A Reinvestigation of the Vilsmeier Reaction of 3-Phenyl-5-isoxazolinone. Isolation of 1,3-Oxazin-6-ones

David J. Anderson

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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A report in the literature described[1] the reaction of 3-phenyl-5-isoxazolone (1) with an excess of $POCl_3$ in DMF under Vilsmeier conditions, to afford the alleged trichloro isoxazole **2** and the bis adduct **3** (Scheme I). It was also reported that **2** in refluxing methanol–NaOMe gave the methoxyisoxazolecarboxaldehyde **4** (11%).

Reaction of **2** with 10% NaOH at room temperature for 2 h was claimed to give the (dichloromethylene)azirine **5** (61%). In view of the apparent ease of formation of this unusual azirine and my own interest in such molecules,[2] it was decided to examine its mode of formation and, hopefully, its chemistry. The physical data provided for **2** was somewhat troubling, especially the extremely low field (δ 10.5) position of the $CHCl_2$ proton.

In my hands, when **1** was allowed to react with $POCl_3$ in excess DMF, the primary compound formed was the dimethylamino isoxazolone **6**[3] (Scheme II).

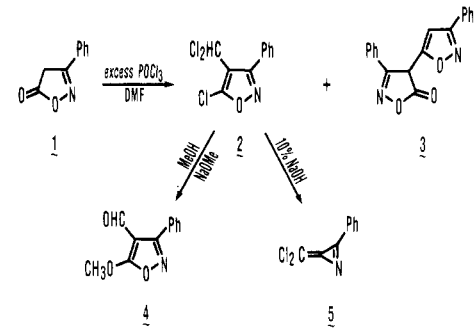
When the reaction time was extended or the temperature raised to 80 °C, an additional product was isolated. This material showed an aldehydic proton in the NMR spectrum at δ ($CDCl_3$) 9.73 together with five aromatic protons and a $N(CH_3)_2$ group. The two methyl groups were distinct singlets at δ 3.22 and 3.30, whereas those of **6** were at δ 3.25 and 3.72 with the lower field one considerably broadened due to restricted rotation[4] and the proximity of the carbonyl, suggesting the syn stereochemistry shown. Whereas, the carbonyl absorption in **6** was at 1685 cm^{-1}, the absorptions in the new product were at 1788, 1760, and 1736 cm^{-1}. This data, coupled with other spectroscopic and analytical information suggested that this new material had the oxazinone structure **7**. This was confirmed by an X-ray determination.[5] In a separate experiment, oxazinone **7** was formed cleanly from **6** with $POCl_3$–excess DMF. In addition, when **6** was allowed to react with diethylformamide–$POCl_3$, the $N(Et)_2$ oxazinone **8** was formed. A possible mechanism for the transformations is shown in Scheme III.

The isoxazolone **1** reacts via its enol form with the Vilsmeier reagent **9** to afford **10**, which loses HCl to give **6** (which may be isolated under mild conditions). Under more forcing reaction conditions, **6** can react with excess Vilsmeier reagent as shown through the ring nitrogen to give intermediate **11**. Loss of proton from **11** with concomitant ring opening affords **12**, which can recyclize to give the ring expanded oxazinone **13**. Loss of chloride ion from **13** affords the iminium ion **14**, which upon hydrolytic workup gives the aldehyde **7**.

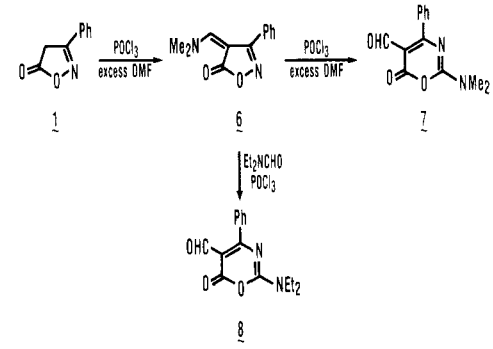
When **1** was allowed to react with excess $POCl_3$ in DMF at 70–80 °C for 1 h, a new material (52%) was isolated as a white solid, mp 44–45.5 °C. Elemental and mass spectral analysis indicated a formula of $C_{10}H_6NO_2Cl$. The IR spectrum had ν_{max} at 1698 and 1692 cm^{-1}, and the NMR spectrum exhibited an aldehydic proton at δ ($CDCl_3$) 9.93 plus five aromatic protons. This new material has been assigned to the chloroisoxazole aldehyde **15** (Scheme IV). The chloro aldehyde **15** could also be formed from **6**, but its formation was competitive with ring expansion to **7**.

