Palladium-Catalyzed, Microwave-Assisted Synthesis of 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazines: An Improved Catalytic System and Multicomponent Process

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Abstract: An improved palladium-catalyzed system is established for the synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines from less reactive ethyl 2-(2-chlorophenoxy)alkanoates and aryl amines under controlled microwave heating, employing 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) as the ligand. Moreover, a high-yielding, three-component reaction protocol is disclosed for the efficient one-pot synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines from 2-halophenols, ethyl 2-bromoalkanoates, and aryl amines. Microwave heating at high temperature is necessary to achieve high yields with 2-chlorophenol. A wide range of substrates is tolerated affording the desired products in good to excellent yields.

Key words: multicomponent reactions, microwave irradiation, palladium-catalyzed, 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines, cascade process

Diversity-oriented synthesis of small organic molecules with biological activity is a technique of great value for drug discovery.[1] With the development of high-throughput screening technology,[2] the efficient preparation of libraries of analogues of bioactive small molecules is possible. Hence, the search for novel strategies to improve synthetic efficiency and increase structural variation is very important in organic synthesis. For such purposes, multicomponent reactions (MCRs)[3] are recognized as valuable tools, as they can incorporate a large degree of diversity into molecular scaffolds, from simple and readily available building blocks, in a single synthetic step. Moreover, multicomponent procedures do not necessitate the isolation of intermediates, and introduce all or most of the atoms originating from three or more starting materials into the newly formed products, making the strategy significantly more efficient and economic compared to their multistep alternatives. Furthermore, both synthetic efficiency and yield can be improved greatly by using microwave irradiation,[4] particularly for transition-metal-catalyzed transformations. Thus, the development of new, metal-catalyzed multicomponent reactions under microwave irradiation for accessing privileged heterocycles has attracted the attention of synthetic chemists.[5]

We are interested in the 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffold as it represents a privileged, drug-like, heterocyclic skeleton,[6] which is often present in bioactive natural products.[7] A variety of approaches have been established to access this heterocyclic system.[8] These include, amongst others, the use of 2-aminophenols[9] or 2-nitrophenols[10] as starting materials, a copper–palladium-catalyzed tandem O-alkylation–amidation sequence,[11] palladium-catalyzed intramolecular O-arylation,[12] and a tandem Ugi four-component Mitsunobu cyclization.[13] However, a common limitation of these approaches was the adoption of a stepwise synthetic sequence, which had a dramatic influence on the synthetic efficiency. Moreover, in the corresponding metal-catalyzed protocols, only aryl iodides and bromides were employed,[11a,b,12] and we found that aryl chlorides provided the desired products in far lower yields due to their poor reactivity.[11c] We previously disclosed an efficient one-pot synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines employing an Ugi four-component reaction sequence, followed by base-mediated O-alkylation.[14] However, this procedure was stepwise and the substitution diversity was limited. We have also reported that 2-alkyl-4-aryl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **1** could be synthesized efficiently from ethyl 2-(2-halophenoxy)alkanoates **2** and aryl amines through a sequence involving palladium–(±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene [(±)-BINAP] catalyzed intermolecular amination and spontaneous thermal intramolecular amidation (Scheme 1).[15] This protocol had three disadvantages: 1) the starting ethyl 2-(2-halophenoxy)alkanoates **2** had to be prepared in advance from 2-halophenols **3** and ethyl 2-bromoalkanoates **4** in *N*,*N*-dimethylformamide in the presence of potassium carbonate (K_2CO_3), which had a dramatic influence on the synthetic efficiency; 2) when ethyl 2-(2-chlorophenoxy)alkanoates were employed, only a moderate yield (up to 45%) could be achieved;[15] 3) the reaction time was long (up to 24 h). Therefore, a more efficient protocol for accessing 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **1** is desirable.

