Asian Journal of Chemistry; Vol. 23, No. 7 (2011), 2947-2950

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

# Synthesis of 2*H*-1,4-Benzoxazin-3(4*H*)-ones *via* Smiles Rearrangement

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(*Received*: 2 August 2010; *Accepted*: 9 March 2011) AJC-9704

An efficient synthetic route for novel 2*H*-1,4-benzoxazin-3(4*H*)-ones *via* smiles rearrangement is developed. Reaction of primary amine and chloroacetyl chloride gave 2-chloroacetamide, which reacted with 2-chlorophenol, followed by Smiles rearrangement to obtain a series of new 2*H*-1,4-benzoxazin-3(4*H*)-ones (yield 45-90 %).

**Key Words: Smiles rearrangement, 2*H*-1,4-Benzoxazin-3(4*H*)-one, Synthesis, Hindered molecule.**

## INTRODUCTION

Benzo[1,4]oxazin-3(4*H*)-one-based compounds are a very important class of compounds, which are widely used in medicinal chemistry and have shown various biological activities such as antifungal[1], antinociceptive[2], antidepressant activity[3] and exhibit as inotropic agent[4], anticonvulsant agent[5], inhibitors of PI3Kinase$\gamma$[6], inhibitors against tyrosine kinases[7] and behave as other agents[8,9]. In addition, the member of this family is also used as photochromic agents[10] and coupling agent for oxidative hair dyes[11]. The importance of these pharmacological properties attracts a great attention while few methods for their preparation were reported. The main methods reported for the synthesis of 1,4-oxazinones were achieved by reaction of 2-aminophenols with 2-haloalkanoyl halides. The alternative method is achieved by the reduction of 2-nitrophenols to 2-aminophenols and then followed by the reaction with 2-haloalkanoyl halides.

As a part of our program aimed at the development of simple procedures for the preparation of biological heterocycles, we have recently reported the synthesis of benzo-[1,4]oxazin-3(4*H*)-ones assisted by Smiles rearrangement under conventional heating condition or microwave irradiation[12]. As an intramolecular nucleophilic aromatic substitution reaction, Smiles rearrangement provides easy access to preparation of 1,4-oxazinones. It converts simply-synthesized precursor to difficultly-prepared molecular structures. We here represent Smiles rearrangement to prepare novel 2*H*-1,4-benzoxazin-3(4*H*)-ones including sterically hindered molecules.

## EXPERIMENTAL

Melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR, respectively) with tetramethylsilane as the internal reference on Bruker Advance 300 FT spectrometer. Chemical shifts were reported in parts per million. Mass spectra (MS) were measured by ESI. Silica gel (70-230 mesh) was used for flash column chromatography. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck GF254) with UV indicator.

**General procedure for the preparation of N-subsituted 2-chloroacetamides 2a-g:** To a magnetically stirred solution of the amine (**1a-g**) (1.0 mmol) and $K_2CO_3$ (1.1 mmol) in $CH_3CN$ (20 mL) cooled by ice bath to 0 ºC, chloro acetylchloride (1.3 mmol) was added slowly. The reaction mixture was stirred at room temperature for 8-24 h. The solvent was removed under vacuum and water was added to the residue. The precipitates obtained was filtered and washed by water, dried and used for the next step without further purification.

**General procedure for the preparation of N-substituted 2-(2-chlorophenoxy) acetamide 4a-g:** The solution of 2-chlorophenol (**2a-g**) (1.0 mmol), N-subsituted-2-chloroacetamide (1.1 mmol), $K_2CO_3$ (1.1 mmol) in $CH_3CN$ (20 mL) was refluxed for 3-6 h. After completion of the reaction, the solution was cooled; solvent was evaporated under reduced pressure. The residue was poured into water (20 mL) and adjusted at pH 6-7 and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$.

Filtration of $MgSO_4$ and evaporation of solvent under vacuum gave the corresponding N-substituted 2-(2-chlorophenoxy) acetamide (**4a-g**).