In the original article[1] it was suggested that **15** was a possible labile intermediate. In a pure state I have found it quite manageable. Its structure was confirmed by the facile oxidation to the chloro acid[6] **17** with silver oxide. Treatment of **15** with excess $POCl_3$–DMF at ca. 70 °C/1 h provided a trichloro derivative (90%) as a white solid, mp 49–50 °C. The IR spectrum demonstrated the lack of a carbonyl, and the NMR spectrum showed a one-proton singlet at δ ($CDCl_3$) 6.62 plus five aromatic protons. The singlet in the NMR spectrum compares favorably to the position[7] of the $CHCl_2$ proton in α,α-dichlorotoluene at δ

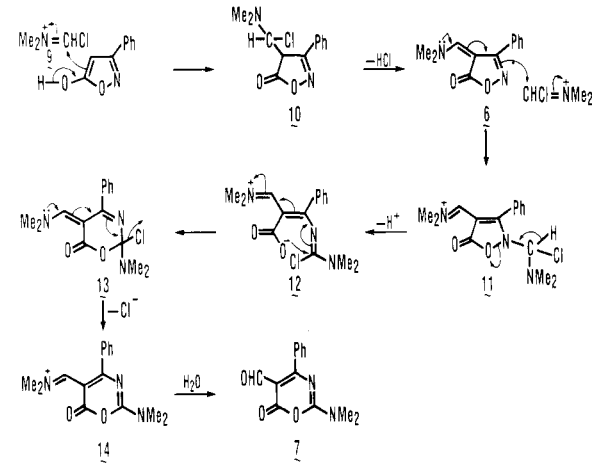
Scheme I



Scheme II



Scheme III



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(7) *Sadtler Proton NMR Spectra Index*, No. 685.

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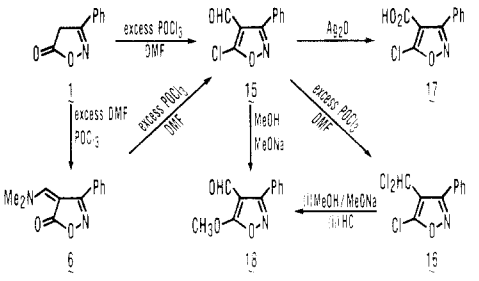
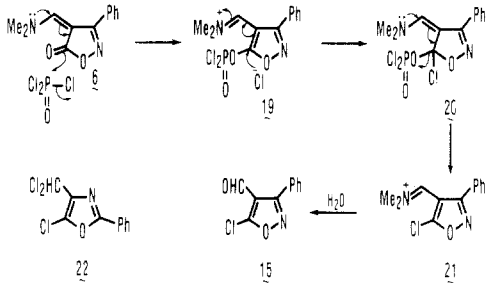
Scheme IV



Scheme V



(CCl$_4$) 6.60. The above data suggested that the structure for the trichloro compound was the isoxazole **16**. The spectral and physical properties of **16** are completely different to those reported[1] earlier for **2** (mp 118 °C, δ 10.5 for $CHCl_2$). In addition, **16** was stable to 10% NaOH at room temperature and was not converted to the azirine **5**.

