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Preparation and Cyclization of 4-Chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide

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ABSTRACT: *Chloroformylation of 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide* **4** *with Vilsmeier reagent (DMF/$POCl_3$) led to the formation of cyclic β-chlorovinylaldehyde (4-chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide* **5***). Compound* **5** *reacted with formamidine, o-aminophenol, 1,2-phenylenediamine, aminopyrazole, and aminotetrazole to give the corresponding heterocyclic compounds.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:200–204, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20094

INTRODUCTION

The Vilsmeier reagent, $HCONR^1R^2/POCl_3$, has found extensive application in the synthesis of aldehyde derivatives and formamidines [1]. The reagent is an equilibrium mixture of two iminium salts, the more reactive being the β-phosphoryliminium chloride (A) rather than the β-chloroiminium phosphate (B) [2] (Fig. 1).

We recently reported that application of the Vilsmeier's reaction to acetylphosphonate led stereospecific formation of (*Z*)-β-phosphonyl-β-chlorovinylaldehyde [3]. We investigated this synthesis more deeply and widened it to 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide **4**. Chloroformylation of 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide **4** with Vilsmeier reagent (DMF/$POCl_3$) afforded successfully cyclic β-chlorovinylaldehyde **5** (4-chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide). **5** is a very useful intermediate for the synthesis of heterocyclic compounds.

RESULTS AND DISCUSSION

The action of DMF/$POCl_3$on 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide **4** at 30°C led to the sole product 4-chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide **5** in 64.5% yield (Scheme 1). The reaction of **5** with formamidine, aminopyrazole, aminotetrazole, *o*-aminophenol, 1,2-phenylenediamine, and 5-phenyl-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles gave the corresponding heterocyclic compounds **6–10** in the presence of K_2CO_3 (Scheme 2). These heterocyclic compounds were all characterized by their ^1H, ^{13}C NMR, and elemental analysis.

Of all the new compounds, compounds **9a, 9b**, and **10** have a seven-membered ring, which is commonly considered unfavorable because of the high strain in seven-membered ring. X-ray diffraction analysis of a single crystal of **10** further established the structure [4]. As depicted in Fig. 2, there undoubtedly exists a seven-membered ring C_{11}-C_{10}-C_9-S_1-C_8-N_3-N_4. Selective bond distances and angles are listed under Fig. 2.

On treatment of 4-chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide **5** with 1,2-phenylenediamine and aminopyrazole in the presence of K_2CO_3,

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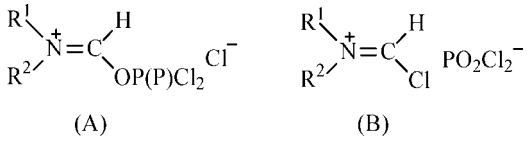


FIGURE 1 The two forms of Vilsmeier reagent.

which gave the expected compounds **7a** and **9b**, respectively, we also obtained small amounts of the imines **11** and **12** that resulted by the reaction of the formyl group of **5** with the amino group of aminopyrazole or 1,2-phenylenediamine (Scheme 3).

As shown in Scheme 3, a plausible pathway for this reaction would consist of two steps: in the first step, 1,2-addition of the amino groups of aminopyrazole or 1,2-phenylenediamine to the formyl group of **5** gives imines **11** and **12**; in the second step, intramolecular nucleophilic substitution of the nitrogen atom in **11** or **12** with chlorine atom on C_4 in them forms the final compounds **7a** and **9b**.

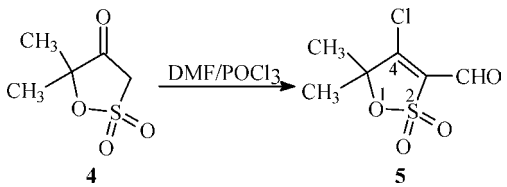
The reaction of 4-chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide **5** with hydrazine, hydroxylamine in the presence of K_2CO_3 can only give the intermediates hydrazones **13** and oxime **14** (Scheme 4), which cannot cyclize further to give the corresponding pyrazoles or isoxazole in the presence of NaH, K_2CO_3, or DMAP.

