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Microwave-assisted one-pot synthesis of benzo[*b*][1,4]oxazin-3(4*H*)-ones via Smiles rearrangement

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Abstract

An efficient method for the synthesis of benzo[*b*][1,4]oxazin-3(4*H*)-ones via Smiles rearrangement using a microwave-assisted one-pot, three-step reaction has been developed. Various benzo[*b*][1,4]oxazin-3(4*H*)-ones are obtained in good yields (55–86%) from the corresponding substituted 2-chlorophenols and primary amines in short reaction time (18–40 min).

Benzo[1,4]oxazin-3(4*H*)-one derivatives are one of the important classes of heterocyclic compounds and have shown to exhibit a wide range of biological activities such as anti-inflammatory, antiulcer, antipyretic, antihypertensive, antifungal, as receptor antagonists, potassium channel modulators, antirheumatic agents and antihypertensive agents.[1–9] Hence, the synthesis of this class of compounds has been attracted by several synthetic organic chemists. Most of the available methods in the literature involve the use of either substituted 2-aminophenols or 2-nitrophenols as starting materials, which were transformed to benzo[1,4]oxazin-3(4*H*)-one scaffold by the stepwise sequential reactions.[10,11] For example, in the case of 2-aminophenol, which was initially treated with 2-haloalkanoyl chloride or bromide to form 2-amidophenols, which then underwent a base mediated intramolecular O-alkylation under heating condition. Later, a few one-pot methods have been developed using the same starting materials.[12] However, the use of these starting materials is limiting the diversity of the products based on their availability. Recently, Yuan and co-workers have used 1,5-difluoro-2,4-dinitrobenzene as a starting material for the synthesis of a diverse benzo[1,4]-oxazin-3-one-based compounds.[13] In contrast to these existing methods, we herein described an efficient one-pot method for the synthesis of benzo[1,4]oxazin-3(4*H*)-one derivatives using 2-chlorophenols as starting materials. This one-pot reaction proceeds via a three-step sequence involving Smiles rearrangement[14] to provide the desired products in good yields.

The concept of our process, illustrated in Scheme 1, is based on using simple starting materials, such as substituted 2-chlorophenol (**1**), 2-chloroacetyl chloride and primary amine (**2**), to form a ring system (**3**) under microwave irradiation (MW). The commercial availability of such starting materials makes this approach sufficiently diversity oriented, thus fulfilling the recent demand for the generation of large combinatorial chemical libraries. Moreover, this novel one-pot three-step reaction provides a quick and efficient entry to functionalized benzo[1,4]oxazin-3(4*H*)-one derivatives of biological interest.

In view of the high efficiency of Cs_2CO_3 in our earlier work on the synthesis of the titled compounds,[15] we have chosen it as a base to perform this one-pot reaction[16] and the results are summarized in Table 1. We first examined

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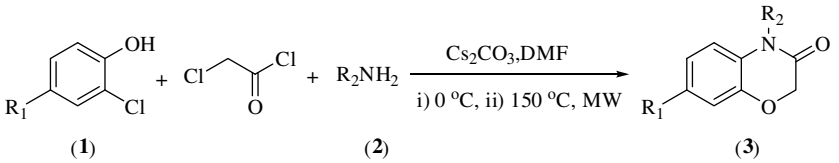


R_1= Cl, Br, F
R_2= alkyl, aryl

Scheme 1. One-pot synthesis of benzo[1,4]oxazin-3(4*H*)-ones.

Table 1
One-pot synthesis of benzo[1,4]oxazin-3(4*H*)-one derivatives[a]