5-Chloroisoxazoles have been reported[6,8] to react with alkoxide to afford 5-alkoxyisoxazoles. Thus, treatment of **15** with methanolic methoxide rapidly converted it to the methoxy aldehyde **18**. The latter compound could also be formed in high yield from **16** via its dimethyl acetal. The properties of **18** [mp 92 °C, CHO at δ ($CDCl_3$) 9.74] differed from those reported[1] for **4** [mp 110 °C, CHO at δ 10.6].

The mechanism for the formation of **15** from **1** via **6** is shown in Scheme V.

After the formation of **6** from **1** with 1 equiv of Vilsmeier reagent **6** reacts with the excess $POCl_3$ via the carbonyl oxygen to afford **19**. Chloride then attacks the 5-carbon to afford **20**, which eliminates the phosphorus moiety to give the iminium ion **21**, hydrolysis of which upon workup gives the chloro aldehyde **15**. It is considered unlikely that **21** would be chlorinated further to **16**; instead **15** has to be isolated and then treated separately with $POCl_3$ to give **16**.

I have examined a variety of combinations of $POCl_3$/DMF to reproduce the original work, but I have been unsuccessful in isolating any materials that have the same melting points or spectral data. A possible structural assignment in the original work[1] for the trichloro derivative **2** as the isomeric oxazole **22** (formed from thermal rearrangement of the isoxazole) was eliminated by comparison[9] of the mp of **22** (97 °C) with **2** (118 °C). At this stage, I am unable to make positive suggestions as to the correct structures in the original article.[1]

Experimental Section

3-Phenyl-4-[(dimethylamino)methylene]-5-isoxazolone (6). Dimethylformamide (14.0 g, 192 mmol) was cooled in an ice bath and phosphorus oxychloride (10.7 g, 70 mmol) added dropwise over 30 min. 3-Phenyl-5-isoxazolone (10.3 g, 64 mmol) was then added over 2 min and the reaction stirred at room temperature for 30 min and then at 60 °C for 30 min. After cooling, the reaction mixture was partitioned between water (500 mL) and chloroform (500 mL), while neutralizing with 5% $NaHCO_3$. The organic layer was separated and the aqueous layer washed with chloroform (250 mL). The combined organic extracts were washed with water (2 × 250 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized three times from chloroform/Skelly B to afford pale yellow plates (4.8 g, 35%): mp 145.0–146.5 °C (lit.[3] mp 152–153 °C); IR (Nujol) ν 1685, 1609, 1520, 1380, 1146, 1080, 962, 864, 753, 690, 650 cm^{-1}; NMR ($CDCl_3$) δ 3.25 (s, 3 H, NCH_3), 3.72 (brd, s, 3 H, NCH_3), 7.08 (s, 1 H, =CH), 7.43 (s, 5 H, Ar); MS, *m/e* (relative intensity) 216 (57), 215 (100), 171 (13), 158 (13), 144 (27), 115 (46), 77 (24). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.55; N, 12.96. Found: C, 66.31; H, 5.14; N, 12.79.

2-(Dimethylamino)-5-formyl-4-phenyl-1,3-oxazin-6-one (7). Phosphorus oxychloride (10 mL, 9.44 g, 129 mmol) was added slowly to dimethylformamide (25 mL, 23.6 g, 323 mmol) cooled in an ice bath. After the addition was complete, 3-phenyl-5-isoxazolone (1.61 g, 10 mmol) was added dissolved in DMF (5 mL). The reaction was stirred at room temperature for 2 h and then at 80 °C for 3 h. After cooling, the mixture was poured into ice–water (400 mL) and neutralized carefully with $NaHCO_3$. The precipitate was filtered, dissolved in chloroform (150 mL) and dried over $MgSO_4$. Removal of the solvent gave a yellow solid (1.73 g, 71%), which was recrystallized from chloroform–hexane as large yellow granules: mp 161.5–162.5 °C; IR (Nujol) ν 1788, 1760, 1736, 1600, 1505, 1400, 760 cm^{-1}; NMR ($CDCl_3$) δ 3.22 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3), 7.30–7.75 (m, 5 H, Ar), 9.73 (s, 1 H, CHO); MS, *m/e* (relative intensity) 244 (71), 216 (15), 200 (31), 199 (14), 172 (28), 146 (15), 129 (31), 116 (16), 72 (100). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.92; N, 11.47. Found: C, 63.86; H, 4.98; N, 11.40.

