

Article

## Methyl Carbonium Ion Migration during the Reaction of 4-Chloro-5-methoxy-3(2*H*)-pyridazinone with Trifluoroethylation Agents

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**Abstract:** To synthesize 4-chloro-5-methoxy-2-( $\beta$ -trifluoroethyl)-3(2*H*)-pyridazinone (**4**), the reactions of 4-chloro-5-methoxy-3(2*H*)-pyridazinone (**5**) with  $\text{RCH}_2\text{CF}_3$  ( $\text{R} = \text{I, TsO, MsO, TfO}$ ) in different solvents were studied. It was found that methyl group migration took place during this reaction. An oxonium salt **9** was suggested as the active intermediate for the formation of the byproduct 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**7**) and 4-chloro-2-methyl-5-( $\beta$ -trifluoroethoxy)-3(2)-pyridazinone (**8**).

**Keywords:** 4,5-Dichloro-3(2*H*)-pyridazinone; 4-Chloro-5-methoxy-3(2*H*)-pyridazinone;  $\beta$ -Trifluoroethylation; Oxonium; Methyl group migration; Alkylation.

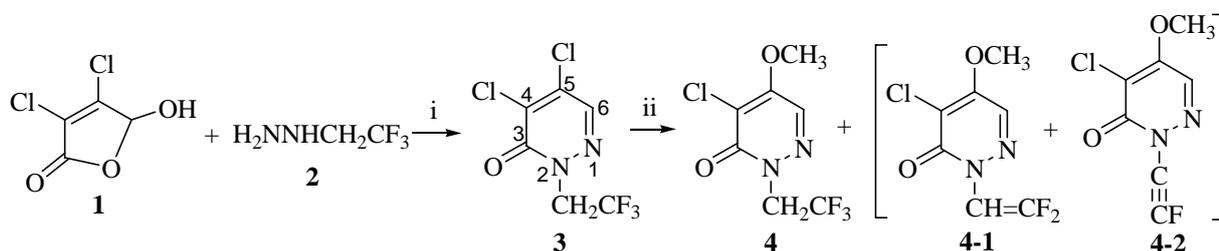
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### Introduction

It is well-known that the incorporation of fluorine atoms into organic molecules often has profound effects on their chemical and physical properties [1-2], thus there has been considerable interest in organofluorine compounds as pharmaceutical and agrochemical agents [3-4]. Among fluorine-containing groups, the  $\beta$ -trifluoroethyl moiety has been found in many drug molecules, where it can retard or prevent oxidative dealkylation of an *N*-, *S*-, or *O*-alkyl function [5-10]. 2-Substituted 4-chloro-5-methoxy-3(2*H*)-pyridazinones are key intermediates in the synthesis of agrochemically and

pharmaceutically important 2,4,5-trisubstituted-3(2*H*)-pyridazinones [11-15]. Although several approaches to nonfluorinated 2-substituted 4-chloro-5-methoxy-3(2*H*)-pyridazinones have been well documented in the prior literatures [16-17],  $\beta$ -trifluoroethylated 2,4,5-trisubstituted-3(2*H*)-pyridazinones are much less known. This is ascribed to the absence of practical and convenient methods for the introduction of the  $\beta$ -trifluoroethyl group into organic compounds. We failed to synthesize 4-chloro-5-methoxy-2-( $\beta$ -trifluoroethyl)-3(2*H*)-pyridazinone (**4**) by treatment of 4,5-dichloro-2-( $\beta$ -trifluoroethyl)-3(2*H*)-pyridazinone (**3**), which was prepared from reaction of mucochloric acid (**1**) and  $\beta$ -trifluoroethyl hydrazine (**2**) [18], with sodium methoxide (MeONa) in methanol under reflux, because the  $\beta$ -trifluoroethyl group was sensitive to the strong base. Elimination happened after treating **3** with strong base, and instead of compound **4**, a low yield of a mixture (most probably a mixture of **4-1** and **4-2**, according  $^1\text{H-NMR}$ ) was obtained, which could contain trace amounts of **4** [19]. On the other hand, a weaker base like potassium carbonate ( $\text{K}_2\text{CO}_3$ ) failed to catalyze the substitution (Scheme 1). In this paper, we report the  $\beta$ -trifluoroethylation of 4-chloro-5-methoxy-3(2*H*)-pyridazinone (**5**) to synthesize compound **4**, while proposing formation of an oxonium salt **9** during the reaction of compound **5** with  $\text{LCH}_2\text{CF}_3$  ( $\text{L} = \text{I}, \text{TsO}, \text{MsO}, \text{TfO}$ ) under different conditions, to further form 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**7**) and 4-chloro-2-methyl-5-trifluoroethyl-3(2*H*)-pyridazinone (**8**), in different ratios and yields, respectively.

