II** furnished the product **3**. This compound, when treated with another mole of 2-aminophenol, a rare pentacyclic bis-benzoxazine adduct, **21**, was formed possibly through the intermediacy of oxycarbonium ion **III**. This oxycarbonium ion is formed under the influence of 2-aminophenol and is stabilized due to benzylic, allylic groups and also due to oxycarbonium ion effects. In case of 3-aryl-2*H*-benzo[*b*][1,4]thiazin-2-ones, phencyl bromide undergoes –SH alkylation with thiol group to intermediate **IV** followed by cyclization (to **V**) and water elimination to intermediate **VI**. In situ air oxidation of the intermediate **VI** under the reaction conditions leads to compound **15** as an exclusive product.



SCHEME 3 Plausible mechanism of formation of 2-aryl-1,4-benzoxazines and bis-benzoxazine adducts

2 | CONCLUSIONS

In conclusion, we established a new strategy to synthesize 2-aryl-1,4-benzoxazines and 3-aryl-2*H*-benzo[*b*][1,4]thiazin-2-one under ultrasonication conditions without the involvement of any catalyst. Its scope was demonstrated on a wide range of substrates with different substitutions and functionalities. We also elaborated its scope toward rarely occurring bis-benzoxazine adducts present in natural products. Further exploration of these scaffolds toward the medicinal chemistry program is currently underway.

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DATA AVAILABILITY STATEMENT

Supporting data is available

ORCID

Bilal A. Bhat https://orcid.org/0000-0002-0239-7625

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