It is well known that the ligand plays a central role in palladium-catalyzed transformations. Thus we continued our research on this palladium-catalyzed cascade process with a ligand screen, and employing ethyl 2-(2-chlorophenoxy)acetate (**2a**) and 4-methylaniline as model substrates. In order to improve the synthetic efficiency, controlled microwave heating at high temperature (150 °C) was employed. The results are listed in Table 1. Palladium(II) acetate [$Pd(OAc)_2$] and (±)-BINAP were employed as the precatalyst and ligand, respectively. Af-

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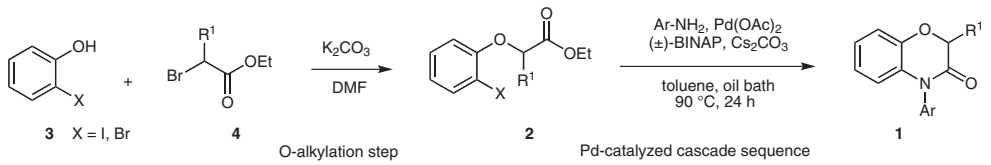
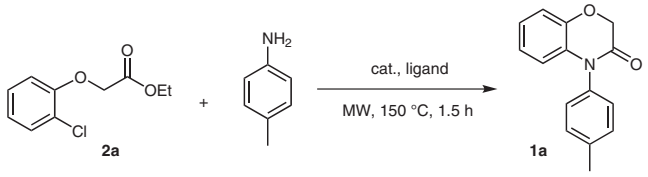


Scheme 1 Our previously reported strategy toward 2-alkyl-4-aryl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **1**

ter heating a mixture of **2a** and 4-methylaniline in toluene under microwave heating at 150 °C for 1.5 hours, the desired product, 3,4-dihydro-4-(4-methylphenyl)-3-oxo-2*H*-1,4-benzoxazine (**1a**) was obtained in a low 28% yield (Table 1, entry 1). To our delight, when the ligand was replaced with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), the yield was improved greatly, affording **1a** in an excellent 95% yield (Table 1, entry 2). Two other bidentate phosphine ligands were investigated (Xantphos and dppf), but neither was as efficient as XPhos (Table 1, entries 3 and 4).

Table 1 Optimization of the Ligand for the Synthesis of 3,4-Dihydro-4-(4-methylphenyl)-3-oxo-2*H*-1,4-benzoxazine (**1a**) under Microwave Heating[a]

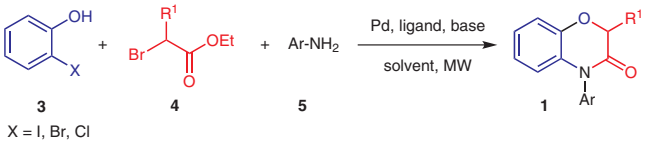


Entry	Ligand (mol%)	Yield (%)[b]
1	(±)-BINAP (10)	28
2	XPhos (20)	95
3	Xantphos (10)	71
4	dppf (10)	13

[a] Reaction conditions: ethyl 2-(2-chlorophenoxy)acetate (**2a**) (0.3 mmol), 4-methylaniline (0.45 mmol), $Pd(OAc)_2$ (10 mol%), ligand, Cs_2CO_3 (0.6 mmol), toluene (4 mL), MW, 150 °C, 1.5 h.
[b] Yield of isolated product.

Next, the generality of this more powerful catalytic system was investigated using anilines containing different substituents (Table 2). The reaction of ethyl 2-(2-chlorophenoxy)acetate (**2a**) and 3,5-dimethylaniline proceeded smoothly under the optimized conditions, affording the desired product **1b** in an excellent 95% yield (Table 2, entry 1). Anilines containing electron-withdrawing groups (CO_2Et, CF_3 and CN) tolerated these conditions, providing the corresponding products **1c**–**e** in 87%, 93% and 81% yields, respectively (Table 2, entries 2–4). Notably, when a mixture of **2a** and 4-trifluoromethylaniline was heated in an oil bath at 100 °C for 17 hours, the desired product was obtained in a slightly lower yield of 88%, indicating that microwave heating at higher temperature decreased the reaction time. Also, the reaction was compatible with an aniline containing an electron-donating group. For example, when 4-methoxyaniline was employed, the corresponding benzoxazine **1f** was obtained in 92% yield (Table 2, entry 5). In addition, the reaction of 4-trifluoromethoxyaniline and 1-naphthylamine with ethyl 2-(2-chlorophenoxy)acetate (**2a**) afforded the corresponding products **1g** and **1h** (Table 2, entries 6 and 7) in 90% and 93% yields, respectively. Interestingly, reaction of 3-aminopyridine gave the desired product **1i** in 91% yield (Table 2, entry 8).