**Scheme 1.** Direct introduction of trifluoroethyl group to the diazine **3**.

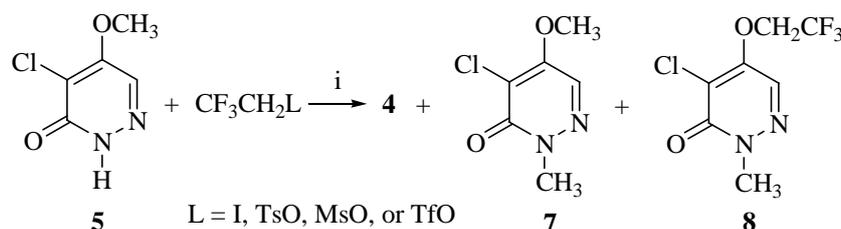


*Reagents and conditions:* i).  $\text{C}_2\text{H}_5\text{OH}$ , reflux; ii).  $\text{K}_2\text{CO}_3/\text{CH}_3\text{OH}$ , reflux or  $\text{CH}_3\text{ONa}/\text{CH}_3\text{OH}$ , reflux.

## Results and Discussion

4,5-Dichloro-2-( $\beta$ -trifluoroethyl)-3(2*H*)-pyridazinone (**3**) can be prepared from the reaction of mucochloric acid (**1**) and  $\beta$ -trifluoroethyl hydrazine (**2**) [18]. However, the methoxyl substitution on the 5-chloro of compound **3** was very difficult due to the elimination of  $\beta$ -trifluoroethyl group by the base, resulting in a mixture of compound **4**, **4-1** and **4-2** [17-19] (Scheme 1). Therefore, we tried to prepare **4** by  $\beta$ -trifluoroethylation of the corresponding 4-chloro-5-methoxy-3(2*H*)-pyridazinone (**5**) with several different agents.

Reaction of **5** with  $\beta$ -trifluoroethyl methanesulfonate ( $\text{MsOCH}_2\text{CF}_3$ ) in the presence of  $\text{K}_2\text{CO}_3$  in HMPA at  $140^\circ\text{C}$  (Table 1, entry 5) afforded exclusively 4-chloro-2-methyl-5-( $\beta$ -trifluoroethyl)-3(2*H*)-pyridazinone (**8**) in 65% yield. When the reaction was carried out in DMF, we obtained only 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**7**) in 40% yield. When sodium hydride ( $\text{NaH}$ ) was used instead of  $\text{K}_2\text{CO}_3$  (Table 1, entry 6), a mixture of compound **4** and **8** was obtained.

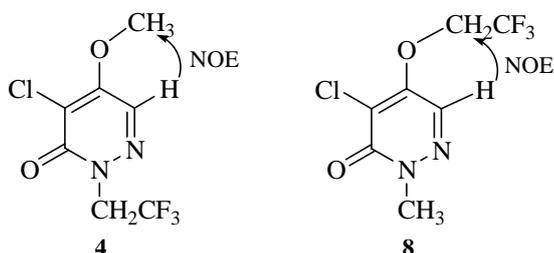
**Scheme 2.** Synthesis of compound **4** with **7** and **8** as by-products.