**General procedure for the preparation of 2*H*-1,4-benzoxazin-3(4*H*)-ones 5a-g:** The solution of N-substituted 2-(2-chlorophenoxy)acetamide (**2a-g**) (1.0 mmol) and $Cs_2CO_3$ (1.2 mmol) in DMF (20 mL) was refluxed for 3-5 h. After completion of the reaction, the solvent was removed under vacuum and water (20 mL) was added into the residue. The pH was adjusted to 6-7 and extracted with ethyl acetate. The ethyl acetate extract was washed with brine and dried over anhydrous $MgSO_4$. The residue obtained was purified by silica gel column chromatography to obtain the corresponding substituted benzo[b][1,4]oxazin-3(4*H*)-ones (**5a-g**).

**4-Propyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one (5a):** Colourless oil. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3051, 2962, 2917, 2850, 1689, 1606, 1593, 1501, 1467, 1403, 1373, 1316, 1278, 1252, 1238, 1215, 1127, 1055, 749. $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.98 (3H, t, *J* = 7.5 Hz), 1.69-1.71 (2H, m), 3.89 (2H, t, *J* = 7.5 Hz), 4.59 (2H, s), 6.99-7.01 (4H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 11.3, 20.5, 42.7, 67.7, 115.0, 117.2, 122.8, 123.8, 128.6, 145.5, 164.4. MS (ESI) m/z: 192 $[M + 1]^+$.

**4-Cyclohexyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one (5b):** Light-yellow solid. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3048, 2931, 2854, 1682, 1605, 1591, 1498, 1466, 1454, 1365, 1273, 1124, 1056, 748; $^1$H NMR (300 MHz, $CDCl_3$) δ: 1.25-1.40 (m, 3H), 1.71 (d, 1H, *J* = 10.8 Hz), 1.85 (dd, 4H, *J* = 21.0, 12.9 Hz), 2.37 (dd, 2H, *J* = 24.6, 12.0 Hz), 4.12-4.16 (m, 1H), 4.47 (s, 2H), 7.00-7.18 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 25, 26, 29, 56, 68, 116, 117, 122, 124, 130, 146, 166. MS (ESI) m/z: 232 $[M + 1]^+$.

**4-*tert*-Butyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one (5c):** Light-yellow oil. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3045, 2978, 2933, 1689, 1602, 1496, 1459, 1351, 1295, 1268, 1054, 759; $^1$H NMR (300 MHz, $CDCl_3$) δ: 1.66 (s, 9H), 4.38 (s, 2H), 7.01-7.20 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 29.7, 58.7, 71.4, 117.2, 121.3, 121.8, 124.1, 130.6, 149.5, 171.7. MS (ESI) m/z: 206 $[M + 1]^+$.

**4-Phenethyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one (5d):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3080, 3029, 2975, 2930, 1682, 1604, 1506, 1461, 1409, 1325, 1270, 1058, 771, 743, 705; $^1$H NMR (300 MHz, $CDCl_3$) δ: 2.96 (t , 2H, *J* = 9.0 Hz), 4.14 (t, 2H, *J* = 9.0 Hz), 4.58 (s, 2H), 7.02-7.00 (m, 4H), 7.34-7.25 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 33.5, 42.7, 67.7, 114.9, 117.4, 123.0, 124.0, 126.9, 128.5, 128.7, 128.9, 138.2, 145.5, 164.3. MS (ESI) m/z: 254 $[M + 1]^+$.

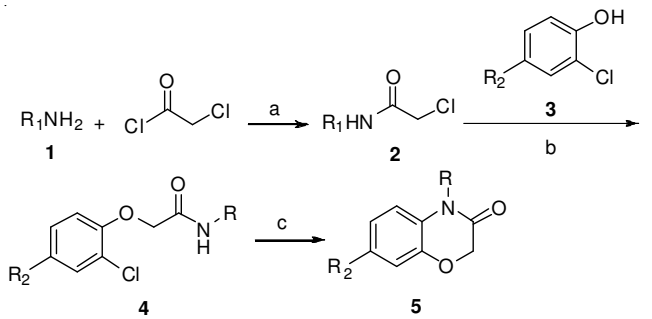
**4-(Naphthalen-1-yl)-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one (5e):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3052, 2918, 2853, 1701, 1592, 1578, 1530, 1508, 1466, 1440, 1400, 1308, 1272, 1245, 1111, 1032, 791, 768, 756; $^1$H NMR (300 MHz, $CDCl_3$) δ: 4.83 (s, 2H), 6.87 (d, 1H, *J* = 7.5 Hz), 7.09 (t, 1H, *J* = 7.8 Hz), 7.32 (t, 1H, *J* = 7.8 Hz), 7.42 (t, 2H, *J* = 7.5 Hz), 7.54 (t, 2H, *J* = 6.9 Hz), 7.83-7.86 (m, 1H), 8.37-8.46 (m, 1H), 8.53 (d, 1H, *J* = 7.8 Hz), 9.16-9.18 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 67.6, 105.6, 121.3, 122.1, 122.9, 125.1, 125.6, 125.9, 126.8, 127.8, 127.9, 129.1, 133.8, 134.6, 152.5, 166.2. MS (ESI) m/z: 274 $[M - 1]^+$.

