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Novel synthesis of pyridazino[4,5-*b*][1,4]oxazin-3,8-diones☆

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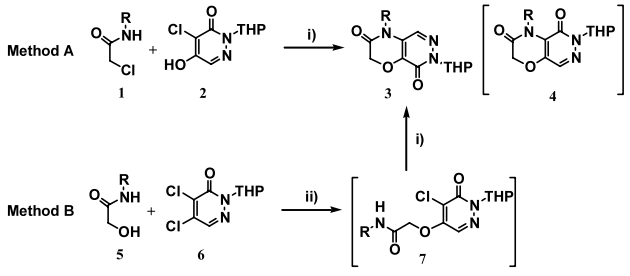
Abstract—A novel and effective synthesis of pyridazino[4,5-*b*][1,4]oxazin-3,8-diones via Smiles rearrangement is presented. Treatment of *N*-substituted 2-chloro(or hydroxy)acetamide, 2-tetrahydropyranyl-4-chloro-5-hydroxy(or chloro)pyridazin-3-one and cesium carbonate in refluxing acetonitrile was afforded the corresponding pyridazino[4,5-*b*][1,4]oxazin-3,8-diones in excellent yield.

Heterocycle fused-[1,4]oxazines have attracted considerable interest owing to their biological activities.[1–3] Synthesis of some heterocycle fused-[1,4]oxazines has been reported.[4] In the course of studying the inhibitors of multi-drug resistant (MDR) pumps, we came upon a need for pyridazino[4,5-*b*][1.4]oxazin-3,8-di ones. However, to the best of our knowledge, synthesis of pyridazino[4,5-*b*][1,4]oxazin-3,8-dione system has not been reported. Therefore, we attempted to synthesize pyridazino[4,5-*b*][1,4]oxazin-3,8-dione derivatives **3**. According to the methods published to date,[4] heterocycle fused-[1,4]oxazines such as benzo[1,4]oxazine or pyrido[3,2-*b*][1,4]oxazine are formed by direct cyclization of 2-haloacetyl halide or ethyl 2-halopropionate with 2-aminophenol or 2-amino-3-hydroxypyridine. If 4-amino-5-hydroxypyridazin-3-one derivative is reacted with 2-haloacetyl halide according to reported methods, pyridazino[4,5-*b*][1,4]oxazin-3,5-dione **4** instead of **3** should be obtained because both NH_2 and OH groups are present in pyridazinone. In this case, pyridazino[4,5-*b*][1,4]oxazin-3,8-dione system can not be formed. However, the cyclization of 4-chloro-5-hydroxypyridazin-3-one with *N*-substituted 2-chloroacetamide **1** via Smiles rearrangement would form the desired compound **3**. Therefore, we attempted to synthesize pyridazino[4,5-*b*][1,4]oxazin-3,8-diones **3** by a novel approach utilizing Smiles rearrangement.[5] Since the pyridazine ring must have an electron-deficient carbon in order for Smiles rearrangement to occur on the pyridazine ring, we chose 2-haloacetamide **1** and 2-tetrahydropyranyl-4-chloro-5-hydroxypyridazin-3-one (**2**) as the starting materials. We herein report an efficient, one-pot method for the syntheses of **3** via Smiles rearrangement using **1** (or **5**) and **2** (or **6**) (Scheme 1).

We easily prepared *N*-substituted acetamides **1** in quantitative yield by addition of the appropriate amine to 2-chloroacetyl chloride in CH_2Cl_2, and *N*-substituted



Scheme 1. *Reagents and conditions*: (i) Cs_2CO_3, CH_3CN, reflux; (ii) K_2CO_3, DMF, rt.

Keywords: pyrodazino[4,5-*b*][1,4]oxazine; Smiles rearrangement.
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2-hydroxyacetamides **5** was obtained by condensing the amine with ethyl glycolate in neat condition. On the other hand, 2-tetrahydropyranylpyridazin-3-ones **2**[6] and **6**[7] were synthesized from commercially available 4,5-dichloropyridazin-3-one via one step (for **6**) or three steps (for **2**).