2-(Diethylamino)-5-formyl-4-phenyl-1,3-oxazin-6-one (8). Phosphorus oxychloride (5 mL, 8.38 g, 54.6 mmol) was added dropwise over 2 min to ice-cooled diethylformamide (10 mL, 9.1 g, 90 mmol). The mixture was stirred for 5 min, and then the dimethylamino isoxazolone **6** (1.0 g, 4.6 mmol) was added. After warming to room temperature, the reaction was then heated on a steam bath for 40 min. Upon cooling the mixture was slowly added to a cold saturated $NaHCO_3$ solution. The precipitate was filtered, dried (0.90 g, 77%, mp 92–95 °C), and then recrystallized from acetone–Skellysolve B to afford bright yellow prisms (0.66 g, 51%): mp 94–96 °C; IR (Nujol) ν 1789, 1762, 1683, 1661, 1655, 1594, 1521, 1513, 1268, 1085, 1002, 772, 754, 736, 617 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 6 H, 2 × CH_3), 3.60 (q, J = 7.5 Hz, 2 H, NCH_2), 3.72 (q, J = 7.5 Hz, 2 H, NCH_2), 7.30–7.75 (m, 5 H, Ar), 9.81 (s, 1 H, CHO); UV (EtOH) λ_{max} (ϵ) 204 (16 100), 256 (19 150), 280 (sh, 9800), 342 (19 100); MS *m/e* (relative intensity) 272 (100), 200 (52), 172 (33), 129 (43), 116 (22), 104 (23), 100 (70), 72 (94). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.87; H, 5.92; N, 10.19.

5-Chloro-4-formyl-3-phenylisoxazole (15). Dimethylformamide (65 mL, 61.4 g, 0.84 mol) was added over 5 min to phosphorus oxychloride (160 mL, 268 g, 1.75 mol). The temperature rose to 70 °C, and then 3-phenyl-5-isoxazolone (16.1 g, 0.1 mol) was added. The temperature was maintained at 70–80 °C for 1.5 h, and then the reaction was allowed to cool. The mixture was poured slowly over ice–water (3 L) with vigorous stirring. The water was decanted off, and the residual gummy material was dissolved in methylene chloride (300 mL) and dried ($MgSO_4$) to afford a red oil (12.0 g). The original aqueous extract was treated with methylene chloride (2 × 250 mL) to afford additional red oil (4.0 g). The combined oils were chromatographed over silica gel by eluting with 1:1 methylene chloride–Skellysolve B to afford the aldehyde as a clear syrup (9.64 g, 46%), which slowly crystallized. Recrystallization from ether–Skellysolve B gave white plates: mp 44–45.5 °C; IR (Nujol) ν 1698, 1692, 1546, 791, 780, 768, 721, 717, 699 cm^{-1}; NMR ($CDCl_3$) δ 7.35–7 .70 (m, 3 H, Ar), 7.70–8.00 (m, 2 H, Ar), 9.93 (s, 1 H, CHO); MS, *m/e* (relative intensity) 209 (4), 207 (18), 172 (12), 144 (100), 143 (25), 116 (30), 104 (30), 77 (71), 76 (20). Anal. Calcd for $C_{10}H_6ClNO_2$: C, 57.85; H, 2.91; N, 6.75; Cl, 17.08. Found: C, 57.35; H, 2.96; N, 6.62; Cl, 16.85.

