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First I_2–K_2CO_3-promoted sequential C–N and C–O bond forming approach for one-pot synthesis of 1,4-benzoxazines

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ABSTRACT

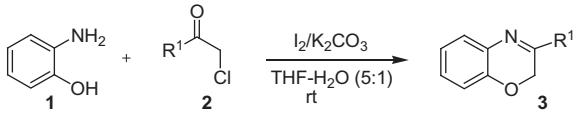
I_2–K_2CO_3 combination has been found to be an efficient, reusable, and inexpensive catalyst system for the one-pot synthesis of 3-aryl-2*H*-benz[1,4]oxazine via rapid C=N and C–O bond formation. No by-product formation, operational simplicity, ambient temperature, and high yield (85–94%) are the attractive features of the envisaged reaction. The reported one-pot synthesis of 1,4-benzoxazine involves the application of I_2–K_2CO_3 catalyst system for the first time and proceeds via in situ imine formation followed by intramolecular ring transformation cascades.

Benzoxazines have been a vital part of molecular skeletons for design of a variety of biologically active compounds.[1,2] These compounds are valuable building blocks for the synthesis of more complex derivatives ranging from herbicides and fungicides to some natural products.[3] Several benzoxazinone derivatives have been reported to be potassium channel openers in vascular smooth muscle. Photochemical transformation and other derivatization of benzoxazines to other heterocyclic structures and chiral intermediates,[4] play a lead role for the synthesis of many pharmaceutical compounds. For example, levofloxacin, an active antibacterial drug contains this structural motif.[5] Therefore, their synthesis has attracted much attention in recent years and many versatile methodologies being the result of active studies for the synthetic development of benzoxazines have been carried out.[6–11]

The Literature reports various routes to substituted benzoxazines which include mainly cyclocondensation of aminophenols with suitable dihalo derivatives,[7] intramolecular copper-catalyzed O-arylation of β-aminoalcohols,[8] and epoxide opening of aminoalcohols followed by cyclocondensation.[9] Notably, alternative methods other than cyclocondensation include alkylation of *o*-nitrophenol with haloester followed by reductive cyclization[10] and epoxide opening with *o*-halosulfonamides followed by cyclization.[11] Furthermore, Heravi et al. had disclosed recently a new method for the synthesis of 1,4-benzoxazines by the condensation of *o*-aminophenols and 2-bromo-1-aryl ethanones using $HClO_4$-SiO_2 as catalyst at reflux temperature.[6c] However, all of the reported methods suffer from one or more disadvantages such as higher reaction temperature, longer reaction time, and lower yields. Thus, development of more convenient and green protocol for the synthesis of benzoxazines is highly required.

In view of the above valid points, we disclose herein, the first report on molecular iodine/K_2CO_3-catalyzed one-pot synthesis of 1,4-benzoxazines via sequential C=N and C - O bond formation. The reported reaction for the target 1,4-benzoxazine **3** involved the stirring of a mixture of *o*-aminophenol **1** and α-haloketones **2** in the presence of molecular iodine and K_2CO_3 as catalyst system (Scheme 1). Herein, the molecular iodine in the presence of potassium carbonate has been found to be an efficient, eco-friendly, readily available, and cost effective catalyst-system for the synthesis of target 1,4-benzoxazine. Iodine being a mild Lewis acid as well as an oxidant has been used in many organic transformations and in organic synthesis.

In our preliminary experimentation, we investigated the optimization of reaction conditions with regard to both catalyst and solvent. Here, *o*-aminophenol **1** and 2-chloro-1-phenylethanone



Scheme 1. Synthesis of benzoxazinones **3** from *o*-aminophenol **1** and α-haloketone **2**.

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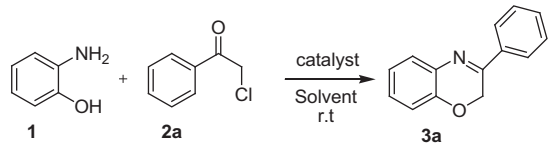
Table 1
Optimization of the reaction conditions for one-pot synthesis of 1,4-benzoxazine **3a**[a]



Entry	Catalyst (mol %)	Base	Time (h)[b]	Solvent	Yield (%)[c]
1	I_2 (10)	K_2CO_3	8	THF–H_2O	92
2	$CuCl_2.2H_2O$ (10)	K_2CO_3	8	THF–H_2O	57
3	$CeCl_3$ (10)	K_2CO_3	8	THF–H_2O	59
4	$CeCl_3.7H_2O$ (10)	K_2CO_3	8	THF–H_2O	63
5	I_2 (5)	K_2CO_3	8	THF–H_2O	68
6	I_2 (15)	K_2CO_3	8	THF–H_2O	92
7	I_2 (10)	Na_2CO_3	8	THF–H_2O	71
8	I_2 (10)	$NaHCO_3$	8	THF–H_2O	69
9	I_2 (10)	K_2CO_3	8	THF	77
10	I_2 (10)	K_2CO_3	8	CH_2Cl_2	74
11	I_2 (10)	K_2CO_3	8	CH_3CN	71
12	I_2 (10)	K_2CO_3	8	THF–Bu^{t}OH	86
13	I_2 (10)	K_2CO_3	8	THF–MeOH	81
14	I_2 (10)	—	8	THF–H_2O	—
15	—	K_2CO_3	8	THF–H_2O	—