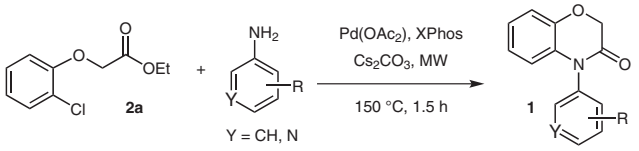
At this stage, we had established an improved catalytic system for synthesizing 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **1** from ethyl 2-(2-chlorophenoxy)acetate (**2a**), via controlled microwave heating in a significantly shorter reaction time of 1.5 hours. However, two synthetic steps were required to obtain the target molecule. We envisaged that it might be possible to perform the O-alkylation step and the subsequent palladium-catalyzed cascade sequence in one-pot to establish a three-component process from 2-halophenols **3**, ethyl 2-bromoalkanoates **4**, and aryl amines **5**, since only a base and solvent were needed for both steps (Scheme 2). If successful, the synthetic efficiency would be greatly improved. To the best of our knowledge, there have been no prior reports on a multicomponent approach for accessing 2-alkyl-4-aryl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines.



Scheme 2 A multicomponent strategy for the synthesis of 2-alkyl-4-aryl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **1**

We reasoned that the key to the success of the multicomponent process would be the compatibility of both conditions. Therefore, conditions for both the O-alkylation and palladium-catalyzed cascade process were further investigated. As shown in Scheme 3, the reaction of ethyl 2-(2-iodophenoxy)acetate (**2b**) with 4-methylaniline in toluene in the presence of palladium(II) acetate, XPhos and Cs_2CO_3 afforded the desired product, 4-(4-methylphenyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine (**1a**) in 91% yield under microwave irradiation at 150 °C for one hour. However, *N*,*N*-dimethylformamide was not a good solvent for this palladium-catalyzed cascade process as the yield decreased to 64%. To our delight, the use of toluene as the solvent and cesium carbonate (Cs_2CO_3) as the base led to smooth O-alkylation of 2-iodophenol with ethyl 2-bromoacetate, under microwave heating at 100 °C for 30 minutes, to furnish the acetate **2b** in 85% yield.

Table 2 Synthesis of 3,4-Dihydro-4-aryl-3-oxo-2*H*-1,4-benzoxazines **1** via the Microwave-Assisted, Palladium-Catalyzed Cascade Process[a]



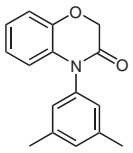
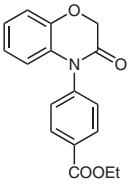
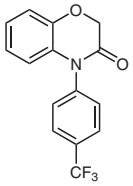
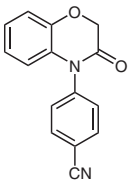
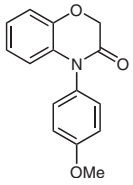
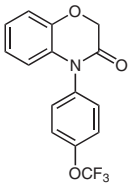
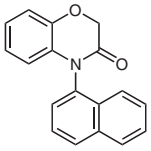
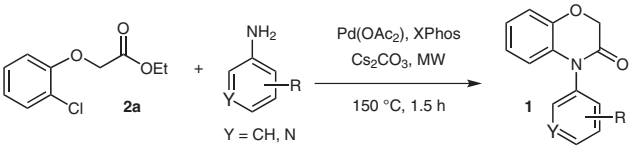
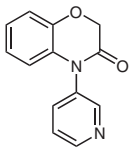
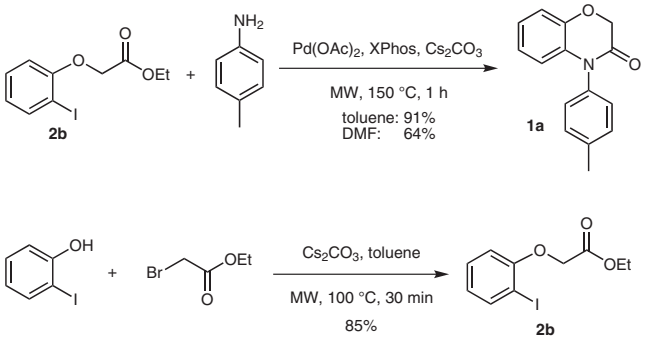
Entry	Product	Yield (%)[b]
1	**1b** 	95
2	**1c** 	87
3	**1d** 	93 (88)[c]
4	**1e** 	81
5	**1f** 	92
6	**1g** 	90
7	**1h** 	93