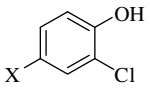
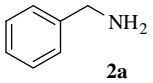
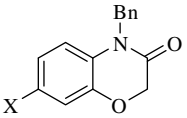
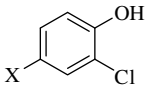
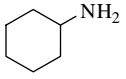
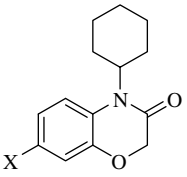
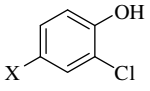
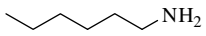
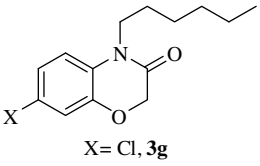
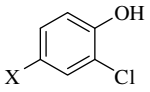
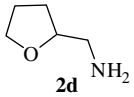
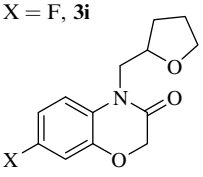
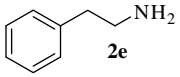
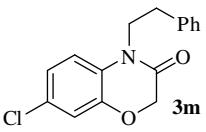
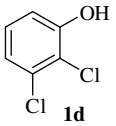
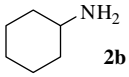
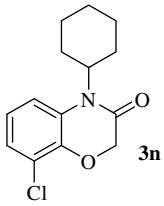
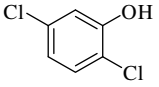
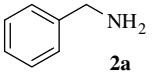
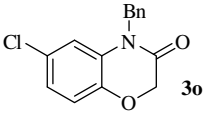
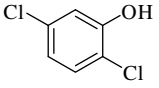
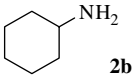
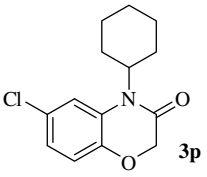
Entry	Phenol	Amine	Product[b]	Time (min)	Yield[c] (%)
1	 X= Cl, **1a**	 **2a**	 X= Cl, **3a**	28	70
2	X = Br, **1b**	**2a**	X = Br, **3b**	18	70
3	X = F, **1c**	**2a**	X = F, **3c**	35	64
4	 X= Cl, **1a**	 **2b**	 X= Cl, **3d**	18	72
5	X = Br, **1b**	**2b**	X = Br, **3e**	35	70
6	X = F, **1c**	**2b**	X = F, **3f**	30	86
7	 X= Cl, **1a**	 **2c**	 X= Cl, **3g**	30	75
8	X = Br, **1b**	**2c**	X = Br, **3h**	35	65
9	X = F, **1c**	**2c**	X = F, **3i**	35	78
10	 X= Cl, **1a**	 **2d**	 X= Cl, **3j**	30	80
11	X = Br, **1b**	**2d**	X = Br, **3k**	40	72
12	X = F, **1c**	**2d**	X = F, **3l**	25	82
13	**1a**	 **2e**	 **3m**	25	86
14	 **1d**	 **2b**	 **3n**	25	75

Table 1 (*continued*)

Entry	Phenol	Amine	Product[b]	Time (min)	Yield[c] (%)
15	 **1e**	 **2a**	 **3o**	30	55
16	 **1e**	 **2b**	 **3p**	35	62

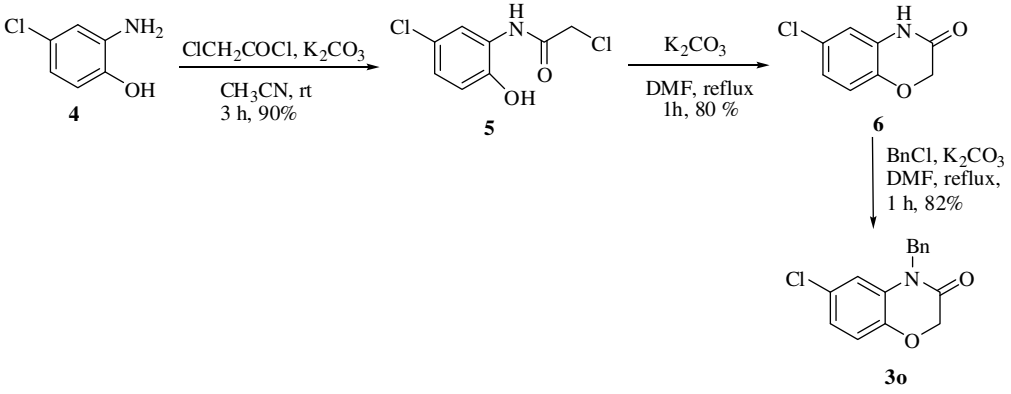
[a] Reaction conditions: $ClCH_2COCl$, Cs_2CO_3, (i) 0 °C; (ii) 150 °C, MW.
[b] All the products were characterized by mp, MS, ^1H and ^{13}C NMR spectra.
[c] Isolated yields after column purification.

the reaction of 2,4-dichlorophenol **1a** with chloroacetyl chloride and benzyl amine **2a** in the presence of Cs_2CO_3 under microwave irradiation at 150 °C for 28 min to obtain the desired benzo[1,4]oxazin-3(4*H*)-one **3a** in 70% yield (entry 1). This result encouraged us to explore the reactivity of other 2-chlorophenol substrates **1b** and **1c** with benzyl amine **2a** independently in the presence of chloroacetyl chloride and Cs_2CO_3 under microwave irradiation to yield the corresponding products **3b** and **3c** (entry 2 and 3). After this success, a few other amines viz., cyclohexyl amine **2b**, *n*-hexyl amine **2c** and tetrahydrofurfuryl amine **2d** were also treated with chloroacetyl chloride and 2-chlorophenols **1a**, **1b** and **1c** in the presence of Cs_2CO_3 under microwave irradiation and it was found that the transformation proceeded well to give the desired products **3d** to **3l** in good yields (entries 4–12). The synthesis of benzo[1,4]oxazin-3(4*H*)-ones **3m** to **3p** from the corresponding 2-chlorophenol and amine was also successful using the present protocol (entries 13–16). The GC–MS spectra of the all the products clearly indicated the formation of the corresponding product and IR, ^1H and ^{13}C NMR spectra further confirmed the structures of benzo[1,4]oxazin-3(4*H*)-ones **3a**–**p**.