CONCLUSIONS

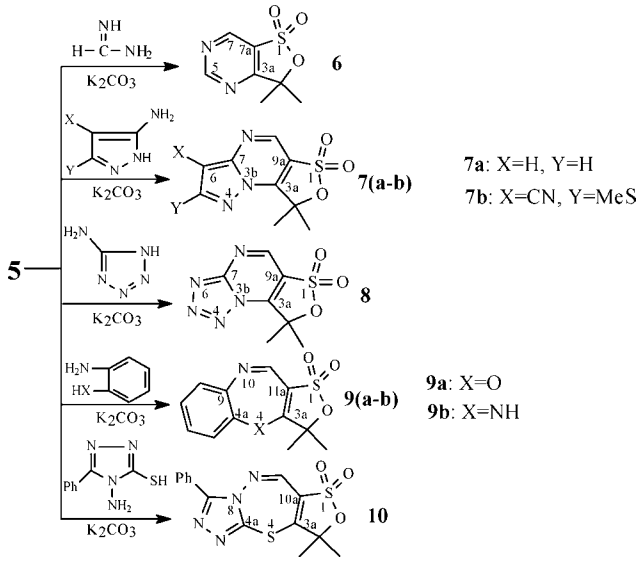
In conclusion, chloroformylation of 5,5-dimethyl-1,2-oxathiole-4-one 2,2-dioxide **4** with Vilsmeier reagent ($DMF/POCl_3$) led to 3-carbaldehyde-4-chloro-5,5-dimethyl-1,2-oxa-thiolene 2,2-dioxide **5**. Compound **5** is a very useful intermediate in organic synthesis. It reacted with formamidine, *o*-aminophenol, 1,2-phenylenediamine, aminopyrazole, and aminotetrazole to give the corresponding heterocyclic compounds in high yields.

EXPERIMENTAL

Melting points were determined with a Thomas–Hoover melting points apparatus. ^1H NMR spectra



SCHEME 1



SCHEME 2

were determined with a Bruker AC-P30 in $CDCl_3$ $(CD_3)_2CO$ or DMSO solution. Chemical shifts were reported in ppm (δ) downfield from Me_4Si. Elemental analyses were performed on a Yanaco CHN Corder MT-3 apparatus.

Synthesis of Compound **4**

To a mixture of acetone cyanohydrin **1** (4.0 mL, 43.8 mmol) in dry CH_2Cl_2 (25 mL) and Et_3N (12 mL, 87.5 mmol)) was added dropwise methane sulfonyl chloride (4.8 mL, 62.1 mmol) whilst maintaining the temperature between 0 and 5°C. The reaction was allowed to reach room temperature and was stirred

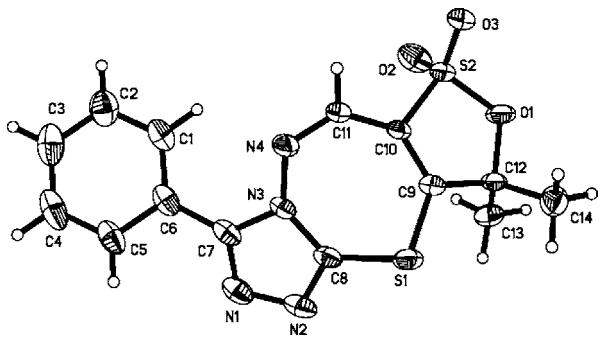
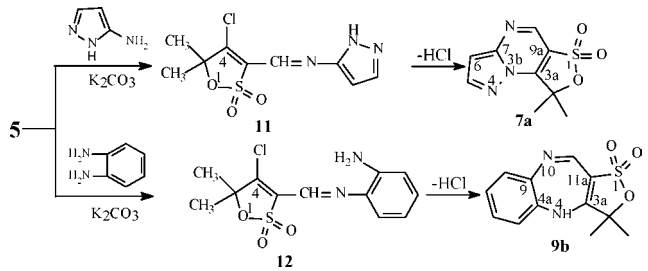
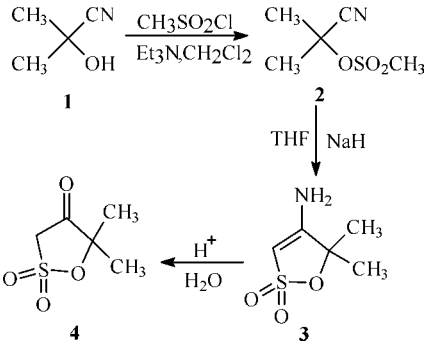


FIGURE 2 X-ray structure of compound **10**. The hydrogen atoms are omitted for clarity. Selective bond distance (Å) and angles (°): S(1)–C(8) = 1.723(4), S(1)–C(9) = 1.748(3), C(9)–C(10) = 1.338(4), C(10)–C(11) = 1.448(3), C(11)–N(4) = 1.275(4), N(4)–N(3) = 1.389(4). C(10)–C(11)–N(4) = 131.5(3), C(11)–N(4)–N(3) = 118.2(3), C(8)–S(1)–C(9) = 98.58, S(1)–C(9)–C(10) = 123.9(3).