Table 2 Synthesis of 3,4-Dihydro-4-aryl-3-oxo-2*H*-1,4-benzoxazines **1** via the Microwave-Assisted, Palladium-Catalyzed Cascade Process[a] (continued)



Entry	Product	Yield (%)[b]
8	**1i** 	91

[a] Reaction conditions: ethyl 2-(2-chlorophenoxy)acetate (**2a**) (0.3 mmol), aryl amine (0.54 mmol), $Pd(OAc)_2$ (10 mol%), XPhos (20 mol%), Cs_2CO_3 (1.05 mmol), toluene (4.0 mL), MW, 150 °C, 1.5 h.
[b] Yield of isolated product.
[c] Reaction run in an oil bath at 100 °C for 17 h.



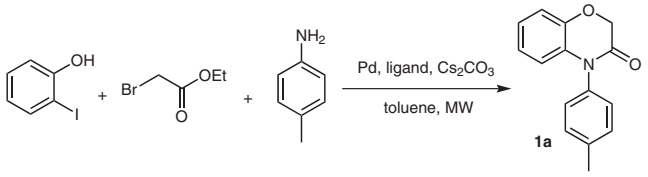
Scheme 3 Investigation of the palladium-catalyzed cascade process and O-alkylation under microwave heating

Having established the best solvent and base, the catalyst, ligand, temperature, reaction time, and catalyst loading for this three-component reaction were optimized using 2-iodophenol, ethyl 2-bromoacetate, and 4-methylaniline as model substrates. The results are summarized in Table 3. Inspired by the preliminary results obtained for the O-alkylation and palladium-catalyzed cascade processes under microwave heating, a stepwise heating approach was adopted. Thus, on heating a mixture of 2-iodophenol, ethyl 2-bromoacetate, and 4-methylaniline in the presence of palladium(II) acetate (10 mol%), XPhos (20 mol%), and cesium carbonate in toluene at 100 °C for 30 minutes, and then at 150 °C for one hour, the desired product, 4-(4-methylphenyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine (**1a**) was isolated in 35% yield (Table 3, entry 1). Gratifyingly, extending the reaction time to 90 minutes at 100 °C and then two hours at 150 °C, respectively, resulted in an improved 63% yield, along with a 31% yield of the intermediate, ethyl 2-(2-iodophenoxyl)acetate (**2b**) (Table 3,

entry 2). Further extending the reaction time and using higher loadings of palladium(II) acetate (15 mol%) and XPhos (30 mol%) led to a 95% yield of the product (Table 3, entry 3). Reducing the loadings of palladium(II) acetate and XPhos to 12 mol% and 24 mol%, respectively, did not affect the yield (94%, Table 3, entry 4). Despite the excellent yield, a total reaction time of five hours was required. Pleasingly, direct heating of the reaction mixture at 150 °C for three hours led to an excellent 96% yield of **1a** (Table 3, entry 5). Lowering the catalyst and ligand loadings to 10 mol% and 20 mol%, respectively, resulted in a slightly reduced 92% yield (Table 3, entry 6). However, further reducing the loadings of the catalyst and ligand to 5 mol% and 10 mol%, respectively, gave only a 36% yield of **1a** (Table 3, entry 7). Three bidentate phosphine ligands [(±)-BINAP, Xantphos, dppf] were screened, but none of these proved to be as efficient as XPhos (Table 3, entries 8–10). Finally, palladium(II) chloride ($PdCl_2$) and tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] were investigated as precatalysts. Palladium(II) chloride was not a good choice as only a 64% yield of product **1a** was obtained (Table 3, entry 11). On the other hand, tris(dibenzylideneacetone)dipalladium(0) proved to be an effective precatalyst providing the desired product in 93% yield (Table 3, entry 12).