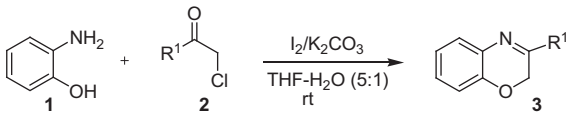
[a] The reaction was performed using *o*-aminophenol **1** (1 equiv) and **2a** (1 equiv) with I_2 (10 mol %) and K_2CO_3 (3 equiv) at rt.
[b] Time taken to complete the reaction.
[c] Yield of isolated pure product **3a**.

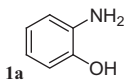
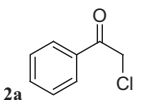
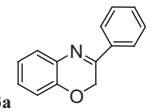
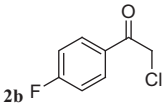
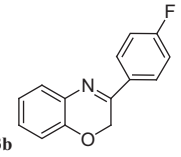
(**2a**) were chosen as model substrates for the synthesis of representative 1,4-benzoxazine **3a** and the reaction was performed at room temperature under a positive pressure of nitrogen (Table 1). Several catalysts were tested under the present reaction condition and I_2 with K_2CO_3 was found to be the most efficient catalyst among $CuCl_2$. $2H_2O$, $CeCl_3$ and $CeCl_3$. $7H_2O$ (Table 1, entries 1–4). The optimum loading for the I_2 was found to be 10 mol % together with K_2CO_3 (Table 1, entries 1, 5 and 6). When the amount of I_2 was decreased from 10 to 5 mol% relative to substrate **1**, the yield of the target 1,4-benzoxazine **3a** reduced (Table 1, entries 1 and 5), but the use of 15 mol% of I_2 did not enhance the yield (Table 1, entries 1 and 6). The reaction did not occur in the absence of either iodine (Table 1, entry 15) or K_2CO_3 (Table 1, entry 14). Different inorganic bases were tested viz., K_2CO_3, Na_2CO_3 and $NaHCO_3$ and the best result was obtained by using K_2CO_3 (Table 1, entries 1, 7 and 8). Next, optimization of the solvent for the synthesis of **3a** was also investigated by employing the I_2/K_2CO_3 catalyst system. Different solvents (THF, CH_2Cl_2, CH_3CN, THF–H_2O and THF–Bu^{t}OH, THF–methanol) were examined and better results were obtained using THF in combination with protic polar solvents (Table 1, entries 1, 12 and 13) as compared to those aprotic polar solvents (Table 1, entries 10 and 11), but the best yield was obtained with THF–H_2O solvent system (Table 1, entry 1). Thus THF–H_2O (5:1) solvent system was used throughout the reaction. Substrate scope investigations revealed that a variety of α-haloketone **2** reacted smoothly with different *o*-aminophenol **1** to afford the corresponding target 1,4-benzoxazines **3** in excellent yield (Table 2) with highest yield of 94% (Table 1, entry 5). Thus, the optimized synthesis involved by stirring a mixture of *o*-aminophenol **1** (1 equiv), α-haloketones **2** (1 equiv), I_2 (10 mol%), and K_2CO_3 (3 equiv) in 5 mL of THF–H_2O at room temperature for 7–8 h under a nitrogen atmosphere affording the target compound 1,4-benzoxazine **4** in excellent yields (Table 2).

A plausible mechanism for the formation of 1,4-benzoxazine **3** is depicted in Scheme 2. The new methodology involves Lewis acid catalyzed ring cyclization via dehydrohalogenation. Herein, the nitrogen of *o*-aminophenol attacks as nucleophile on carbonyl carbon of α-haloketone, followed by protonation of oxygen atom which leads to dehydration and in situ generation of imine **5**. Furthermore, nucleophilic attack of oxygen atom of *o*-aminophenol on the carbon bearing leaving halogen group of the α-haloketone results in ring-cyclization which in turn in the target 1,4-benzoxazine **3** via dehydrohalogenation. To our understanding, the more nucleophilicity of nitrogen than oxygen and subsequently the stability of in situ generated imine **5** is the main driving force for the formation of target compound **3** as the depicted reaction pathway in Scheme 2. Presumably, iodine plays a key role in the reaction in the imine formation and ring cyclization step by polarizing the carbonyl group of the substrate, thereby enhancing the electrophilicity of the carbonyl carbon, which facilitates the nucleophilic attack of nitrogen of *o*-aminophenol. All the reactions were clean and the products were characterized by their IR, ^1H and ^{13}C NMR spectroscopic data and further confirmed by comparison of their mp, TLC, IR, and ^1H, ^{13}C NMR data with authentic samples obtained commercially or prepared by the literature methods.[6,12]