*Reagents and conditions:* i). see Table 1.

**Table 1.** Reactions of compound **5** with different alkylation reagents.

Entry		Condition	Product (yield)	Time
1	ICH <sub>2</sub> CF <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> /DMF, 80 °C	<b>4</b> (5%), <b>7</b> (20%)	12 h
2	TsOCH <sub>2</sub> CF <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> /DMF, 120 °C	No product	20 h
3	MsOCH <sub>2</sub> CF <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> /18-crown-6/DMF, 120 °C	<b>7</b> (40%)	20 h
4	MsOCH <sub>2</sub> CF <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> /18-crown-6/1,4-Dioxane, reflux	<b>4</b> (trace), <b>7</b> (35%)	20 h
5	MsOCH <sub>2</sub> CF <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> /18-crown-6/HMPA, 140 °C	<b>8</b> (45%)	20 h
6	MsOCH <sub>2</sub> CF <sub>3</sub>	NaH/18-crown-6/HMPA, 140 °C	<b>4</b> (15%), <b>8</b> (25%)	20 h
7	TfOCH <sub>2</sub> CF <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> /18-crown-6/HMPA, 60 °C	<b>4</b> (40%), <b>7</b> (25%)	24 h

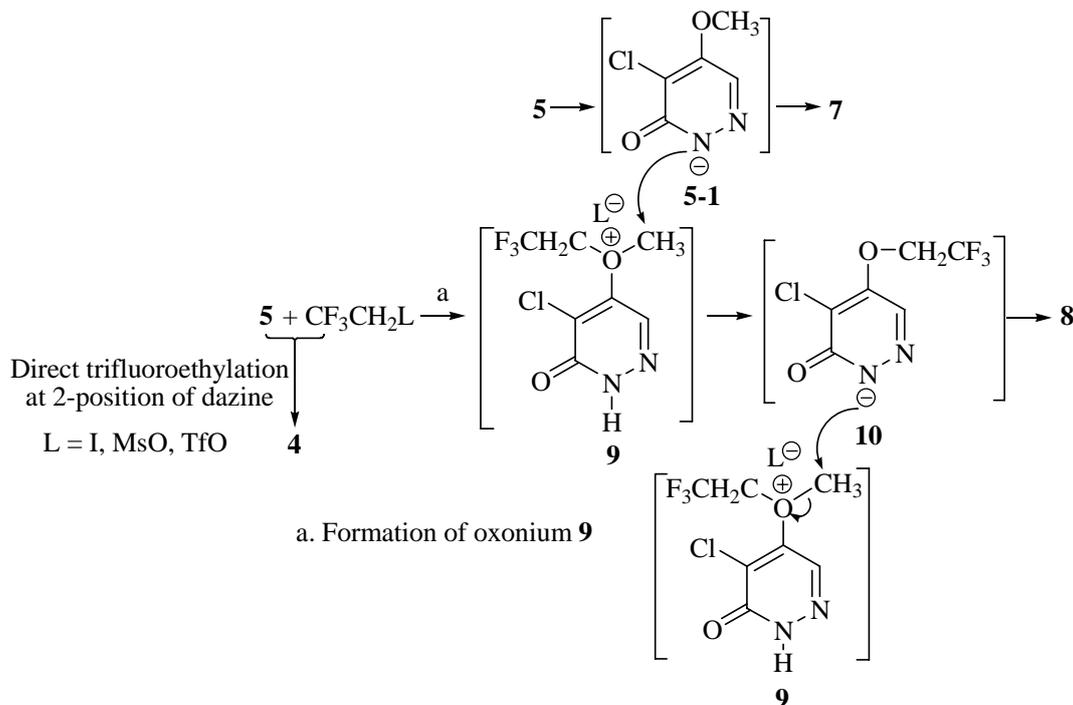
Compounds **4** and **8** are a pair of isomers. The substitution position on **4** and **8** was confirmed by 1D NOE NMR spectroscopy. Both **4** and **8** were subjected to a 1D NOE difference experiment. Irradiation of the methyl peak of **4** gave signal enhancement for protons at position 6, whereas, irradiation of the H-6 proton of **8** resulted in enhancement of the methylene proton NMR signal, in good agreement with the structural assignment (Figure 1).