With optimized conditions in hand, the generality of the process was investigated and the results are presented in Table 4. Three 2-halophenols (X = I, Br, Cl), three ethyl 2-bromoalkanoates **4** (R^1 = H, Me, Et), and various aryl amines were examined. We found that 2-iodophenol, 2-bromophenol, and even the much less reactive 2-chlorophenol were compatible, indicating that microwave heating at high temperature was beneficial for the process. Aryl amines including 4-methylaniline, aniline, and 3,5-dimethylaniline tolerated the reaction conditions, affording the corresponding products **1a**, **1m**, and **1b** in excellent yields, ranging from 92–96% (Table 4, entries 1–3). Moreover, the conditions were compatible with anilines bearing both electron-withdrawing (4-CO_2Et and 4-CF_3) and electron-donating (4-OMe) groups, furnishing the corresponding products **1c**, **1d**, and **1f** in excellent 78–97% yields (Table 4, entries 4–6). The reaction of 4-trifluoromethoxyaniline, 2-halophenols, and ethyl 2-bromoacetate proceeded smoothly, affording the benzoxazine **1g** in yields of 88–93% (Table 4, entry 7). With bulky 1-naphthylamine, slightly lower yields (78–84%) were obtained (Table 4, entry 8). Interestingly, when bulkier methyl 2-bromopropanoate was employed (Table 4, entry 9), the yield decreased dramatically to 46%. However, a slightly improved yield of 56% was achieved when the reaction mixture was first heated at 100 °C for two hours, and then at 150 °C for three hours. In contrast, reaction of more hindered ethyl 2-bromobutanoate did not afford the desired heterocycle **1k**, although the O-alkylation prod-

Table 3 Optimization of the Three-Component Approach[a]

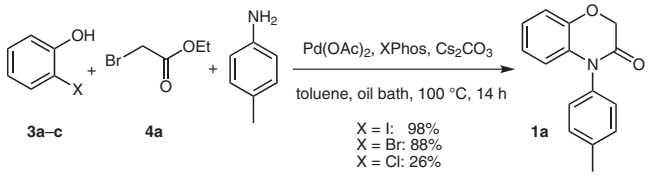


Entry	Catalyst (mol%)	Ligand (mol%)	Conditions (MW)	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	XPhos (20)	100 °C, 0.5 h, then 150 °C, 1 h	35
2	$Pd(OAc)_2$ (10)	XPhos (20)	100 °C, 1.5 h, then 150 °C, 2 h	63[c]
3	$Pd(OAc)_2$ (15)	XPhos (30)	100 °C, 2 h, then 150 °C, 3 h	95
4	$Pd(OAc)_2$ (12)	XPhos (24)	100 °C, 2 h, then 150 °C, 3 h	94
5	$Pd(OAc)_2$ (12)	XPhos (24)	150 °C, 3 h	96
6	$Pd(OAc)_2$ (10)	XPhos (20)	150 °C, 3 h	92
7	$Pd(OAc)_2$ (5)	XPhos (10)	150 °C, 3 h	36
8	$Pd(OAc)_2$ (12)	(±)-BINAP (12)	150 °C, 3 h	42
9	$Pd(OAc)_2$ (12)	Xantphos (12)	150 °C, 3 h	27
10	$Pd(OAc)_2$ (12)	dppf (12)	150 °C, 3 h	13
11	$PdCl_2$ (12)	XPhos (24)	150 °C, 3 h	64
12	$Pd_2(dba)_3$ (6)	XPhos (24)	150 °C, 3 h	93

[a] Reaction conditions: 2-iodophenol (0.3 mmol), ethyl 2-bromoacetate (0.45 mmol), 4-methylaniline (0.54 mmol), Pd catalyst, ligand, Cs_2CO_3 (1.05 mmol), toluene (4.0 mL), MW heating.
[b] Yield of isolated product.
[c] Ethyl 2-(2-iodophenoxyl)acetate (**2b**) was isolated in 31% yield.