In summary, we have developed a novel method for the preparation of 1,4-benzoxazines catalyzed by molecular iodine in conjunction with potassium carbonate. The present protocol involves

Table 2
One pot synthesis of 1,3-oxazines **3**[a]



Entry	Aminophenol **1**	α-Haloketone **2**	Reaction time (h)[b]	1,4-Benzoxazine **3**	Yield (%)[c,d]
1	 **1a**	 **2a**	8	 **3a**	92
2	**1a**	 **2b**	7	 **3b**	85

(*continued on next page*)

Table 2 (*continued*)

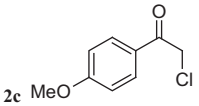
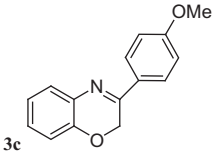
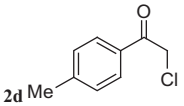
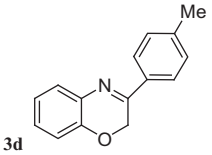
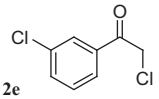
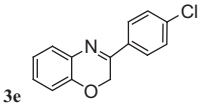
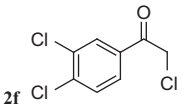
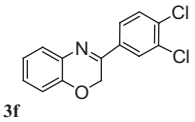
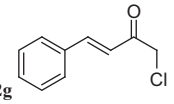
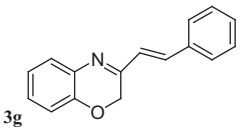
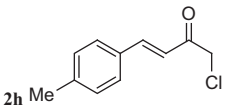
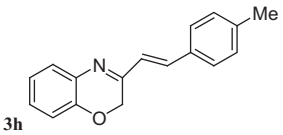
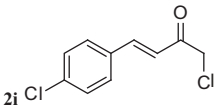
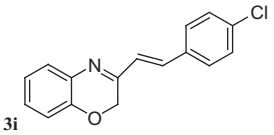
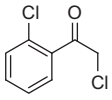
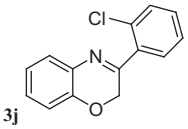
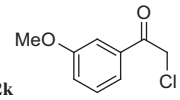
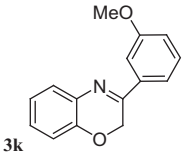
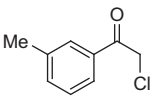
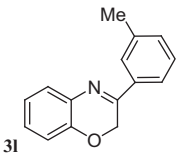
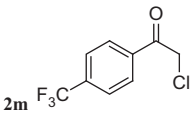
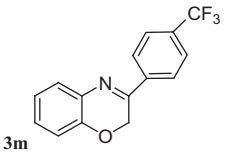
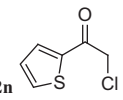
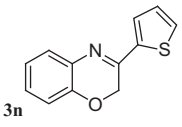
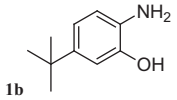
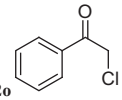
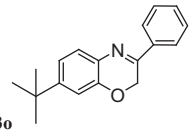
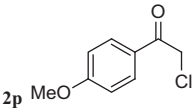
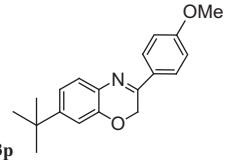
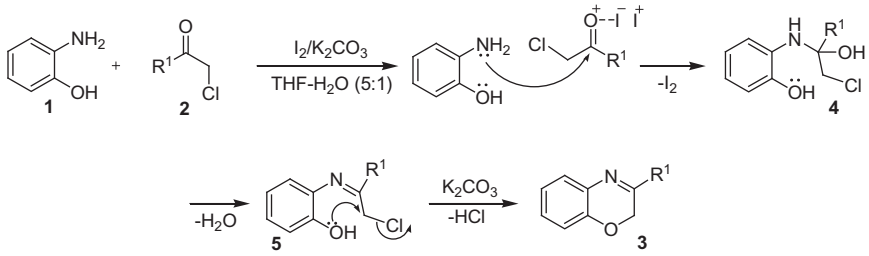
Entry	Aminophenol **1**	α-Haloketone **2**	Reaction time (h)[b]	1,4-Benzoxazine **3**	Yield (%)[c,d]
3	**1a**	 **2c**	7.5	 **3c**	92
4	**1a**	 **2d**	8	 **3d**	90
5	**1a**	 **2e**	7	 **3e**	94
6	**1a**	 **2f**	7.5	 **3f**	92
7	**1a**	 **2g**	7.5	 **3g**	89
8	**1a**	 **2h**	8	 **3h**	91
9	**1a**	 **2i**	8	 **3i**	90
10	**1a**	 **2j**	8	 **3j**	89
11	**1a**	 **2k**	8	 **3k**	91
12	**1a**	 **2l**	8	 **3l**	89
13	**1a**	 **2m**	7.5	 **3m**	90
14	**1a**	 **2n**	8	 **3n**	92