**Figure 1.** NOE between H-6 and methyl or trifluoroethyl group in compound **4** or **8**.

Both compounds **7** and **8** have methyl groups on the *N*-2 position. To determine whether these methyl groups come from the solvents or from the substrate **5**, compound **5** was treated with  $\beta$ -trifluoroethyl methanesulfonate (MsOCH<sub>2</sub>CF<sub>3</sub>) in 1,4-dioxane, yielding **7** (35%) as the major product, with only trace amounts of **4** (Table 1, entry 4). It is obvious that compound **7** and **8** might be formed by the methyl migration from *O*-5 of compound **5**. When **5** was allowed to react with  $\beta$ -trifluoroethyl trifluoromethanesulfonate (TfOCH<sub>2</sub>CF<sub>3</sub>) in the presence of K<sub>2</sub>CO<sub>3</sub> and 18-crown-6 in HMPA at 60 °C (Table 1, entry 7), compound **4** was obtained in 40% yield, while **7** was obtained in 25% yield.

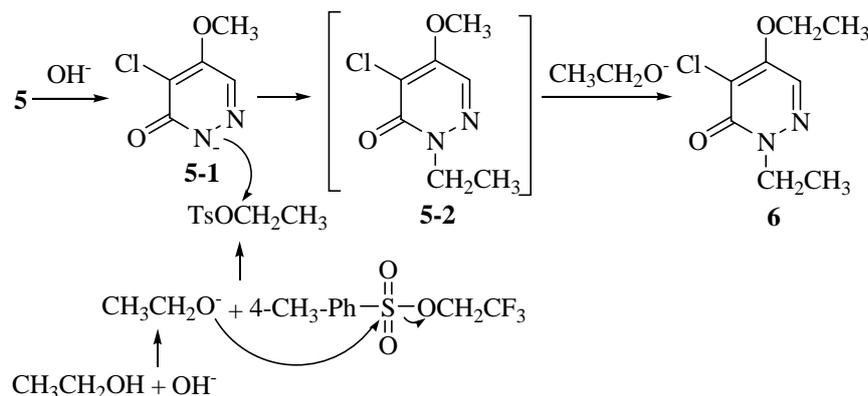
Reaction of **5** with  $\beta$ -trifluoroethyl iodide ( $\text{CF}_3\text{CH}_2\text{I}$ ) in the presence of  $\text{K}_2\text{CO}_3$  in DMF (entry 2) provided compound **4** in very low yield (5%), while **7** in 20% yield. We presumed that intramolecular elimination happened for  $\text{CF}_3\text{CH}_2\text{I}$  at basic condition and high temperature.

**Scheme 3.** Possible mechanism for the formation of compounds **7**, **8** and oxonium ion **9**.

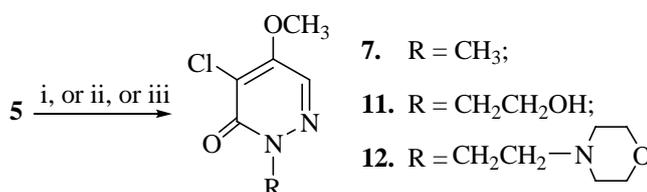


Based on these observations, a possible mechanism for the formation of compounds **4**, **7** and **8** was proposed (Scheme 3).  $\text{ICH}_2\text{CF}_3$  and  $\text{MsOCH}_2\text{CF}_3$  as alkylating reagents could attack *N*-2 of compound **5** to yield compound **4**, while the carbonium ion  $\text{CF}_3\text{CH}_2^+$  could form the oxonium salt **9** with compound **5**. The formation of compound **8** was proposed by methyl carbonium ion migration from oxonium salt **9** to the intermediate **10**. And oxonium salt **9** reacted with compound **5** via an intermolecular methyl carbonium ion migration to yield compound **7** [20].