uct, ethyl 2-(2-bromophenoxy)butanoate, was isolated in 70% yield (Table 4, entry 10). These two results indicated that the three-component process was sensitive to the size of the ethyl 2-bromoalkanoate input, which was inconsistent with our previously reported palladium-catalyzed, two-component process.[15] Interestingly, when 4-chloroaniline was employed, the unexpected dehalogenated product, 3,4-dihydro-4-phenyl-3-oxo-2*H*-1,4-benzoxazine (**1m**), instead of the desired benzoxazine **1l**, was obtained as the only heterocyclic product in a very low yield of 27% (Table 4, entry 11). As a result of the high reactivity of our catalytic system, which promotes the coupling reaction of aryl chlorides, most of the initially formed product **1l** would further react with excess 4-chloroaniline to give oligomeric materials. The dechlorinated by-product **1m** would be formed via protonolysis of the palladium(II) intermediate derived from oxidative addition of **1l** to palladium(0).

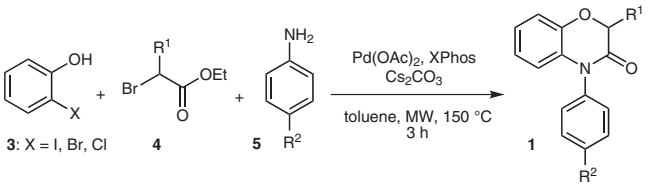
The advantages of microwave heating over conventional heating for this three-component reaction were also examined. Thus, reactions of 2-iodophenol, 2-bromophenol, and 2-chlorophenol with ethyl 2-bromoaceate and 4-methylaniline were carried out in an oil bath at 100 °C for 14 hours. The expected product **1a** was obtained in 98%, 88%, and 26% yields (Scheme 4). These results show that microwave heating at high temperature was essential to achieve high yields with 2-chlorophenol and thereby improve the synthetic efficiency.



Scheme 4 Synthesis of 3,4-dihydro-4-(4-methylphenyl)-3-oxo-2*H*-1,4-benzoxazine (**1a**) via the three-component reaction in an oil bath

In summary, an efficient palladium-catalyzed procedure has been developed for accessing 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines from less reactive ethyl 2-(2-chlorophenyl)alkanoates and amines. The use of XPhos as the ligand was found to be crucial for enhanced catalytic activity. In addition, a one-pot, three-component approach has been established for the efficient synthesis of the target heterocycles from 2-halophenols, ethyl 2-bromoalkanoates, and aryl amines. It was found that microwave heating at high temperature had significant advantages in terms of improving the synthetic efficiency and achieving high yields compared to conventional heating, particularly with 2-chlorophenol as one of the substrates. The reported protocol tolerates a broad range of substrates, provides high yields of the desired products, and should be attractive for the synthesis of libraries of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines.

Table 4 Three-Component Synthesis of 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazines under Microwave Heating[a]



3: X = I, Br, Cl 4 5 1

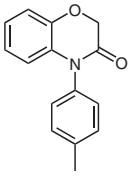
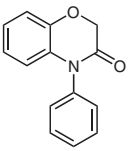
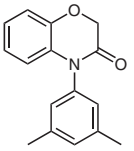
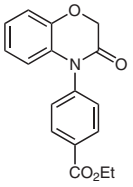
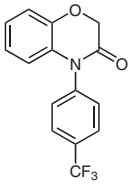
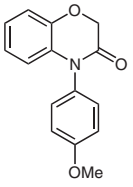
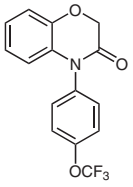
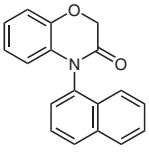
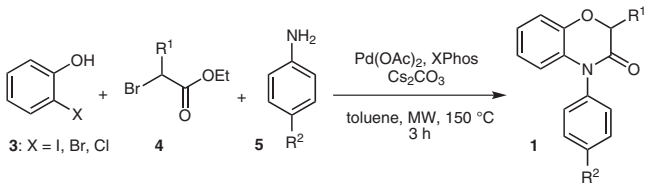
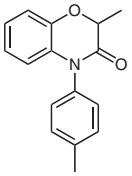
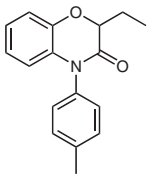
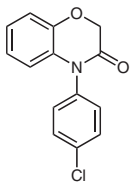
Entry	Product	Yield (%)
1	**1a** 	X = Br (96) X = Cl (93)
2	**1m** 	X = Br (96) X = Cl (92)
3	**1b** 	X = I (94)
4	**1c** 	X = I (89)[b] X = Cl (97)
5	**1d** 	X = I (95)[b] X = Br (84) X = Cl (85)
6	**1f** 	X = I (94) X = Br (78) X = Cl (95)
7	**1g** 	X = I (88)[b] X = Br (93) X = Cl (89)
8	**1h** 	X = I (79) X = Br (84) X = Cl (78)