**7-Methyl-4-phenethyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one (5f):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3081, 3052, 3021, 2948, 2920, 2858, 1682, 1620, 1519, 1453, 1411, 1331, 1277, 1193, 1145, 1053, 797, 749, 699; $^1$H NMR (300 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 2.94 (t, 2H, *J* = 9.0 Hz), 4.11 (t, H, *J* = 9.0 Hz), 4.53 (s, 2H), 6.90-6.81 (m, 3H), 7.33-7.20 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 20.6, 33.2, 42.4, 67.6, 114.4, 117.7, 123.2, 125.8, 126.6, 128.5, 128.7, 133.8, 138.0, 145.1 ,163.9. MS (ESI) m/z: 268 $[M + 1]^+$.

**7-Methyl-4-(naphthalen-1-yl)-2*H*-benzo[b][1,4]-oxazin-3(4*H*)-one (5g):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3052, 2919, 2851, 1696, 1588, 1533, 1509, 1464, 1401, 1385, 1271, 1235, 1109, 790, 767; $^1$H NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 4.81 (s, 2H), 6.85-6.92 (m, 1H), 7.26-7.29 (m, 1H), 7.41-7.43 (m, 1H), 7.53-7.55 (m, 3H), 7.61-7.62 (m, 1H), 7.85-7.86 (m, 1H), 8.36-8.38 (m, 1H), 9.11-9.13 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 21.3, 67.6, 105.5, 119.9, 121.3, 121.7, 122.1, 125.0, 125.6, 125.9, 126.8, 127.8, 129.7, 133.4, 134.6, 138.1, 152.4, 166.0. MS (ESI) m/z: 290 $[M + 1]^+$.

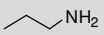
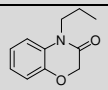
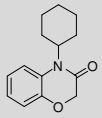
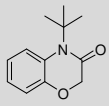
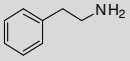
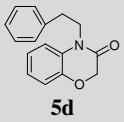
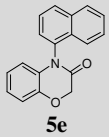
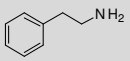
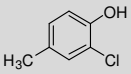
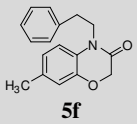
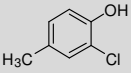
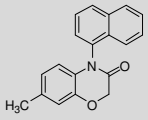
## RESULTS AND DISCUSSION

First, reaction of primary amine **1** and chloroacetyl chloride at 1:1 mole ratio assisted by potassium carbonate in acetonitrile produced 2-chloro-N-substituted acetamide **2**. The obtained acetamide **2** reacted with 2-chlorophenols **3**, easily giving O-alkylation product **4**. The intermediate **4** underwent Smiles rearrangement to furnish 2*H*-1,4-benzoxazin-3(4*H*)-one **5** under cesium carbonate in DMF (**Scheme-I**). The results were moderate in terms of yields (45-90 %). According to the results, the reaction of amine and chloroacetyl chloride simply underwent in acetonitrile and dichloromethane can be also used as solvent. Usually the reaction completed within 8 h, while reaction of *tert*-butylamine and chloroacetyl chloride took 2 day period, yielding more than 95 %. For this reaction, 8 h reaction time only led to low yield less than 40 %. The steric effect of bulky *tert*-butyl group caused to longer reaction time for this reaction. The O-alkylation of phenols to **4** was obtained with one equivalent of amide **2**, one equivalent of phenol **3** and 1.2-1.5 equivalent of potassium carbonate in refluxed acetonitrile, in 85-95 % yield. Smiles rearrangement of **4** in presence of cesium carbonate under refluxed DMF afforded the 2*H*-1,4-benzoxazin-3(4*H*)-one **5**. As shown in Table-1, reaction of either simple amines or sterically hindered amines with 2-chlorophenols gave 2*H*-1,4-benzoxazin-3(4*H*)-ones as major product, yielding 45-90 %. It is important to note that 4-*tert*-butyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, as a sterically hindered molecule was also obtained in high yield through Smiles rearrangement approach, which is quite difficult to be prepared by other methods.

