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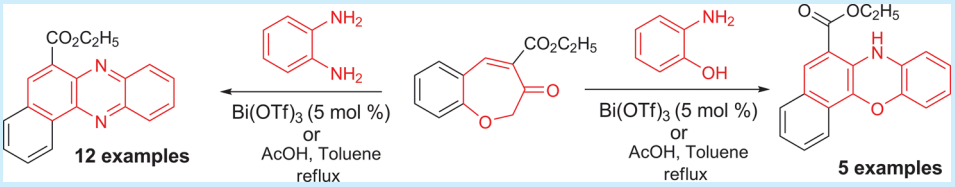
A Novel Approach for C–C, C–N, and C–O Bond Formation Reactions: A Facile Synthesis of Benzophenazine, Quinoxaline, and Phenoxazine Derivatives via Ring Opening of Benzoxepines

Bhimapaka China Raju,*[,†] Kasagani Veera Prasad,[†] Gannerla Saidachary,[†] and Balasubramanian Sridhar[‡]

[†]Natural Product Chemistry Division, [‡]Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad, 500 007, India

Supporting Information



ABSTRACT: A new one-pot protocol has been developed for the synthesis of benzophenazine, quinoxaline, and phenoxazine derivatives by the reaction of benzoxepine-4-carboxylates with benzene-1,2-diamines, ethane-1,2-diamine, and 2-aminophenols in the presence of $Bi(OTf)_3$ (5 mol %) under mild conditions in very good yields. The present protocol opens a new way for C–C, C–N, and C–O bond-formation reactions in a single-step process. The structural assignment was confirmed by X-ray analysis.

Phenazines, quinoxalines, and phenoxazines are important heterocyclic compounds in the pharmaceutical industry.[1] Phenazines and their derivatives have found application in a wide variety of therapeutics, which include antibiotic, antimicrobial, antimalarial, antiparasitic, and antitumor activities.[2] The phenazine derivatives were also reported as photosensitizers in photodynamic therapy (PDT).[3] Quinoxalines[4] are benzoheterocycles possessing various pharmacological activities including anticancer, antimicrobial, and building blocks of organic semiconductors. Phenoxazine is an important pharmacophore present in Actinomycin D, a chemotherapy drug,[5] and several phenoxazines have been reported as anticancer agents,[6,1c] MDR modulators,[7] and potent specific inhibitors of Akt signaling.[8] Further, *N*-benzoylated phenoxazines have been reported as tubulin polymerization inhibitors.[9] The phenoxazines and benzophenoxazines were also reported as fluorescent dyes.[10] Therefore, the development of novel synthetic methods for these heterocycles continues to be an active area of research. Few synthetic approaches have been reported as depicted below.

The approaches for the synthesis of phenazines consist of (Scheme 1): (a) base catalyzed condensation of anilines with nitrobenzenes at 200 °C[11a] (Wohl–Aue method); (b) fusing of two molecules of 4-substituted nitrosobenzene under acidic conditions[11b] (Bamberger–Ham method); (c) dehydrative condensation of benzo[1,2,5]oxadiazole-1-oxide with nucleophiles[11c] (Beirut reaction); (d) condensation of catechols with benzene-1,2-diamine[11d] or in presence of PbO_2; and (e) sequential palladium(II) catalyzed aryl amination (Buchwald–Hartwig).[11e–h] Methods a–d received limited attention due to the harsh reaction conditions with poor yields.[11a–d] Quinoxalines are usually synthesized by condensation of aryl-1,2-diamines with epoxides or dicarbonyl compounds or their equivalents.[12] The approaches for the synthesis of phenoxazines consist of the following: (1) Smiles rearrangements[13a–d] of 2′-aminodiaryl ethers; (2) reaction between 2-aminophenols and chalcones;[13e] (3) Cu-catalyzed preparation of substituted phenoxazine derivatives;[7] and (4) base catalyzed cyclization of *N*-acetyl aryloxyanilides.[13f] However, the development of simple and novel methodologies for these heterocycles is still required.

