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One-pot regioselective annulation toward 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds under controlled microwave heating☆

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Abstract—An efficient and general synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines under controlled microwave heating has been established. It consists of a microwave-assisted reductive N-arylmethylation of substituted 2-aminophenols with aromatic aldehydes followed by a one-pot base-mediated regioselective O-alkylation of the *N*-arylmethyl-2-aminophenols with 2-bromoalkanoates to give the acyclic intermediates, which cyclize spontaneously to furnish the benzoxazine scaffolds in good to excellent yields. It was found that microwave heating over 180 °C was necessary for ring closure of the acyclic intermediates possessing an electron-withdrawing group.

1. Introduction

A variety of naturally occurring and synthetic bioactive compounds are known to possess the 2*H*-1,4-benzoxazine scalffold.[1] For instance, the enediyne antitumor antibiotic, C-1027,[2] consists of a 2-methylene-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine moiety in the chromophore subunit. Many derivatives of 2*H*-1,4-benzoxazine have been reported as plant resistance factors against microbial disease and insects,[3] serotonin-3 (5-HT_3) receptor antagonists,[4] potassium channel modulators,[5] antirheumatic agents,[6] antihypertensive agents,[7] inotropic vasodilator agents,[8] cannabinoid receptor agonists,[9] intracellular calcium antagonists,[10] neuroprotective antioxidants,[11] and others.[12a,b] 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine skeleton is also considered as the bioisoster of 2(3*H*)-benzoxazolone[12c] and can be used as the privileged scaffold in drug design. From the synthetic point of view, 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine **1** presents a heterocycle system with three points of structural diversity (X, Y, and Z) on the aromatic ring, the nitrogen, and the C2 carbon (Fig. 1). 2-Aminophenols **2** and 2-nitrophenols **3** are the common building blocks for the synthesis of **1**.[1b] Normally, stepwise synthetic sequences were adopted, for example, 2-nitrophenols underwent an O-alkylation followed by nitro reduction and subsequent intramolecular *N*-substitution.[6,9,13] In the case of 2-aminophenols, protection and deprotection manipulations were used to achieve the desired regioselectivity.[14] When treating 2-aminophenols with 2-haloalkanoyl chlorides or bromides N-acylation took place to give 2-(*N*-2′-haloacylamino)phenols, which underwent an intramolecular O-alkylation on heating at ca. 70 °C in the presence of a base to afford 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines.[4c,5a–c,8,13a] Microwave heating up to 80 °C was used in a recent synthesis.[5c] However, for the electron-deficient 2-(*N*-2′-haloacylamino)phenols, higher temperatures were required for complete cyclization.[15] Moreover, various annulation methods including Pd-catalyzed reactions have been reported for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines.[7,10,14a,16] In connection with our previous studies on synthesis of indoles,[17,18] benzofurans,[19a] and benzoxazines[19b] from substituted 2-aminophenols, we report here a regioselective annulation approach

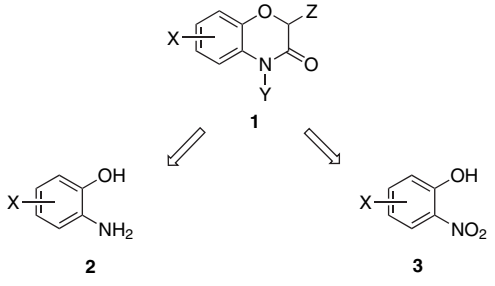

Figure 1. Common building blocks for 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds **1**.

☆ Part 6 of Chemistry of Aminophenols. For Part 5, see Ref. 19b.
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for rapidly accessing 4-arylmethyl-3,4-dihydro-2-alkyl-3-oxo-2*H*-1,4-benzoxazines in aqueous DMF under controlled microwave heating.[20]

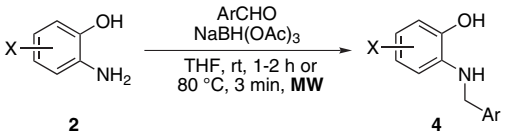
2. Results and discussion

In order to avoid the nitro reduction step in the synthesis starting from 2-nitrophenols **3**, we selected 2-aminophenols **2** as the building blocks in the current work. Although 2-haloalkanoyl halides were found to give an excellent regioselectivity in reactions with **2**,[4c,5a–c,8,13a,15] a recent study reported that reactions of 2-aminophenols with acyl chlorides at 210 °C under microwave irradiation for 15 min afforded benzoxazoles.[21] We preferred to use mild and easily handling 2-bromoalkanoates[4d] as the annulation agents, which are also suitable for running reactions in aqueous media. In our previous study,[19b] we found that heating a mixture of 2-aminophenol **2** (X=H) with ethyl 2-bromopropionate in NMP at 180 °C in the absence of a base resulted in almost exclusive formation of 3-methyl-3,4-dihydro-2-oxo-2*H*-1,4-benzoxazine along with some N,O-bisalkylation byproduct. It was found that a base such as DBU could preferentially remove the phenolic proton and promote O-alkylation of 2-aminophenols with 2-bromoalkanoates, leading to the formation of acyclic intermediates, which then underwent in situ intramolecular amidation at high temperatures under controlled microwave heating to furnish the scaffolds **1** (Y=H). By heating a mixture of 2-aminophenols **2**, ethyl 2-bromopropionate, and DBU in NMP at 180 °C for 3 min, we prepared a number of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazines in 44–82% yields. However, with bulky 2-bromoalkanoates, significantly reduced yields were obtained for the desired benzoxazine products.[19b] Moreover, the reactions of *N*-substituted 2-aminophenols have not been generally investigated for the one-pot synthesis except for one report where ethyl bromoacetate was reacted with *N*-methyl 2-aminophenols in refluxing MeOH in the presence of 10% aqueous NaOH.[4d] It is the purpose of our current study to establish a reliable, general, and efficient procedure for synthesis of the 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds **1** with three points of diversity at X, Y, and Z.