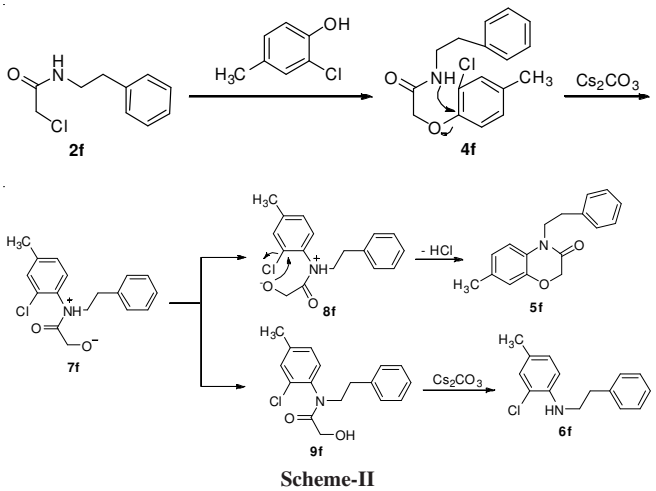



**Scheme-I:** Reagent and conditions: (a) $K_2CO_3$, $CH_3CN$, 0 ºC-r.t.; (b) $K_2CO_3$, $CH_3CN$, reflux; (c) $Cs_2CO_3$, DMF, 150 ºC

TABLE-1
SYNTHESIS OF 2*H*-1,4-BENZOXAZIN-3(4*H*)-ONES 5 *VIA* SMILES REARRANGEMENT

| Entry | Amine | Phenol | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  |  |  **5a** | 74 |
| 2 |  |  |  **5b** | 90 |
| 3 |  |  |  **5c** | 88 |
| 4 |  |  |  **5d** | 45 |
| 5 |  |  |  **5e** | 76 |
| 6 |  |  |  **5f** | 48 |
| 7 |  |  |  **5g** | 72 |

However, under identical conditions used for **4d**, Smiles rearrangement directly led to the formation of 4-phenethyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one **5d** (45 %) and 2-chloro-N-phenethylaniline **6d** (42 %) and the rearrangement of **4f** led to the formation of 7-methyl-4-phenethyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one **5f** (48 %) and 2-chloro-4-methyl-N-phenethylaniline **6f** (40 %). As shown in **Scheme-II**, Smiles rearrangement of 2-(2-chloro-4-methylphenoxy)-N-phenethylacetamide **4f** furnished the intermediate **7f**, which gave 7-methyl-4-phenethyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one **5f** as the cyclized product with the loss of hydrochloride and on hydrolysis afforded 2-chloro-4-methyl-N-phenethylaniline **6f**. These compounds were separated and reliably identifiable by IR, NMR and MS spectral data.




**Scheme-II**

## Conclusion

In summary, the application of Smiles rearrangement in the synthesis of 2*H*-1,4-benzoxazin-3(4*H*)-ones was further developed. Thus viable synthetic routes have been successfully used for the reaction of simple, sterically hindered alkyl and arylalkyl primary amines, chloroacetyl chloride and 2-chlorophenols to prepare various 2*H*-1,4-benzoxazin-3(4*H*)-ones, some of which are quite difficult to be synthesized by other existing methods. However, the reaction of arylalkyl amines, chloroacetyl chloride and 2-chlorophenols will be studied for the reaction mechanism in our future research.

## ACKNOWLEDGEMENTS

This work was supported by the Fundamental Research Funds for the Central Universities, P.R. China (XDJK2009C080) and National Natural Science Foundation of China (21002081).

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Schiaffella and R. Fringuelli, *Bioorg. Med. Chem*., **10**, 3415 (2002).
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