5-Chloro-4-(dichloromethyl)-3-phenylisoxazole (16). Phosphorus oxychloride (25 ml) was added to the aldehyde **15**

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(2.0 g, 9.64 mmol) dissolved in chloroform (5 mL) and DMF (5 mL). The reaction was heated under reflux for 1 h and then allowed to cool and poured into ice-water (500 mL). Saturated $NaHCO_3$ was cautiously added over 1.5 h to effect neutralization, and the resulting mixture extracted with methylene chloride (2 × 400 mL). The organic extracts were washed with water (2 × 400 mL), dried ($MgSO_4$), filtered, and evaporated to yield a yellow oil. Chromatography over silica gel (100 g), eluting with 1:1 methylene chloride–Skellysolve B afforded the trichloroisoxazole as a clear syrup, which slowly crystallized (2.28 g, 90%). Recrystallization from ether–Skellysolve B gave white prisms: mp 49–50 °C; IR (Nujol) ν 1595, 1570, 1445, 1400, 1206, 1100, 952, 883, 777, 752, 740, 694 cm^{-1}; NMR ($CDCl_3$) δ 6.62 (s, 1 H, $CHCl_2$), 7.35–7.90 (m, 5 H, Ar); MS, *m/e* (relative intensity) 265 (2), 263 (7), 261 (7), 228 (35), 226 (56), 162 (11), 140 (15), 138 (48), 128 (20), 77 (100), 76 (11). Anal. Calcd for $C_{10}H_6Cl_3NO$: C, 45.74; H, 2.29; N, 5.34; Cl, 40.54. Found: C, 45.41; H, 2.45; N, 5.41; Cl, 40.57.

5-Chloro-3-phenylisoxazole-4-carboxylic Acid (17). A solution (10 mL, 10 mmol) of 1 M sodium hydroxide was added to a stirred solution of silver nitrate (0.85 g, 5 mmol) in water (10 mL). After the mixture was stirred for 10 min, the chloroaldehyde **15** (0.50 g, 2.41 mmol) was added and stirring continued for 5 h. The reaction was filtered and the filtrate treated with concentrated HCl (ca. 1 mL). The resultant yellow precipitate was filtered and washed with a little water and dried. Recrystallization from chloroform–hexane gave the chloro acid as very pale yellow crystals (0.394 g, 73%): mp 180 °C dec (lit.[6] mp 176–179 °C); IR (Nujol) ν 2660, 2560, 1680, 1572, 1548, 1300, 1155, 1140, 760 cm^{-1}; MS, *m/e* (relative intensity) 225 (14), 223 (42), 188 (67), 144 (75), 116 (33), 77 (100), 63 (15). Anal. Calcd for $C_{10}H_6ClNO_3$: C, 53.72; H, 2.70; N, 6.26; Cl, 15.85. Found: C, 53.47; H, 2.77; N, 5.73; Cl, 15.98.

5-Methoxy-3-phenylisoxazole-4-carboxaldehyde (18). The chloroaldehyde **15** (1.0 g, 4.82 mmol) was stirred in methanol (25 mL), and 120 drops (ca. 1.5 mL) of a 25% solution of sodium methoxide in methanol was added. After 1 h the solvent was removed and the residue partitioned between ether (100 mL) and water (50 mL). The ether was dried ($MgSO_4$), filtered, and evaporated to afford the methoxy compound (0.92 g, 94%), mp 89–91 °C. Recrystallization from hexane gave white flakes (0.67 g, 68%): mp 92 °C; IR (Nujol) ν 1694, 1681, 1586, 1573 (s), 792, 773, 739, 693 cm^{-1}; NMR ($CDCl_3$) δ 4.32 (s, 3 H, OCH_3), 7.35–7.60 (m, 3 H, Ar), 7.65–7.90 (m, 2 H, Ar), 9.74 (s, 1 H, CHO); MS, *m/e* (relative intensity) 203 (34), 144 (92), 130 (50), 129 (33), 116 (28), 104 (32), 77 (100). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.10; H, 4.60; N, 6.92.