We prepared a variety of *N*-arylmethylated 2-aminophenols **4a–i**[22] from **2** and four representative electron-rich and electron-deficient aromatic aldehydes (Table 1) under microwave heating (80 °C, 3 min).[23] The yields of **4a–i** were comparable to those obtained from the reactions at room temperature (1–2 h), despite that direct reduction of aldehydes by $NaBH(OAc)_3$ is a known competitive side-reaction, especially for strongly electron-deficient aldehydes.[24] An improved yield for the microwave-assisted reaction was achieved for compound **4d** (58%), which was accompanied by bis-arylmethylation byproduct (20%) at room temperature. The high-throughput rate is a unique strength of the microwave-assisted reactions.

The annulation of **4a–c** with ethyl 2-bromoalkanoates was examined using microwave heating in a mixture of DMF–H_2O (2:1) with dissolved K_2CO_3 as the base for avoiding generation of 'hot spots', which may damage the reaction vial (Table 2). On the basis of the results we can conclude

Table 1. Reductive N-alkylation of **2** at room temperature and under controlled microwave heating[a]



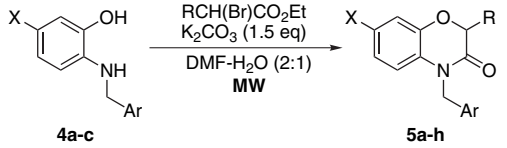
2 **4**

Entry	**2**: X	**4**	Yield (%)[b]
1	H	**4a**: X=H, Ar=2-furyl	73 (95)
2	5-Me	**4b**: X=5-Me, Ar=Ph	79 (97)
3	5-Me	**4c**: X=5-Me, Ar=2-furyl	75 (90)
4	4,5-$(CH_2)_4$–	**4d**: X=4,5-$(CH_2)_4$–, Ar=2-furyl	58 (48)[c]
5	4-NO_2	**4e**: X=4-NO_2, Ar=2-furyl	81 (98)
6	4-Cl	**4f**: X=4-Cl, Ar=2-furyl	86 (99)
7	4-Cl	**4g**: X=4-Cl, Ar=Ph	91 (99)
8	4-Cl	**4h**: X=4-Cl, Ar=4-$MeOC_6H_4$	80
9	4-Cl	**4i**: X=4-Cl, Ar=3-pyridinyl	87

[a] Compound **2** (1 equiv), 1.1 equiv of ArCHO, and 3 equiv of $NaBH(OAc)_3$ were used. All reactions with microwave heating were carried out on a commercial technical microwave reactor with temperature and pressure controlling capacity.
[b] Isolated yields of **4**. The numbers given in the parentheses are the yields for the room temperature reactions.
[c] The bisalkylation byproduct was isolated in 20% yield.

the following points: (a) use of 2 equiv of 2-bromoalkanoates gave slightly higher yields (Table 2, entry 2 vs entry 1); (b) N,O-bisalkylation byproducts were not observed even using excess 2-bromoalkanoates with R≠H; (c) annulations using 2-bromoacetate (R=H) always formed N,O-bisalkylation byproducts and lower temperatures afforded higher yields of the desired products (Table 2, entry 6 vs entry 5 and entry 7 vs entry 10); and (d) for the reactions of bulky 2-bromoalkanoates, excellent yields were obtained at high reaction temperatures (Table 2, entries 11–13 vs entries 8 and 9). Moreover, we found that the microwave-assisted annulation reactions of bulky bromo esters at 180 °C gave comparable chemical yields as to those obtained from

Table 2. One-pot annulation of **4a–c** under microwave heating[a]



4a-c **5a-h**

Entry	*T* (°C), *t* (min)	**5**	Yield (%)[c]
1	100, 20[b]	**5a**: X=R=H, Ar=2-furyl	64[d]
2	100, 20	**5a**: X=R=H, Ar=2-furyl	68[d]
3	100, 20	**5b**: X=H, R=Et, Ar=2-furyl	75
4	100, 25	**5c**: X=H, R=*n*-Pr, Ar=2-furyl	74
5	120, 15[b]	**5d**: X=Me, R=H, Ar=Ph	51[d]
6	100, 20[b]	**5d**: X=Me, R=H, Ar=Ph	60[d]
7	80, 15[b]	**5e**: X=Me, R=H, Ar=2-furyl	74[d] (80)
8	100, 20[b]	**5g**: X=Me, R=Et, Ar=2-furyl	68
9	100, 20[b]	**5h**: X=Me, R=*n*-Pr, Ar=2-furyl	67
10	180, 20	**5e**: X=Me, R=H, Ar=2-furyl	62[d]
11	180, 20	**5f**: X=Me, R=Me, Ar=2-furyl	85
12	180, 20	**5g**: X=Me, R=Et, Ar=2-furyl	81 (92)
13	180, 20	**5h**: X=Me, R=*n*-Pr, Ar=2-furyl	80 (74)

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] $RCH(Br)CO_2Et$ (1.5 equiv) was used.
[c] Isolated yields of **5**. The numbers given in the parentheses are the yields for the room temperature reactions (DMF, 3–4.5 h).
[d] Various amounts of N,O-bisalkylation byproducts were detected.