Our research focused on the synthesis of biologically active heterocyclic compounds,[14] and feasible reactions of carbonyl compounds/salicylaldehydes with 3-oxobutanoates bearing chloro or trifluoro substituents. In this context, we studied the reactivity of carbonyl compounds with ethyl 4,4,4-trifluoro-3-oxobutanoate using piperidine in CH_2Cl_2 at room temperature to provide a series of (*E*)-α,β-unsaturated esters and ketones.[15] Next, we studied the reactivity of various salicylaldehydes with ethyl 4-chloro-3-oxobutanoate using piperidine to provide 2*H*-chromenes,[16a] interim these derivatives were successfully converted to corresponding 2,3-dihydrobenzoxepine-4-carboxylates.[16b] Now, the present manuscript describes a novel method for the preparation of benzophenazine, quinoxaline, and phenoxazine derivatives in one pot from benzoxepine-4-carboxylates.

In an initial experiment, we conducted the reaction between the benzoxepine-4-carboxylate (**1a**, 1 equiv) and benzene-1,2-diamine (**2a**, 1 equiv) at 110 °C. This afforded ethyl benzo[*a*]phenazine-6-carboxylate **3a** in 30% isolated yield (Table 1, entry 1). The phenazine derivative **3a** was fully

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Scheme 1. Approaches for the Synthesis of Phenazines

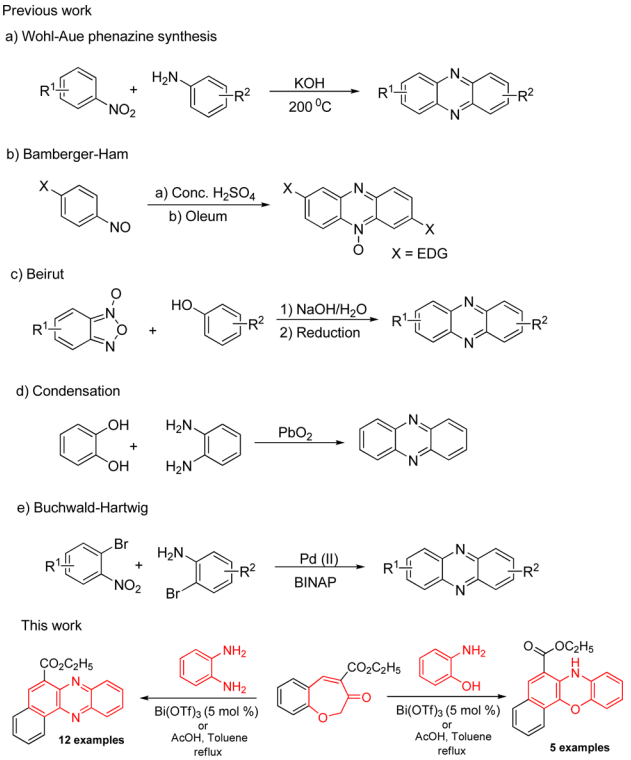
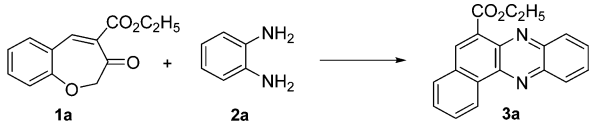


Table 1. Optimization of the Reaction Conditions



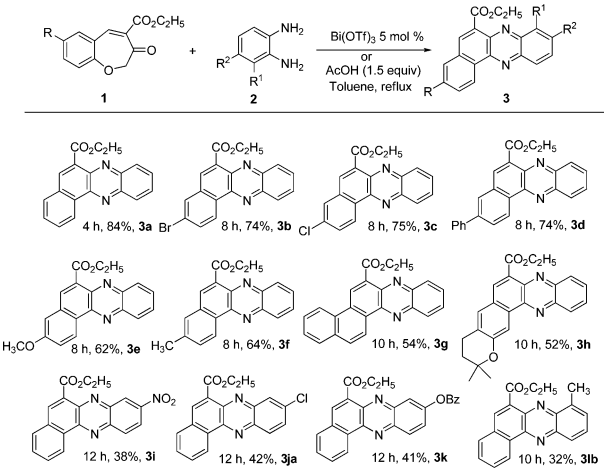
entry	catalyst (equiv)	solvent	time (h)	yield (%)[d]
1[a]	–	–	48	30
2[b]	$Bi(OTf)_3$ (0.05)	toluene	18	32
3[b]	$Bi(OTf)_3$ (0.10)	toluene	36	44
4[c]	**$Bi(OTf)_3$ (0.05)**	**toluene**	**04**	**84**
5[c]	$Bi(OTf)_3$ (0.05)	MeOH	12	58
6[c]	$Bi(OTf)_3$ (0.05)	DCM	12	60
7[c]	$Bi(OTf)_3$ (0.05)	CH_3CN	12	52
8[c]	$Bi(OTf)_3$ (0.05)	THF	12	–
9[b]	$La(OTf)_3$ (0.05)	toluene	24	18
10[c]	$La(OTf)_3$ (0.05)	toluene	08	65
11[b]	AcOH	–	24	10
12[c]	AcOH	–	16	28
13[b]	AcOH (1.5)	toluene	20	34
14[c]	AcOH (1.5)	toluene	05	72
15[c]	H_2SO_4 (1.0)	toluene	20	42
16[c]	HCl (1.0)	toluene	20	48
17[c]	$AlCl_3$ (1.0)	CH_3CN	16	63
18[c]	$AlCl_3$ (1.0)	toluene	20	28
19[c]	$FeCl_3$ (1.0)	toluene	20	59
20[c]	I_2 (1.0)	toluene	16	12
21[c]	BMIM-Cl	–	24	12
22[c]	*p*-TsOH (1.0)	toluene	16	64