Firstly, the treatment of *N*-substituted acetamides **1g** with 4-chloro-5-hydroxypyridazin-3-one derivative **2** in the presence of excess Cs_2CO_3 in refluxing acetonitrile for 43 h afforded only **3g** in 59% yield,[8] but this reaction could not progress at room temperature. On the other hand, we attempted the cyclization of **5g** with **6** for establishing the mechanism of the cyclization. Reaction of 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one (**6**) with **5g** in the presence of potassium carbonate in DMF at room temperature for 2 h gave the corresponding **7g** instead of **3g** in 95% yield.[8] According to the literature,[9] the reactivity of the carbon at 5-position for 4,5-dichloro-2-substituted-pyridazin-3-one is also higher than the carbon at 4-position. Treatment of **7g** with cesium carbonate in refluxing acetonitrile also afforded **3g** in excellent yield.[8] One-pot reaction of **5g** with **6** without purification of **7g** also gave **3g** in 91% yield (entry 7). The structure of **7g** was confirmed by X-ray analysis (Fig. 1).[10]

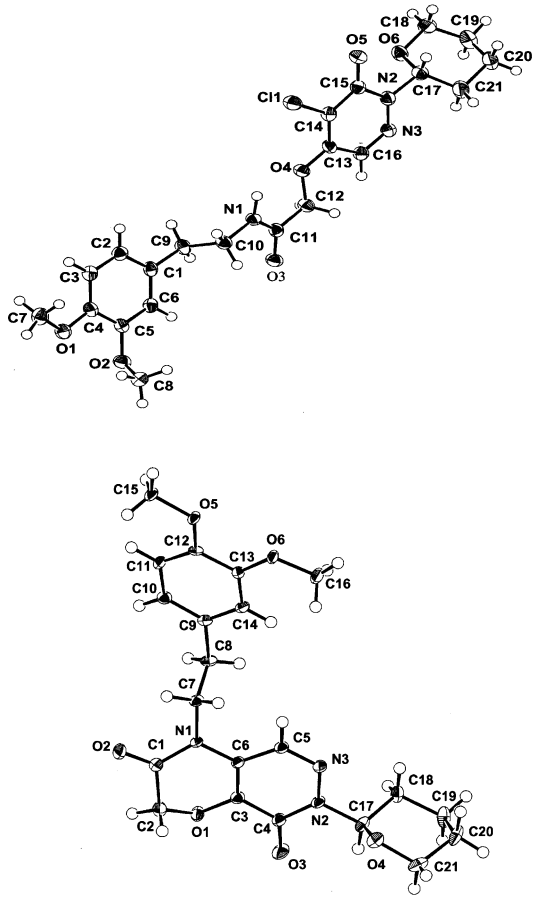


Figure 1. ORTEP plots for X-ray crystal structures of cyclized **3g** and **7g** of intermediate.

Table 1. Yield of pyridazino[4,5-*b*][1,4]oxazin-3-ones **3** by methods A and B

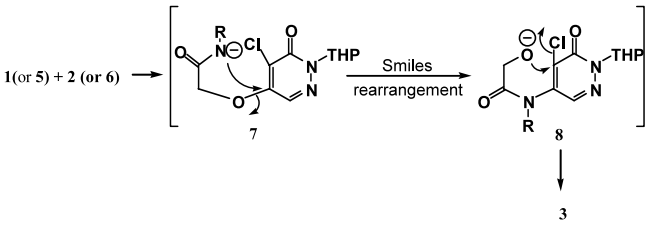
Entry	R	Time(h) A / B[b]	**3**	**3**, Yield(%)[a] A / B[b]
1	H_3C	49 / 4	**3a**	65 / 92
2		42 / 5	**3b**	53 / 93
3		72 / 5	**3c**	62 / 94
4		60 / 4	**3d**	68 / 92
5		48 / 3	**3e**	55 / 94
6		48 / 4	**3f**	67 / 94
7	MeO, MeO	43 / 4	**3g**	59 / 91
8		52 / 5	**3h**	61 / 92[c]
9		60 / 9	**3i**	33 / 88[d]
10	N H	83 / 10	**3j**	27 / 58

