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# One-Pot Synthesis of Pyridazino[1,4]oxazin-3-ones

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# One-Pot Synthesis of Pyridazino[1,4]oxazin-3-ones

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### ABSTRACT

Pyridazino[1,4]oxazin-3-ones were conveniently prepared in a onepot condensation of *N*-substituted 2-chloroacetamides with various 5-chloro-pyridazin-6-ones via rearrangement of a spiro-aminoketal intermediate.

*Key Words:* One-pot synthesis; Multi-drug resistant; X-ray analysis; Pyridazino[1,4]oxazin-3-ones.

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#### INTRODUCTION

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The widespread occurrence of fused [1,4]oxazin-3-ones in bioactive natural products and pharmaceuticals has made them important targets for synthetic chemists.<sup>[1]</sup> While several protocols are available for the construction of [1,4]oxazin-3-ones, most involve multiple steps, require highly corrosive reagents and afford poor yields.<sup>[2-7]</sup> Consequently, there is still considerable demand for more economic and versatile syntheses of fused [1,4]oxazin-3-ones. In the course of our studies related to the development of novel inhibitors of multi-drug resistant (MDR)<sup>[8]</sup> pumps, we identified the pyridazino[1,4]oxazin-3-ones ring system **3** as a critical pharmacophore. Herein, we report a convenient, one-pot route to **3** via condensation of *N*-substituted 2-chloroacetamides **1** with readily available 5-chloro-pyridazin-6ones **2** (Sch. 1) and the likely annulation mechanism.

Acetamides 1 were easily prepared in 97% yield by addition of the appropriate amine to 2-chloroacetyl chloride in CH<sub>2</sub>Cl<sub>2</sub>. The other precursor, 4-hydroxy-5-chloro-pyridazin-6-one 2,<sup>[9]</sup> was obtained in three steps from commercially available 4,5-dichloropyridazin-6-one.<sup>[10]</sup> Notably, the choice of base for the union of 1 and 2 proved to be very important. Strong bases, e.g., NaOH, NaH, and KOt-Bu, did not give cyclized product regardless of temperature. However, K<sub>2</sub>CO<sub>3</sub> in acetonitrile solvent at reflux proved suitable. In any conditions, 3' was not found. The scope of the reaction was investigated with a variety of substitutions and the results are summarized in Table 1. n-Aliphatic (entries 1 and 2), cyclo-aliphatic (entries 3-6), heterocyclic (entries 7 and 8), and aromatic (entries 9-16) N-substituents on 2-chloroacetamide 1 were well tolerated. In contrast, changing  $R_1 = H$  to  $R_1 = Me$  at the C2-position of 2 slowed the reaction rate and generally resulted in a modest decrease in yield. This is consistent with an initial  $S_N 2$  addition of the C4oxygen of 2 to the C2-position on 1 (Sch. 2). Any increase in the steric congestion at this center would retard the reaction rate.

A mechanistic scenario consistent with the preceding observations and products is outlined in Sch. 2. Following the initial  $S_N 2$  nucleophilic substitution of the hydroxyl group of **2** intermediate **4** undergoes subsequent



Scheme 1.



#### Synthesis of Pyridazino[1,4]oxazin-3-ones

Entry	R	$R_1$	Amide 1	Time (hr)	<b>3</b> Yield <sup>a</sup> (%)
1	H₃C <sup>_CH</sup> 2CH2	Н	1a	49	65 ( <b>3a</b> )
2	~ ~ ~	CH <sub>3</sub>	10	48	21 ( <b>3D</b> )
3 4	Ŭ	H CH <sub>3</sub>	lc 1d	42 48	53 ( <b>3c</b> ) 33 ( <b>3d</b> )
5 6	$\bigcirc$	H CH <sub>3</sub>	1e 1f	72 61	62 ( <b>3e</b> ) 40 ( <b>3f</b> )
7 8	$\sim$	H CH <sub>3</sub>	1g 1h	60 72	68 ( <b>3g</b> ) 36 ( <b>3h</b> )
9	$\bigcirc$	H	1i	48	55 ( <b>3i</b> )
10 11 12	$\tilde{\mathbb{C}}$	СН <sub>3</sub> Н СН <sub>3</sub>	1j 1k 1l	48 60	46 ( <b>3j</b> ) 66 ( <b>3k</b> ) 45 ( <b>3l</b> )
13	MeO	Н	1m	43	59 ( <b>3m</b> )
14	Meo	$CH_3$	1n	116	40 ( <b>3n</b> )
15 16	آثار	H CH <sub>3</sub>	10 1p	52 60	61 <sup>b</sup> ( <b>3o</b> ) 33 <sup>c</sup> ( <b>3p</b> )

Table 1. Formation of N-substituted [1,4]-oxazin-3-ones via intermediate 4.

<sup>a</sup>Isolated yield based on 1.

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intramolecular Michael addition to give the spiro-aminoketal 5. Migration of the spiro-oxygen, possibly assisted by the nitrogen lone pair, with concomitant displacement of the adjacent chloride and subsequent aromatization with loss of a proton evolves 3. In all cases (especially, entry 3), intermediate 4 could be isolated. Subjecting 4 to the same reaction condition then afforded oxazine 3 in excellent yield.



Scheme 2.