SCHEME 3



SCHEME 5

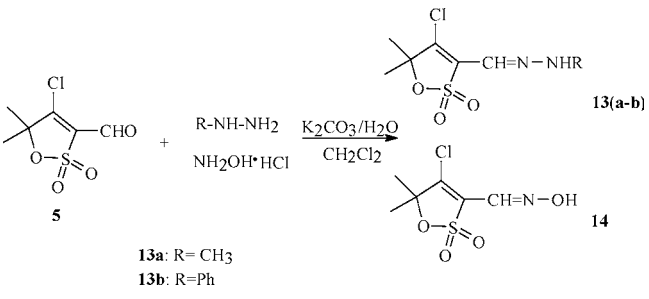
for 2 h. The mixture was filtered over Celite to remove triethylamine hydrochloride, and the filtrate was evaporated. Column chromatography (2:1 mixture of petroleum ether and AcOEt as the eluent) of the residue yielded compound **2** (5.30 g, 74%) as a colorless oil.

Compound **2** (0.43 g, 2.65 mmol) in dry THF (12 mL) was stirred with 60% NaH dispersion in oil (0.13 g, 3.18 mmol, 1.2 equiv) for 3 h at r.t. Water was added slowly to destroy the excess NaH, and the mixture was extracted with AcOEt (3 × 30 mL). The dried organic layer ($MgSO_4$) was evaporated to yield a white solid **3** that was recrystallized from CH_2Cl_2:acetone = 2:1 as colorless plates (0.305 g, 71%): mp 175–176°C (lit [5] mp 175–176°).

To a solution of **3** (0.305 g, 1.87 mmol) in EtOH (10 mL) was added concentrated HCl (1 mL) and then the mixture was stirred for 5 min. The mixture was filtered over Celite, and the filtrate was evaporated to leave a solid residue that, upon recrystallization from hexane: toluene (2:1), gave **4** (0.21 g, 66%) as colorless plates: mp 58–59°C (lit [4] mp 59°C) (see Scheme 5).

*The Preparation of 4-Chloro-5,5-dimethyl-3-formyl-1,2-oxathiolene 2,2-dioxide (**5**)*

To a mixture of $POCl_3$ (0.12 mol) in CH_2Cl_2 (15 mL) was added dropwise a solution of DMF (0.12 mol) in CH_2Cl_2 (5 mL) at 0°C under N_2 atmosphere. The mixture was stirred at room temperature for 0.5 h. Then 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide **4** (3.28 g, 0.02 mol) was added dropwise at 0°C. The reaction mixture was stirred for 30 h at room temperature. The mixture was poured slowly through a condenser to a bottle which contained 150 g crushed ice, and stirred for 3 h more. The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 50 mL brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude yellow product was purified by recrystallization from AcOEt : petroleum ether (1:2) to give **5** as white crystals (2.73 g, 64.5%), mp 175–176°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.88 (s, 1H, —C<u>H</u>O), 1.75 [s, 6H, (C<u>H</u>$_3$)$_2$]; ^{13}C NMR (300 MHz, $CDCl_3$): δ = 178.22 (—<u>C</u>HO), 159.64 (C_5), 121.55 (C_4), 90.12 [$(CH_3)_2$—<u>C</u>—O], 26.78 (CH_3—); Anal. Calcd for $C_6H_7SO_4Cl$: C, 34.21; H, 3.35 Found: C, 34.15; H, 3.53.



SCHEME 4

*General Procedure for the Cyclization of Compound **5***

To a mixture of compounds **5** (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of formamidine, aminopyrazole [6,7], aminotetrazole [8], *o*-aminophenol, 1,2-phenylenediamine, or 5-phenyl-4-amino-3-mercapto-(4*H*)-1,2,4-triazole [9], methylhydrazine [10,11], phenylhydrazine, and hydroxylamine hydrochloride (1 mmol) in CH_2Cl_2 or water at 10°C, then K_2CO_3 (1 mmol) in water (2 mL) was added dropwise. The reaction mixture was kept at 30°C for 2–3 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 20 mL saturated brine, dried over Na_2SO_4, filtered, and concentrated. The residue was separated by silica gel using AcOEt : petroleum ether (3:1) as developing solvent to afford corresponding heterocyclic compounds **6–14**, which can be purified by recrystallizing from suitable solvents.