Table 4 Three-Component Synthesis of 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazines under Microwave Heating[a] (continued)



3: X = I, Br, Cl 4 5 1

Entry	Product	Yield (%)
9	**1j** 	X = I (46) X = I (56)[b]
10	**1k** 	X = Br (0)[c]
11	**1l** 	X = Br (0)[d]

[a] Reaction conditions: 2-halophenol (0.3 mmol), ethyl 2-bromoalkanoate (0.45 mmol), aryl amine (0.54 mmol), $Pd(OAc)_2$ (10 mol%), XPhos (20 mol%), Cs_2CO_3 (1.05 mmol), toluene (4.0 mL), MW, 150 °C, 3 h.

[b] Microwave heating at 100 °C for 2 h, and then at 150 °C for 3 h.

[c] The intermediate, ethyl 2-(2-bromophenoxy)butanoate was isolated in 70% yield.

[d] The dehalogenated product, 3,4-dihydro-4-phenyl-3-oxo-2*H*-1,4-benzoxazine (**1m**), was obtained in 27% yield.

Reagents were obtained from commercial suppliers and were used as received. The extent of reaction was monitored by thin-layer chromatography on Yantai silica gel plates (60 F-254), and samples were made visual using UV light or 7% ethanolic phosphomolybdic acid with heating. Flash column chromatography was performed using Qingdao Haiyang silica gel (300–400 mesh). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reactions were heated using a Biotage Initiator 2.5 microwave reactor. IR spectra were obtained using a Nicolet 6700 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively) with residual $CHCl_3$ as the internal reference. Mass spectra (ESI+) were measured using Thermo Fisher Scientific LCQ Sheet instrumentation. Elemental analysis was performed using a Euro Vector EA3000 analyser. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; dppf = 1,1′-bis(diphenylphosphino)ferrocene.

3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazines 1; General Procedure

To a pressure-safe vial (10 mL) containing a magnetic stir bar were added a 2-halophenol (0.3 mmol), an ethyl 2-(2-halophenoxy)alkanoate (0.45 mmol), an aryl amine (0.54 mmol), Cs_2CO_3 (1.05 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 10 mol%), and XPhos (28.5 mg, 0.06 mmol, 20 mol%). The vial was then sealed with a silicon cap, evacuated and back-filled with N_2 through the cap (this procedure was repeated several times), and anhyd degassed toluene (4 mL) was added via a syringe (through the cap). The resulting mixture was heated at 150 °C for 3 h under microwave irradiation. After cooling, the mixture was filtered through Celite and the filter-bed was rinsed with EtOAc. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography on silica gel [EtOAc–PE (60–90 °C)] to afford the corresponding 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine. The yields of the products are given in Table 4.

3,4-Dihydro-4-(4-methylphenyl)-3-oxo-2*H*-1,4-benzoxazine (1a)[11a]

Yield: 68.8 mg (96%); white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.05 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.00 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.86 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.47 (dd, *J* = 8.0, 1.6 Hz, 1 H), 4.79 (s, 2 H), 2.44 (s, 3 H).