We had investigated the reaction of compound **5** with trifluoroethyl *p*-toluenesulfonate ( $\text{TsOCH}_2\text{CF}_3$ ) in the presence of sodium hydroxide ( $\text{NaOH}$ ) in aqueous ethanol, which afforded 4-chloro-5-ethoxy-2-ethyl-3(2*H*)-pyridazinone (**6**) in 70% yield. The mechanism of formation of compound **6** as shown in Scheme 4 is suggested. The more basic ethoxyl group could competitively substitute the trifluoroethoxyl group to form  $\text{TsOCH}_2\text{CH}_3$ , which then reacted with **5**, leading to the *N*-2 ethylation of **5**. The replacement of 5-methoxyl group on the formed *N*-2 ethylation intermediate gave **6**. We also investigated the reaction of compound **5** with other three alkylating reagents (Scheme 5). Methylation of compound **5** with iodomethane ( $\text{CH}_3\text{I}$ ) and potassium carbonate in DMF gave compound **7** in excellent yield.

**Scheme 4.** Ethylation of diazinone **5** at the 2 and 4-positions.

Hydroxyethylation of **5** with sodium hydroxide and 2-bromoethanol also afforded the corresponding 4-chloro-2-( $\beta$ -hydroxyethyl)-5-methoxy-3(2*H*)-pyridazinone (**11**) in good yield. Reaction of **5** with 1-chloro-2-(*N*-morpholino)ethane in the presence of potassium carbonate yielded the expected 4-chloro-5-methoxy-2-{ $\beta$ -(*N*-morpholino)}ethyl-3(2*H*)-pyridazinone (**12**). No carbonium ion shift product was detected in reaction of **5** with 2-bromoethanol or 2-(*N*-morpholino)-1-chloroethane.

**Scheme 5.** Alkylation at the 2-position of diazinone **5**.

*Reagents and conditions:* i).  $K_2CO_3$ /  $CH_3I$ /DMF, 50-60 °C, 2h; ii). 2N NaOH/ $BrCH_2CH_2OH$ / $CH_3CH_2OH$ , reflux, 3h; iii).  $K_2CO_3$ / 2-(*N*-morpholino)-1-chloroethane.

## Conclusions

In summary, the reaction of 4-chloro-5-methoxy-3(2*H*)-pyridazinone (**5**) with  $MsOCH_2CF_3$  or  $TfOCH_2CF_3$  in polar aprotic solvents lead to the formation of an oxonium salt **9** which generated  $\beta$ -trifluoroethyl and methyl carbonium ions. Compound **8** was formed by methyl carbonium ion migration from *O*-5 of the intermediate **9** to *N*-2 of intermediate **10**. Oxonium salt **9** reacted with compound **5** via an intermolecular methyl carbonium ion migration, yielding compound **7**. The  $\beta$ -trifluoroethyl carbonium ion could also be an alkylating reagent, reacting directly with compound **5** to furnish 4-chloro-5-methoxy-2-( $\beta$ -trifluoroethyl)-3(2*H*)-pyridazinone (**4**).

## Acknowledgements

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## Experimental

### General

Column chromatography was performed on silica gel (200-300 mesh). Melting points were determined on a Mel-temp II and are uncorrected. NMR spectra were recorded on a Varian INOVA-500 NMR spectrometer operating at 499.821 MHz for  $^1\text{H}$  and 125.71 MHz for  $^{13}\text{C}$ . Chemical shifts ( $\delta$ ) are referenced to internal TMS and reported in ppm. Splitting patterns were as follows: *s*, singlet; *br*, broad; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet. Mass spectra were recorded under fast bombardment (FAB), on a Micromass Autospect high-resolution mass spectrometer unless noted. Elemental analyses were recorded on PE-240C. Infrared spectra (IR) were obtained with a Nicolet NEXUS-470 FTIR spectrometer as KBr pellets.