[a]110 °C. [b]Room temperature. [c]Reflux. [d]Isolated yields.

characterized using IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopies. The structure of **3a** was further confirmed using single-crystal X-ray diffraction analysis. This work represents the first example of the construction of benzophenazine in one pot, and the usefulness of this reaction is shown by the formation of three new bonds (one C−C bond, two C−N bonds) and two new rings (naphthalene and quinoxaline). To optimize the reaction conditions, the model reaction was investigated with various catalysts and solvents, and the results were summarized in Table 1. The product **3a** was obtained in 32% (18 h), 44% yield (36 h) when the reaction was carried out at room temperature with $Bi(OTf)_3$ (5 mol %).[17] Toluene provided a higher yield (**3a**, 84%) when **1a** was reacted with **2a** in the presence of $Bi(OTf)_3$ (5 mol %) under reflux conditions than did other organic solvents (entries 4−8); hence, toluene was chosen as the solvent for further reactions. Compound **3a** was obtained in 65% yield when the reaction was carried out with $La(OTf)_3$ (entry 10). The catalysts such as protic acids (entries 11−16), Lewis acids (entries 17−20), an ionic liquid (entry 21), and *p*-TsOH (entry 22) were screened. In all the reactions, product **3a** was obtained but in less yields except in the case of acetic acid (72%, entry 14). These experiments showed that the reaction of a 1:1:0.05 mixture of benzoxepine (**1a**), benzene-1,2-diamine (**2a**), and $Bi(OTf)_3$ in toluene under reflux conditions (4 h) provided **3a** in a higher yield.

In order to evaluate the efficiency of the methodology, we investigated the substrate scope present on benzoxepine-4-carboxylates (**1b−l**) and benzene-1,2-diamine (**2b−e**). The electron-withdrawing or -donating groups present on benzoxepine were well tolerated to produce **3b−h** in very good yields, whereas groups present on benzene-1,2-diamine produced **3i−l** in moderate yields (Scheme 2). Thus prepared benzophenazine-6-carboxylate derivatives **3a−l** were well characterized using IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopies.

Scheme 2. Synthesis of Benzophenazine-6-carboxylate Derivatives 3a−l[a−c]



[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), $Bi(OTf)_3$ (5 mol %) or AcOH (1.5 equiv), and toluene (4.0 mL) in a round-bottom flask under reflux. [b] Isolated yield. [c] Regioisomers were obtained for compounds **3j** (95:5), **3k** (98:2), and **3l** (60:40).

To expand the scope of the present method, ethane-1,2-diamine (**2aa**) and propane-1,3-diamine (**2ab**) were examined. Under optimized conditions, **1a** was reacted with ethane-1,2-diamine **2aa** producing benzoquinoxaline-5-carboxylate **4a** in 58% yield (Scheme 3). Phenyl and methoxy groups present on benzoxepine were well tolerated to produce **4b−c**. Under these

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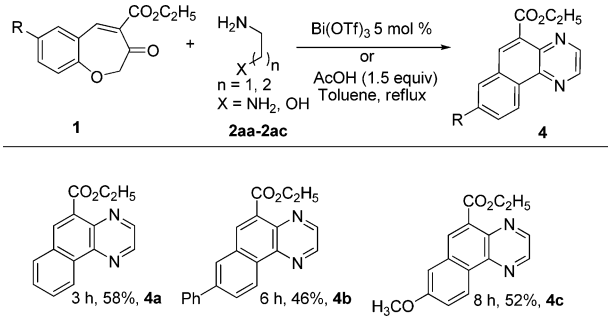
Scheme 3. Synthesis of Benzoquinoxaline-5-carboxylate Derivatives 4a–c[a,b]