3,4-Dihydro-4-(3,5-dimethylphenyl)-3-oxo-2*H*-1,4-benzoxazine (1b)[15]

Yield: 71.3 mg (94%); yellowish amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (s, 1 H), 7.05 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.00 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.91 (s, 2 H), 6.87 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.47 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.78 (s, 2 H), 2.38 (s, 6 H).

3,4-Dihydro-4-(4-ethoxycarbonylphenyl)-3-oxo-2*H*-1,4-benzoxazine (1c)[11a]

Yield: 86.4 mg (97%); white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 1 H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 1 H), 6.88 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 4.79 (s, 2 H), 4.43 (q, *J* = 6.8 Hz, 2 H), 1.43 (t, *J* = 6.8 Hz, 3 H).

3,4-Dihydro-3-oxo-4-(4-trifluoromethylphenyl)-2*H*-1,4-benzoxazine (1d)[11a]

Yield: 83.5 mg (95%); white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.10 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.05 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.92–6.88 (m, 1 H), 6.44 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.79 (s, 2 H).

4-(4-Cyanophenyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine (1e)

Yield: 60.7 mg (81%); yellowish solid; R_f = 0.45 (25% EtOAc–hexane).

IR (KBr) 1686, 1498, 1372, 1299, 1058, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.8 Hz, 2 H), 7.10 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.06 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.92 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.44 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.78 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 145.3, 140.1, 133.8, 129.8, 124.9, 122.9, 118.0, 117.5, 116.9, 112.6, 68.2.

MS (ESI+): *m*/*z* (%) = 251 (50) $[M + H]^+$, 274 (100).

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.70; H, 4.27; N, 10.52.

3,4-Dihydro-4-(4-methoxyphenyl)-3-oxo-2*H*-1,4-benzoxazine (1f)[11a]

Yield: 72.7 mg (95%); white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.4 Hz, 2 H), 7.07–7.05 (m, 3 H), 7.00 (dd, *J* = 8.0, 8.0 Hz, 1 H), 6.87 (dd, *J* = 8.0, 8.0 Hz, 1 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 4.78 (s, 2 H), 3.88 (s, 3 H).

3,4-Dihydro-3-oxo-4-(4-trifluoromethoxyphenyl)-2*H*-1,4-benzoxazine (1g)[15]
Yield: 86.2 mg (93%); yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 4 H), 7.08 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.03 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.90 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1 H), 6.45 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.79 (s, 2 H).

3,4-Dihydro-4-(naphth-1-yl)-3-oxo-2*H*-1,4-benzoxazine (1h)[11c]
Yield: 69.3 mg (84%); yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 7.6 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.56–7.47 (m, 3 H), 7.11 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.99 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.76 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.23 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.91 and 4.84 (ABq, *J* = 15.2, 15.2 Hz, 2 H).

3,4-Dihydro-3-oxo-4-(3-pyridinyl)-2*H*-1,4-benzoxazine (1i)[11a]
Yield: 61.7 mg (91%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.4 Hz, 1 H), 8.59 (s, 1 H), 7.68 (ddd, *J* = 8.0, 2.0, 1.6 Hz, 1 H), 7.50 (dd, *J* = 8.0, 4.8 Hz, 1 H), 7.08 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.03 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.89 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.43 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.78 (s, 2 H).

3,4-Dihydro-2-methyl-4-(4-methylphenyl)-3-oxo-2*H*-1,4-benzoxazine (1j)[11a]
Yield: 42.5 mg (56%); white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.99 (dd, *J* = 7.2, 7.2 Hz, 1 H), 6.86 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.45 (d, *J* = 8.0 Hz, 1 H), 4.81 (q, *J* = 6.8 Hz, 1 H), 2.44 (s, 3 H), 1.66 (d, *J* = 6.8 Hz, 3 H).

3,4-Dihydro-3-oxo-4-phenyl-2*H*-1,4-benzoxazine (1m)[11a]
Yield: 64.8 mg (96%); white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 2 H), 7.51–7.47 (m, 1 H), 7.32–7.30 (m, 2 H), 7.07 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.01 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H), 6.87 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 6.45 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.80 (s, 2 H).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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