*3,3-Dimethyl-2-oxa-1-thia-4,6-diaza-indan 1,1-dioxide (**6**).* White crystals, yield 46.36%, mp 128–129°C; ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 9.45 (s, 1H, H_7), 9.29 (s, 1H, H_5),1.85 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$): δ 170.31 (C_{3a}), 162.25 (C_5), 151.93 (C_7), 125.45 (C_{7a}), 93.09 (C_3), 26.21 (CH_3—); Anal. Calcd for $C_7H_8N_2SO_3$: C, 41.99; H, 4.03; N, 13.99. Found: C, 41.95; H, 4.08; N, 13.93.

*3,3-Dimethyl-8H-2-oxa-1-thia-3b,4,8-triaza-indacene 1,1-dioxide (**7a**).* Yellow crystals, yield 50.2%; mp 213–215°C; ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 9.21 (s, 1H, H_9), 8.41 (s, 1H, H_5), 6.86 (s, 1H, H_6), 1.94 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$): δ 160.35 (C_{3a}), 149.68 (C_9), 149.3 (C_7), 132.57 (C_5), 114.54 (C_{9a}), 98.19 (C_6), 93.44 (C_3), 26.63 ($\underline{C}H_3$—); Anal. Calcd for $C_9H_9N_3SO_3$: C, 39.21; H, 3.66; N, 15.24. Found: C, 39.19; H, 3.76; N, 15.37.

*6-Cyano-3,3-dimethyl-5-methylsulfanyl-1,3-dihydro-2-oxo-1-thia-3b,4,8-triaza-indacene 1,1-dioxide (**7b**).* White crystals, yield 61.29%, mp 237–239°C; ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 7.05 (s, 1H, H_9), 2.75 (s, 3H, —SCH_3), 1.86 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR (DMSO): δ 164.06 (C_{3a}), 162.09 (C_9), 152.72 (C_7), 136.01 (C_5), 122.36 (C_{9a}), 115.46 (—C≡N), 111.79 (C_6), 92.59 (C_3), 25.95 (—2$\underline{C}H_3$), 13.18 ($\underline{C}H_3S$—); Anal. Calcd for $C_{11}H_{10}N_4S_2O_3$: C, 42.57; H, 3.25; N, 18.05. Found: C, 42.40; H, 3.39; N, 17.98.

*3,3-Dimethyl-8H-2-oxa-1-thia-3b,4,5,6,8-penta-aza-indacene 1,1-dioxide (**8**).* White crystals, yield 60.50%, mp 160–162°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.91 (s, 1H, H_9), 1.82 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.75 (C_{3a}), 166.30 (C_7), 154.33 (C_9), 121.16 (C_{9a}), 92.40 [$(CH_3)_2$—$\underline{C}$—O], 26.11 (—2$\underline{C}H_3$); Anal. Calcd for $C_7H_7N_5SO_3$: C, 34.85; H, 2.93; N, 29.03. Found: C, 34.77; H, 2.88; N, 28.93.

*3,3-Dimethyl-3H-2,4-dioxa-1-thia-10-aza-benzo-azulene 1,1-dioxide (**9a**).* White crystals, yield 45.36%, mp 171–172°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–6.98 (m, 4H, Ph), 5.54 (s, 1H, H_{11}), 1.76 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR [$(CD_3)_2CO$]: 157.07 (C_{3a}), 149.64 (C_{11}), 128.03, 127.26, 124.65, 120.70, 117.04 (Ph), 115.57 (C_{10a}), 88.25 [$(CH_3)_2$—$\underline{C}$—O], 26.12 (CH_3—); Anal. Calcd for $C_{12}H_{11}SO_4$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.47; H, 4.18; N, 5.14.

*3,3-Dimethyl-3,4-dihydro-2-oxa-1-thia-4,10-diaza-benzo-azulene 1,1-dioxide (**9b**).* Purple crystals, yield 56.82%; mp 172–173°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.71–6.78 (m, 2H, Ph), 6.54–6.58 (d, J = 6.58 Hz, 1H, H_8), 6.37 (s, 1H, H_{11}), 5.98–6.02 (d, J = 6.58 Hz, 1H, H_5), 1.59 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR [$(CD_3)_2CO$]: δ 171.94 (C_{3a}), 154.12 (C_{11}), 133.34, 130.03, 129.23, 124.92, 123.19, 121.19 (Ph), 117.95 (C_{11a}), 90.90 [$(CH_3)_2$—$\underline{C}$—O], 25.68 (CH_3—) Anal. Calcd for $C_{12}H_{12}N_2SO_3$: C, 54.49; H, 4.57; N, 10.60. Found: C, 54.26; H, 4.62; N, 10.79.