[a] Isolated yield of the Method A based on **1**. Isolated overall yield of the Method B based on **5**.
[b] A: Method A, B: Method B
[c] $[a]^{23}_D$ +105.46(c 1.10, CH_2Cl_2)
[d] $[a]^{23}_D$ -42.69(c 2.6, CH_2Cl_2)

We also investigated the base and solvent effects on the synthesis of **3g** in methods A and B. According to our observation, cesium carbonate (or rubidium carbonate)/ CH_3CN was the most effective system. Whereas, when some other bases such as Li_2CO_3, Na_2CO_3, K_2CO_3, and Ag_2CO_3 were used in cyclization step, the yield of **3** was lower than cesium carbonate. On the other hand, the reaction of **1** with **2** in the presence of a strong base such as NaH, NaOH, KO^{t}Bu gave an unexpectedly only 1,4-disubstituted-piperazine-2,5-dione instead of **3**.

Therefore, compound **3** was synthesized by using methods A and B. The results are summarized in Table 1. Some pyridazino[4,5-*b*][1.4]oxazin-3,8-diones **3** was synthesized from **5** and **6** by method B in excellent yield except for entry 10, whereas cyclization of **1** with **2** gave **3** in 27–68% yield. Consequently, method B is more favourable for the synthesis of **3**.

The cyclizations using methods A and B occurred via three steps; that is, the intermediate **7** was formed in the first step, the intermediate **7** was rearranged to **8** in second step, and then, anion **8** was cyclized in the final step to **3** (Scheme 2).



Scheme 2.

In summary, our method of obtaining pyridazino[4,5-*b*][1,4]oxazin-3,8-diones **3** via Smiles rearrangement is convenient and practical. Our approach using Smiles rearrangement may also be very useful for the synthesis of heterocycle fused-[1,4]oxazine such as pyrido[2,3-*b*][1,4]oxazine. Further work including the application, chemical transformation, and biological activity is under way in our laboratory.

Acknowledgements

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8. Typical experimental procedure of cyclization:
Method A—To a 100 mL flask equipped with a magnetic stirrer was added *N*-substituted 2-chloroacetamide **1g** (28.5 mmol), 4-chloro-5-hydroxypyridazin-3-one **2** (31.3 mmol), and Cs_2CO_3 (65.5 mmol) in acetonitrile (200 mL). The mixture was refluxed for 43 h, the solvent was removed under reduced pressure, and CH_2Cl_2/H_2O was added to the residue. After separating the organic layer, the aqueous layer was also extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography using EtOAc/*n*-hexane (1:2, v/v) as eluent to afford only **3g** in 59% yields.
Method B—To a 100 mL flask equipped with a magnetic stirrer was added *N*-substituted 2-hydroxyacetamides **5g** (11.4 mmol), 2-tetrahydropyranylpyridazin-3-one **6** (12.0 mmol), and K_2CO_3 (25.1 mmol) in DMF (60 mL). The mixture was stirred for 2 h, the solvent was removed under reduced pressure, and CH_2Cl_2/H_2O was added to the residue. After separating the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography using EtOAc/*n*-hexane (1:2, v/v) as eluent to afford only **7g** in 95% yields. And then, a mixture of isolated *N*-substituted 2-[5-chloro-6-oxo-1-(tetrahydropyran-2-yl)-1,6-dihydropyridazin-4-yl-oxy]acetamide **7g** (10.0 mmol) and Cs_2CO_3 (11.0 mmol) in acetonitrile (30 mL) was refluxed for 2 h. After stirring for 30 min at room temperature, the mixture was filtered to give residue. The residue was poured into dichloromethane (80 mL), and the organic layer was washed with water (50 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, the crude **3g** was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:3, v/v) as eluent to afford only **3g** in 96% yields.; **7g**: mp 149–150°C; IR (KBr) 3375, 3068, 2940, 1665, 1609, 1516, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.73–6.82 (m, 3H), 6.63 (bs, D_2O exch., 1H), 6.06 (dd, $J=1.72$, 10.26 Hz, 1H), 4.66 (s, 2H), 4.11 (d, $J=6.4$ Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.62–3.64 (q, $J=6.5$ Hz, 2H), 2.81–2.85 (t, $J=6.7$ Hz, 2H), 1.21–2.18 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 165.78, 157.82, 152.53, 149.12, 130.29, 126.82, 120.63, 111.48, 111.22, 83.90, 68.88, 68.31, 55.87, 55.80, 40.23, 34.89, 28.85, 27.77, 22.66; (*m*/*z*) 452. Anal. calcd for $C_{21}H_{26}ClN_3O_6$ (451.91): C, 55.81; H, 5.80; N, 9.30. Found: C, 55.78; H, 5.77; N, 9.28; **3g**: mp 134–135°C; IR (KBr) 3015, 2978, 2935, 1700, 1639, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 6.70–6.81 (m, 3H), 6.09 (dd, $J=2.44$, 10.82 Hz, 1H), 4.76 (s, 2H), 4.30–4.39 (m, 1H), 4.11 (m, 1H), 4.04 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 2.88 (t, $J=6.5$ Hz, 2H), 1.18–2.17 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 161.76, 154.95, 149.06, 148.05, 136.83, 129.09, 127.20, 124.74, 120.70, 111.63, 82.74,