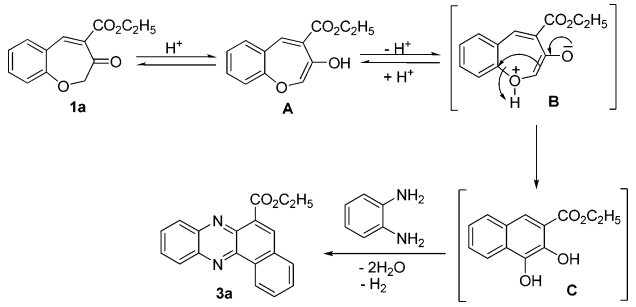


[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), and $Bi(OTf)_3$ (5 mol %) or AcOH (1.5 equiv) in toluene (4.0 mL) under reflux. [b] Isolated yield.

conditions, propane-1,3-diamine **2ab** and 2-amino ethanol **2ac** did not yield the desired products.

A proposed mechanism for this new reaction is shown in Scheme 4. Initially, the reaction was expected to involve

Scheme 4. Proposed Mechanism for Phenazines

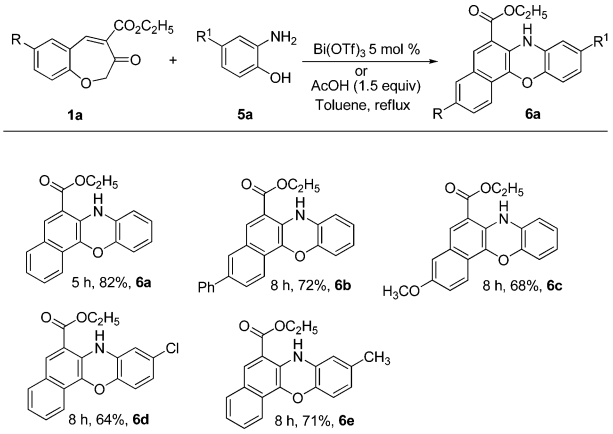


enolization of benzoxepine **1a** to its corresponding enol derivative **A**. Protonation of intermediate **A** would then give oxonium ion **B**. Finally the unstable oxonium ion **B** was rearranged by C–O bond cleavage to form a new C–C bond to give its corresponding ethyl 3,4-dihydroxy-2-naphthoate **C** (^{1}H NMR experiment; see Supporting Information (SI); the naphthoate was isolated and confirmed by D_2O exchange). Condensation of ethyl 3,4-dihydroxy-2-naphthoate **C** with benzene-1,2-diamine in situ provided phenazine derivative **3a**.

Having succeeded in the synthesis of benzophenazines and quinoxalines, we extended this protocol for the preparation of benzophenoxazines. Accordingly, benzoxepines **1a**, **1d–e** were reacted with various substituted 2-aminophenols **5a–e** in the presence of $Bi(OTf)_3$ under optimized conditions to provide a series of benzophenoxazine-6-carboxylates **6a–e** in very good yields (Scheme 5). The formation of benzophenoxazine **6a** is regioselective due to the hydrogen bonding (carboxylate function with the adjacent amine, SI). Under these conditions, the use of 2-aminothiophenol is futile. The phenoxazine derivatives were fully characterized using IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopies. The structure of **6a** was further confirmed using single-crystal X-ray diffraction analysis. This work also represents the first example for the construction of benzophenoxazine in one pot.

In summary, we have developed a novel method for the synthesis of three heterocyclic compounds such as benzophenazines, quinoxalines, and phenoxazines from benzoxepine in

Scheme 5. Synthesis of Benzophenoxazine-6-carboxylate Derivatives 6a–e[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), and $Bi(OTf)_3$ (5 mol %) or AcOH (1.5 equiv) in toluene (4.0 mL) under reflux. [b]Isolated yield.

one pot by C–C, C–N, and C–O bond-forming reactions. Due to the importance of these heterocyclic compounds especially in pharmaceutical and medicinal chemistry, the present protocol can be further extended for the synthesis of various biologically important heterocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data of the products, copies of ^{1}H and ^{13}C NMR spectras and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chinaraju@iict.res.in.

Notes

The authors declare no competing financial interest.

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