The Trichloro Isoxazole 16 and Methoxide. The trichloro isoxazole **16** (200 mg, 0.76 mmol) was stirred in methanol (10 mL) and 70 drops (ca. 0.9 mL) of a 25% methanolic sodium methoxide solution added. After 2 h the solvent was removed and the residue partitioned between water (20 mL) and chloroform (20 mL). The chloroform was dried (Na_2SO_4), filtered, and evaporated to afford the crude acetal 5-methoxy-4-(dimethoxymethyl)-3-phenylisoxazole as a pale yellow viscous oil (200 mg, 99%): NMR ($CDCl_3$) δ 3.34 (s, 6 H, 2 × OCH_3), 4.16 (s, 3 H, OCH_3), 5.18 (s, 1 H, CH), 7.30–7.55 (m, 3 H, Ar), 7.65–7.90 (m, 2 H, Ar). The oil was stirred with 1 N HCl (10 mL) for 1 h and then extracted with chloroform (20 mL). After drying ($MgSO_4$), filtering, and evaporating, there was obtained the crude aldehyde as a white solid (150 mg, 97%). Recrystallization from hexane gave pure 5-methoxy-3-phenylisoxazole-4-carboxaldehyde (**18**) as white plates (114 mg, 74%), mp 92 °C.

Acknowledgment. I thank Arlen J. Taylor for some of the laboratory experiments and Connie Chidester, Charlotte G. Waber, and William Watt for collection and refinement of the X-ray data and determination of the structure of **7**. In addition, I thank Professors Charles W. Rees and Scott Denmark for stimulating mechanistic discussions.

Registry No. **1**, 1076-59-1; **6**, 5272-46-8; **7**, 100230-70-4; **8**, 100230-71-5; **15**, 100230-72-6; **16**, 65926-99-0; **17**, 3357-00-4; **18**, 65927-06-2.

Photochemistry of Methyl Viologen Dicarboxylate and Polycarboxylate Ion Pairs

Guilford Jones, II,* and Matthew B. Zisk

Department of Chemistry, Boston University, Boston, Massachusetts 02215

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Methyl viologen (1,1′-dimethyl-4,4′-bipyridinium ion, MV^{2+}) has received considerable attention in recent years as an efficient relay in the photocatalyzed reduction of water to hydrogen.[1] The tendency of MV^{2+} to ion pair or to form complexes with a variety of "donor" ions or molecules is now recognized as a general feature to be taken into account in the design of photoredox systems.[2-7] For example, the ion pairing or complexation characteristics of MV^{2+} in combination with the familiar donors, EDTA and triethanolamine (TEOA), have been recently described.[8,9] The pH dependence of the enhanced 350–450-nm absorption for complexes of EDTA (K_{eq} = 5.3 and 68 M^{-1} at pH 4.6 and 11.2, respectively) and TEOA (K_{eq} = 0.3 M^{-1}, pH 10.2) clearly demonstrates that the state of protonation of complexing species is important and that both nitrogen lone pair donor moieties and carboxylate charged groups play a role in binding.

As part of a broader study of complexes of methyl viologen,[10] we have investigated the binding of MV^{2+} to a series of simple dicarboxylic acids in water. One focus for the work involves the comparison of binding to acids of different chain length, where the relationship of sites of electrostatic attraction to carboxylate groups would vary with acid structure. Another comparison was made of the behavior of this diacid series with that of two polymers, polyacrylic (PAA) and polymethacrylic (PMAA) acids. For the polyelectrolytes, MV^{2+} would be expected to be attracted to the field of charge on the polymer, which in turn would be altered according to pH and polymer conformation. The binding of a photoredox reagent to polymers is important, since polymers are commonly used to stabilize colloidal metals which act as catalysts for formation of hydrogen from water and related photoredox reactions.[11]

In this paper, we report the spectra and binding properties of MV^{2+} in the presence of relatively high concentrations of the various acids. The results of steady and flash photolysis of MV^{2+} carboxylate ion pairs are reported also, including the observed net decarboxylation of acids and formation of reduced viologen, $MV^{+}\cdot$. Also of interest, is an apparent effect of excitation wavelength on the quantum yield of net electron transfer (higher yields of escaped radicals on irradiation at higher frequencies), a result related to earlier observations made for charge-

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