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X-ray analysis of crystal structure of 4-[2-(3,4-dimethoxy-phenyl)-ethyl]-7-(tetrahydro-pyran-2-yl)-4H,7H-pyridazino[4,5-b][1,4]oxazine-3,8-dione (**3m**) (entry 13) and 2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (**4m**) are shown in Fig. 1.



4m

*Figure 1.* The stereo ORTEP drawing of compound **3m** and **4m** (entry 13).







#### Synthesis of Pyridazino[1,4]oxazin-3-ones

In conclusion, we have developed a novel and versatile procedure for preparing pyridazino[1,4]oxazin-3-ones in one-pot. Further studies directed towards the synthesis of oxazines containing the various heterocyclic moieties using this method are currently being pursued.

## **TYPICAL EXPERIMENTAL PROCEDURE**

**2-Chloroacetamides (compound 1c).** To a solution of cyclohexylamine (5 g, 50.42 mmol), and K<sub>2</sub>CO<sub>3</sub> (8.3 g, 60.05 mmol) in dichloromethane (100 mL) was slowly added chloro acetylchloride (6.26 g, 55.46 mmol) for 30 min at room temperature. After 30 min, the mixture was refluxed for 4 hr. Then, the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was poured into cold water and extracted twice with dichloromethane. The combined organic extracts were washed with water and dried over MgSO<sub>4</sub>. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc, 1:1) to afford **1c** (8.15 g, 92%) as a white solid (hexane/EtOAc, 4:1): m.p. 97–99°C; IR (KBr, cm<sup>-1</sup>) 3413, 3054, 2934, 1670, 1268; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  6.42 (bs, 1H), 4.03 (s, 2H), 3.79 (m, 1H), 1.18–1.94 (m, 9H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  24.7, 25.4, 32.8, 42.7, 48.6, 171.3; Anal. Calcd for C<sub>8</sub>H<sub>14</sub>ClNO: C, 54.70; H, 8.03; N, 7.79. Found: C, 54.67; H, 8.02; N, 7.82.

Annulation procedure (compound 3c). *Method* A: A solution of *N*-substituted halo acetamides 1c (2 g, 11.38 mmol), 4-hydroxy-5-chloro-pyridazin-6-one 2 (2.76 g, 11.95 mmol), and K<sub>2</sub>CO<sub>3</sub> (3.46 g, 25.05 mmol) in acetonitrile (60 mL) was refluxed for 48 hr. After cooling to room temperature, the resulting mixture was stirred for 30 min and filtered, concentrated. Purification of the crude material chromatography on silica gel (elution: hexane/EtOAc, 5:1) afforded the oxazine 3c (2.24 g, 53%) as a white solid (hexane/ EtOAc, 9:1): m.p. 183–184°C; IR (KBr, cm<sup>-1</sup>) 3052, 2978, 1702, 1659, 1274; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.04 (s, 1H), 6.07 (d, *J* = 10.26 Hz, 1H), 4.68 (s, 2H), 4.31–4.39 (m, 1H), 4.11 (m, 1H), 3.73–3.80 (m, 1H), 1.18–2.16 (m, 16H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  22.7, 24.9, 25.1, 26.1, 28.9, 29.9, 30.0, 55.6, 68.3, 68.8, 82.7, 126.0, 128.6, 155.4, 163.3; Anal. Calcd for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>: C, 61.25; H, 6.95; N, 12.60. Found: C, 61.16; H, 6.96; N, 12.67.

*Method B*: A solution of *N*-substituted halo-acetamides **1c** (5 g, 28.46 mmol), 4-hydroxy-5-chloro-pyridazin-6-one **2** (7.23 g, 31.31 mmol), and  $K_2CO_3$  (9.05 g, 65.46 mmol) in acetonitrile (200 mL) was refluxed for 24 hr. After cooling to room temperature, the resulting mixture was stirred for 30 min and filtered, concentrated. Purification of the crude material

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chromatography on silica gel (elution: hexane/EtOAc, 5:1) afforded **3c** (2 g, 19%) accompanied with intermediate **4c** (2.66 g, 28%). **4c**: m.p. 181–182°C; IR (KBr, cm<sup>-1</sup>) 3424, 3058, 2982, 1664, 1260; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.82 (s, 1H), 6.49 (bs, 1H), 6.07 (d, J = 10.51 Hz, 1H), 4.67 (s, 2H), 4.11–4.14 (m, 1H), 3.72–3.86 (m, 2H), 1.23–2.14 (m, 16H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  22.7, 24.5, 24.8, 25.3, 28.9, 29.9, 32.7, 48.1, 68.5, 68.9, 84.0, 127.1, 152.8, 157.8, 164.4; Anal. Calcd for C<sub>17</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>: C, 55.21; H, 6.54; N, 11.36. Found: C, 55.05; H, 6.56; N, 11.40.

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A solution of intermediate **4c** (2 g, 5.40 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.82 g, 5.95 mmol) in acetonitrile (30 mL) was refluxed for 28 hr. After 30 min, the resulting mixture was filtered and concentrated. Purification of the crude material chromatography on silica gel (elution: hexane/EtOAc, 5 : 1) afforded **3c** (1.88 g, 95%) as a white solid.

## ACKNOWLEDGMENT

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