Table 2 (*continued*)

Entry	Aminophenol **1**	α-Haloketone **2**	Reaction time (h)[b]	1,4-Benzoxazine **3**	Yield (%)[c,d]
15	 **1b**	 **2o**	8	 **3o**	91
16	**1b**	 **2p**	8	 **3p**	89

[a] See Experimental Section for general procedure [13].
[b] Time required for completion of the reaction.
[c] Yield of isolated and purified product.
[d] All the compounds synthesized are known. [6,12].



Scheme 2. A plausible mechanism for dehydrohalogenation, C–N, and C–O bond formation to synthesize 1,4-benzoxazines.

simple operation at ambient temperature to give high yields of the products in a one-pot procedure and would be a practical alternative to the existing procedures for the synthesis of such kind of fine chemicals.

References and notes

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13. *General procedure for the synthesis of 1,4-benzoxazine* ***3****:* A flame-dried round bottom flask was charged with *o*-aminophenol **1** (1 equiv), 2-chloro-1-phenylethanone **2** (1 equiv), and I_2 (0.1 mmol) in 5 mL of THF/H_2O (5:1) under positive pressure of nitrogen followed by addition of K_2CO_3 (3 equiv). The resulting solution was stirred for 7–8 h at room temperature (Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was quenched with satd aq Na_2SO_3 until the iodine color almost disappeared and was extracted with $CHCl_3$. The organic layer was washed with satd aq $NaHCO_3$ and brine, and dried over Na_2SO_4. Then the combined organic layer was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (10:1) as eluent to afford analytically pure sample of **3**. The structure of products was confirmed by comparison of their mp, TLC, IR, and ^1H, ^{13}C NMR data with authentic samples obtained commercially or prepared by the literature methods.[6,12] Physical data of representative compound. Compound **3c**: yellow solid, mp 130–132 °C, 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 5.01 (s, 2H), 6.92 (d, J = 8.0 Hz, 1H), 7.09–7.15 (m, 2H), 7.19 (t, J = 5.9 Hz, 1H), 7.32–7.40 (m, 3H), 7.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.4, 73.9, 113.2, 115.4, 116.9, 122.1, 123.5, 124.7, 127.9, 128.9, 134.7, 139.8, 153.2, 161.4, 164.7. EIMS (m/z): 239 (M^+). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 6.27. Found: C, 75.00; H, 5.80; N, 5.56. *Compound* ***3d****:* yellow solid, mp 136–139 °C, 90% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 5.09 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.26–7.38 (m, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.2, 73.1, 115.9, 122.4, 123.6, 126.7, 128.0, 129.1, 130.2, 131.5, 133.7, 139.0, 140.1, 152.6, 164.3. EIMS (m/z): 223 (M^+). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 81.05; H, 5.56; N, 6.05. *Compound* ***3m****:* yellow solid, mp 164–166 °C, 90% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.07 (s, 2H), 6.99 (d, J = 8.1 Hz, 1H), 7.04 (t, J = 7.9 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.5, 115.6, 121.9, 123.1, 124.6, 125.5, 126.9, 128.4, 129.7, 130.9, 132.7, 137.4, 139.8, 152.1, 164.1. EIMS (m/z): 277 (M^+). Anal. Calcd for $C_{15}H_{10}F_3NO$: C, 64.98; H, 3.64; N, 5.05. Found: C, 64.77; H, 4.00; N, 5.33. *Compound* ***3p****:* yellow solid, mp 143–145 °C, 89% yield. ^1H NMR (400 MHz, CDCl3) δ: 1.38 (s, 9H), 5.01 (s, 2H), 6.90 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.44 (t, J = 1.9 Hz, 4H), 7.90–7.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.7, 31.9, 32.8, 40.5, 73.9, 115.6, 120.4, 123.9, 127.9, 129.0, 129.9, 131.1, 132.5, 134.2, 139.0, 143.6, 149.7, 164.8. EIMS (m/z): 265 (M^+). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.78; H, 7.48; N, 5.05.