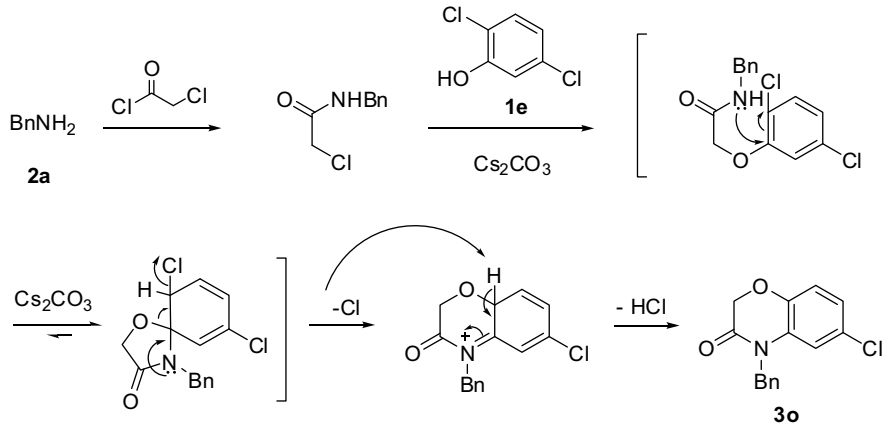
The formation of benzo[1,4]oxazin-3(4*H*)-one product **3o** was confirmed by synthesizing it from the reaction of 4-chloro-2-amino phenol **4** with 2-chloroacetyl chloride using a known stepwise method (Scheme 2). 2-Chloroacetyl chloride was reacted with **4** to afford the intermediate **5**, which was cyclized to afford **6**. Compound **6** was then treated with benzyl chloride to furnish compound **3o**. Product **3o** obtained by two different synthetic routes, that is, from aminophenol **4** (Scheme 2) and from 2,5-dichlorophenol **1e** (Scheme 1) was compared using physical and spectral data. R_f value (TLC), melting point, GC–MS and NMR spectral data of the two compounds were found to be the same.

A mechanistic rationalization for this reaction is provided in Scheme 3 (exemplified by **3o**). The cyclization of O-alkylated product by Smiles rearrangement occurred via two steps: the spiro-type intermediate was formed in the first step, and was rearranged in the second step with the loss of HCl yielding compound **3o**.

In summary, we have developed a one-pot, three-step synthesis of benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives of potential synthetic and pharmacological interest assisted by microwave irradiation via Smiles rearrangement. The use of simple starting materials and short reaction time are the notable advantages of this method, which may find applications in the synthesis of diversified benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives.



Scheme 2. Alternative route for the synthesis of **3o**.



Scheme 3. Proposed mechanism.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.120.

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16. *General experimental procedure*: To a magnetically stirred solution of the appropriate amine **2** (1.0 mmol) and Cs_2CO_3 (3.6 mmol) in dry DMF (10 mL) cooled by ice bath, were added chloroacetyl chloride (1.1 mmol) and **1** (0.8 mmol). The reaction mixture was then placed into microwave oven (KMIC-1.5 kW) at 150 °C and irradiated for the period listed in Table 1. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and the residue was poured into water (20 mL). The aqueous solution was then extracted by ethyl acetate (4 × 30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain the crude product which was purified by column chromatography (silica gel) to afford the desired pure compound. *Spectral data of the selected product* (**3b**): White solid, mp: 116–118 °C; IR (ν cm^{-1}): 3078, 3032, 3001, 2951, 2901, 1688, 1585, 1501, 1496, 1412, 1362, 1291, 1242, 1192, 1143, 1085, 1042, 880, 870, 853, 794, 734, 704, 534; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (s, 2H), 5.13 (s, 2H), 6.72 (d, $J = 8.8$ Hz, 1H), 7.00 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.14 (d, $J = 2.0$ Hz, 1H), 7.21–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.0, 67.7, 116.1, 116.9, 120.3, 125.7, 126.6, 127.7, 128.0, 129.0, 135.4, 146.0, 164.2; MS (EI) *m/z*: 317 (M^+, 77%), 198 (6), 170 (6), 91 (100), 65 (23); Anal. Calcd for $C_{15}H_{12}BrNO_2$ (318): C, 56.62; H, 3.80; N, 4.40. Found: C, 56.51; H, 3.70; N, 4.51.