68.87, 67.40, 55.84, 55.79, 42.73, 33.64, 28.95, 24.80, 22.67; (m/z) 415. Anal. calcd for $C_{21}H_{25}N_3O_6$ (415.45): C, 60.71; H, 6.07; N, 10.11; Found: C, 60.73; H, 6.08; N, 10.09.

One-pot method for synthesis of 3: A mixture of *N*-substituted 2-hydroxyacetamides **5g** (11.4 mmol), 2-tetrahydropyranylpyridazin-3-one **6** (12.0 mmol), and K_2CO_3 (25.1 mmol) in acetonitrile (60 mL) was refluxed until **5g** disappeared. After cooling to room temperature, the mixture was filtered. To the resulting filtrate was added cesium carbonate (11.4 mmol). The reaction mixture was refluxed until the intermediate disappeared. After cooling to room temperature, the mixture was filtered to give residue. The residue was poured into dichloromethane (80 mL), and the organic layer was then washed with water (50 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, the crude **3g** was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:3, v/v) as eluent to afford only **3**.

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10. Crystal data for **3g**: $C_{21}H_{25}N_3O_6$, $F_W=415.45$, monoclinic, space group $P2_1/n$ (No. 14), $a=16.03(2)$, $b=8.37(1)$, $c=16.75(2)$ Å, $\beta=120.0(1)°$, $U=1946(5)$ Å^3; $Z=4$, $D_{calcd}=1.418$ g/cm^3, $F_{000}=880.00$, μ(MoKα)$=1.05$ cm^{-1}, −180°C. Data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer using 2θmax 60.1° with graphite monochromated MoKa radiation ($\lambda=0.71075$ Å). Of 5565 reflections collected, 5565 reflections with $I\geq 3.00\sigma(I)$ were used in the solution. Structure refined to $R=0.081$ and $R_w=0.081$. Crystal data for **7g**: $C_{21}H_{26}ClN_3O_6$, $F_W=451.91$, monoclinic, space group $P2_1/n$ (No. 14), $a=11.889(1)$, $b=8.8066(7)$, $c=20.114(2)$ Å, $b=90.916(5)°$, $V=2105.7(3)$ Å^3, $Z=4$, $D_{calcd}=1.425$ g/cm^3, $F_{000}=952.00$, μ(CuKα): 19.94 cm^{-1}, −180°C. Data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer using 2θmax 136.5° with graphite monochromated CuKα radiation ($\lambda=1.54186$ Å). Of 3695 reflections collected, 3694 reflections with $I\geq 3.00\sigma(I)$ were used in the solution. Structure refined to $R=0.112$ and $R_w=0.182$.