*3,3-Dimethyl-7-phenyl-3H-2-oxa-1,4-dithia-5,6,8,9-tatraaza-cyclopenta-azulene 1,1-dioxide (**10**).* Yellow crystals, yield 72.5%; mp 215–217°C (decompose); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86–7.92 (m, 3H, Ph), 7.51–7.57 (m, 3H, Ph, and C$\underline{H}$=N) 1.83 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$): δ 161.19 (C_{10}), 157.15 (C_{3a}), 142.59 (C_8), 139.99 (C_5), 131.24, 129.51, 128.65, 126.92 (Ph), 124.74 (C_{10a}), 90.47 [$(CH_3)_2$—$\underline{C}$—O], 25.93 (—2$\underline{C}H_3$); Anal. Calcd for $C_{14}H_{12}N_4S_2O_3$: C, 48.26; H, 3.47; N, 16.08. Found: C, 48.14; H, 3.50; N, 16.12.

*(4-Chloro-5,5-dimethyl-2,2-dioxo-2,5-dihydro-[1,2]oxathiol-3-ylmethylene)-(2H-pyrazol-3-yl)-amine (**11**).* White crystals, yield 15.8%; mp 217–219°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.21 (s, 1H, NH—N=C$\underline{H}$), 8.40 (s, 1H, —C$\underline{H}$=N), 6.86 (s, 1H, C=C$\underline{H}$), 1.94 [s, 6H, ($C\underline{H}_3$)$_2$]; Anal. Calcd for $C_9H_{10}N_3SO_3$: C, 45.18; H, 3.79; N, 17.56. Found: C, 45.22; H, 3.86; N, 17.33.

*N-(4-Chloro-5,5-dimethyl-2,2-dioxo-2,5-dihydro-[1,2]oxathiol-3-ylmethylene)-benzene-1,2-diamine (**12**).* Yellow crystals, yield 26.67%, mp 138–139°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H, H—C=N), 7.08–7.13 (m, 2H, Ph), 6.62–6.71(d, J = 7.68 Hz, 1H, Ph), 6.62–6.67 (d, J = 7.68 Hz, 1H, Ph), 2.93 (s, N$\underline{H}_2$), 1.73 [s, 6H, ($C\underline{H}_3$)$_2$]; Anal. Calcd for $C_{12}H_{13}N_2SO_3Cl$: C, 47.74; H, 4.48; N, 9.42. Found: C, 47.92; H, 4.36; N, 9.31.

*N-(4-Chloro-5,5-dimethyl-2,2-dioxo-2,5-dihydro-[1,2]oxathiol-3-ylmethyl-ene)-N′-methyl-hydrazine (**13a**).* White crystals, yield 56.8%, mp 130–131°C; ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 6.94 (s, 1H, C$\underline{H}$=N), 2.97 (s, CH_3N—) 1.67 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$): δ 154.7 ($\underline{C}$H=NNHCH$_3$), 138.85 (C_4), 116.14 (C_3), 89.07 (C_5), 32.65 (NH—$\underline{C}H_3$), 25.74 (2CH_3); Anal. Calcd for $C_7H_{11}N_2SO_3Cl$: C, 35.22; H, 4.66; N, 11.73. Found: C, 34.87; H, 4.98; N, 11.73.

*N-(4-Chloro-5,5-dimethyl-2,2-dioxo-2,5-dihydro-[1,2]oxathiol-3-ylmethylene)-N′-phenyl-hydrazine (**13b**).* Yellow crystals, yield 67.5%, mp 161–162°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (s, 1H, NH), 7.36 (s, C$\underline{H}$=N), 7.30–6.90 (m, 5H, Ph), 1.69 [s, 6H, ($C\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$): δ 142.48 ($\underline{C}$H=NNH), 138.91 (C_4), 121.29 (C_3), 129.62, 129.39, 122.14, 113.64 (Ph), 89.30 (C_5), 25.70 (2CH_3); Anal. Calcd

for $C_{12}H_{13}N_2SO_3Cl$: C, 31.94; H, 3.57; N, 6.21. Found: C, 32.01; H, 3.66; N, 6.17.

*4-Chloro-5,5-dimethyl-2,2-dioxo-2,5-dihydro-[1,2]oxathiole-3-carbaldehyde oxime (***14***)*. White crystals, yield 68.9%, mp 154–155°C; ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 8.64 (s, 1H, —OH), 7.94 (s, C<u>H</u>=N), 1.71 [s, 6H, (C<u>H</u>$_3$)$_2$]; ^{13}C NMR ($CDCl_3$): δ 146.87 (<u>C</u>H=NOH), 137.76 (C_4), 127.14 (C_3), 90.32 (C_5), 25.51 ($2CH_3$). Anal. Calcd for $C_6H_8NSO_4Cl$: C, 47.92; H, 4.36; N, 9.31. Found: C, 48.08; H, 4.46; N, 9.86.

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