*4,5-Dichloro-2-( $\beta$ -trifluoroethyl)-3(2H)-pyridazinone (3)*. Mp 83-85 °C. MS (ESI):  $m/z$  247  $[\text{M}+1]^+$ . Anal. calcd. for  $\text{C}_6\text{H}_3\text{Cl}_2\text{F}_3\text{N}_2\text{O}$ : C 29.18, H 1.22, N 11.34; Found: C 29.19, H 1.26, N 11.34.

*4-Chloro-5-methoxy-3(2H)-pyridazinone (5)*. Mp 123-124 °C.  $^1\text{H}$ -NMR ( $\text{DMSO-d}_6$ )  $\delta$  11.59 (br, 1 H, H-2), 7.78 (s, 1 H, H-6), 4.063 (s, 3 H,  $-\text{OCH}_3$ ).

*4-Chloro-5-ethoxy-2-ethyl-3(2H)-pyridazinone (6)*: To a solution of **5** (1.0 g, 6.2 mmol) in  $\text{C}_2\text{H}_5\text{OH}$  (60 mL) were added  $\text{TsOCH}_2\text{CF}_3$  (6.2 g, 25.2 mmol) and 2 N NaOH (10 mL). The mixture was stirred under reflux for 14 h. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and solution was washed with brine. The organic layer was separated, dried over anhydrous sodium sulfate ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The resulting residue was purified by column chromatography (hexane/ethyl acetate) to give compound **6** (877 mg, 70%) as a colorless solid. Mp 64-66 °C;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  7.79 (s, 1 H, H-6), 4.32 (q,  $J = 7.0$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.24 (q, 2H,  $J = 7.0$  Hz,  $\text{N-CH}_2\text{CH}_3$ ), 1.50 (t,  $J = 7.0$  Hz, 3 H,  $-\text{OCH}_2\text{CH}_3$ ), 1.37 (t,  $J = 7.0$  Hz, 3 H,  $\text{N-CH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.3 (C=O), 154.3 (C-6), 126.7 (C-5), 116.5 (C-4), 66.4 ( $\text{OCH}_2\text{CH}_3$ ), 47.6 ( $\text{N-CH}_2\text{CH}_3$ ), 14.8 ( $-\text{OCH}_2\text{CH}_3$ ), 13.4 ( $-\text{NCH}_2\text{CH}_3$ ); MS (FAB):  $m/z$  203  $[\text{M}+1]^+$ ; Anal. calcd. for  $\text{C}_8\text{H}_{11}\text{Cl}_1\text{N}_2\text{O}_2$ : C 47.42, H 5.47, N 13.82; Found: C 47.13, H 5.44, N, 13.48.

### General procedure for the synthesis of compound 4

To the solution of **5** in solvent were added  $\text{LCH}_2\text{CF}_3$  and base. The mixture was stirred under reflux for 14 h. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure.  $\text{CH}_2\text{Cl}_2$  and water were added. The organic layer was separated and dried over anhydrous sodium sulfate ( $\text{Na}_2\text{SO}_4$ ). After evaporation, the residue was purified by column chromatography (hexane/ethylacetate) to give compound **4** and **7** or **8**.

*4-Chloro-5-methoxy-2-( $\beta$ -Trifluoro)ethyl-3(2H)-pyridazinone (4)*. White powder; mp 90-92 °C;  $\text{IR}_{\text{vmax}}$  ( $\text{cm}^{-1}$ ): 3318-2853 (m), 1671, 1609, 1466, 1385, 1320, 1286, 1267, 1219, 1150, 1106, 892, 772;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  7.88 (s, 1 H, H-6), 4.82 (q,  $J = 8.5$  Hz, 2 H,  $-\text{NCH}_2-$ ), 4.11 (s, 3 H,  $\text{OCH}_3$ );  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  158.5 (C=O), 155.0 (C-6), 127.9 (C-5), 123.0 (q,  $^1J_{\text{C,F}} = 153.6$  Hz,  $-\text{CF}_3$ ), 116.5 (C-4), 58.5

(-OCH<sub>3</sub>), 52.5 (q, <sup>2</sup>J<sub>C,F</sub> = 35.1 Hz, -N-CH<sub>2</sub>-); MS (EI): *m/z* 242.0 [M]<sup>+</sup>; Anal. calcd. for C<sub>7</sub>H<sub>6</sub>Cl<sub>1</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C 34.66, H 2.49, N 11.55; Found: C 34.69, H 2.52, N 11.41.

*4-Chloro-5-methoxy-2-methyl-3(2H)-pyridazinone (7)*. White powder; yield 75%; mp 131 - 133 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.78 (s, 1 H, H-6), 4.07 (s, 3H, -OCH<sub>3</sub>), 3.83 (s, 3 H, N-CH<sub>3</sub>).

*4-Chloro-2-methyl-5-(β-trifluoroethoxy)-3(2)-pyridazinone (8)*. White powder. Mp 164-166 °C. IR<sub>vmax</sub> (cm<sup>-1</sup>) 3409 - 2927 (m), 1653, 1602, 1468, 1397, 1334, 1301, 1271, 1208, 1170, 1111, 1000, 967, 876; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.71 (s, 1 H, H-6), 4.60 (q, 2H, <sup>3</sup>J<sub>H,F</sub> = 7.5 Hz, -OCH<sub>2</sub>-), 3.83 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 158.5 (C=O), 153.5 (C-6), 127.9 (C-5), 122.3 (q, <sup>2</sup>J<sub>C,F</sub> = 153.6 Hz, -CF<sub>3</sub>), 120.1 (C-4), 67.6 (q, <sup>2</sup>J<sub>C,F</sub> = 35.1 Hz, N-CH<sub>2</sub>-), 41.0 (-NCH<sub>3</sub>); MS (EI): *m/z* 242.0 [M]<sup>+</sup>; Anal. calcd. for C<sub>7</sub>H<sub>6</sub>Cl<sub>1</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C 34.66, H 2.49, N 11.55; Found: C 34.76, H 2.56, N 11.38.

*4-Chloro-2-(β-hydroxyethyl)-5-methoxy-3(2H)-pyridazinone (11)*. Mp: 166-168 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.26 (s, 1 H, H-6), 4.83 (brs, 1 H, OH), 4.15 (t, *J* = 6.6 Hz, 2H, -NCH<sub>2</sub>-), 4.07 (s, 3 H, -OCH<sub>3</sub>), 3.69 (t, *J* = 4.5 Hz, 2 H, -OCH<sub>2</sub>); MS (FAB): *m/z* 205.0 [M+1]<sup>+</sup>; Anal. calcd. for C<sub>7</sub>H<sub>9</sub>Cl<sub>1</sub>N<sub>2</sub>O<sub>3</sub>: C 41.09, H 4.43, N 13.69; Found: C 40.80, H 4.46, N 13.74.

*4-Chloro-5-methoxy-2-(β-N-morpholinoethyl)-3(2H)-pyridazinone (12)*. Mp 170-172 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.24 (s, 1 H, H-3), 4.21 (t, *J* = 6.6 Hz, 2H, -NCH<sub>2</sub>-), 4.06 (s, 3 H, -OCH<sub>3</sub>), 4.08 (t, *J* = 4.5 Hz, 4 H, 2 x OCH<sub>2</sub>), 2.62 (t, *J* = 6.6 Hz, 2 H, -NCH<sub>2</sub>), 2.39 (t, *J* = 4.5 Hz, 4 H, 2 x -NCH<sub>2</sub>). MS (EI): *m/z* 273 [M]<sup>+</sup>. Anal. Calcd. for C<sub>11</sub>H<sub>16</sub>Cl<sub>1</sub>N<sub>3</sub>O<sub>3</sub>: C 48.27, H 5.89, N 15.35; Found: C 48.50, H 6.02, N 15.52.

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*Sample Availability:* Samples of the compounds **4**, **6**, **8** are available from the authors.

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