SYNTHESIS, SPECTROSCOPIC AND STRUCTURAL PROPERTIES OF NOVEL SUBSTITUTED 2-TRICHLOROMETHYL-3-PHENYL-1,3-THIAZOLIDIN-4-ONES

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Abstract. The reaction of chloral with substituted anilines resulted in formation of the respective 2,2,2-trichloroethylidene anilines. Subsequent treatment of these imines *in situ* with thioglycolic acid produced a series of substituted 2-trichloromethyl-3-phenyl-1,3-thiazolidin-4-ones. This synthetic route was interesting in light of several other possible intermediates which can be formed on reaction of chloral with amines. High resolution (300 MHz) ^{1}H and ^{13}C magnetic resonance spectra and *ab initio* calculations gave insight into the conformation of the observed products.

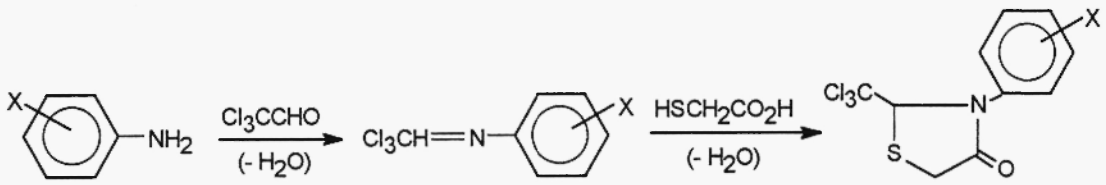
Introduction. Review of the literature shows that the reaction of chloral with amines yields a variety of products depending on amine type and choice of reaction conditions. Chloral reacts exclusively with aliphatic amines to produce N-formyl compounds (1-4). Reaction of equimolar or excess substituted anilines with chloral in benzene gives N,N'-β,β,β-trichloroethylidene-*bis*-substituted anilines, $Cl_3CCH(NH\text{-}C_6H_4X)_2$ (5). However, in polar solvents, i.e. aqueous acetic acid, these same two substrates yield N-arylaminoalcohols, $Cl_3CCH(OH)NHC_6H_4X$ (6). Reaction of chloral with anthranilic acid results in formation of the imine $Cl_3CCH{=}NC_6H_4COOH$ (7). It would therefore appear that any primary amine, aliphatic or aromatic, reacts with chloral to initially form an aminoalcohol (8).

The kinetics (3,4) of the reaction between chloral and some aliphatic cyclic amines, $[C_6H_4(CH_2)_3NH]$, to give formamides (1,2) have been investigated. The reaction is second order overall, first order in each reactant. Unreacted aliphatic amine acts as a strong base which subsequently reacts with the intermediate N-alkylaminoalcohol. Since aliphatic amines are $1x10^6$ more basic than their aromatic counterparts (9), the alcohol proton is removed from the N-alkylaminoalcohol and the trichloromethyl group leaves in a manner similar to the final stage of the iodoform reaction (10).

In the case of the reaction of chloral with aromatic amines the outcome is less clear. The alcohol proton of the N-arylaminoalcohol intermediate is not as labile because of the lower basicity of the aromatic amine. The N-arylamino-alcohol can now be attacked either by the amine acting as a nucleophile to yield the N,N'-β,β,β-trichloroethylidene-*bis*-substituted anilines, $Cl_3CCH(NH\text{-}C_6H4X)_2$, or undergo condensation to the imine. There is some evidence that condensation to the imine can be effected upon heating; however, the imines are generally unstable on attempted isolation (11).

Thiazolidin-4-ones have exhibited a long history of biological activity (12,13). Recently, their employment as a ligand to tin has led to a series of 1:1 complexes which exhibited substantial *in vitro* activity against *Ceratocystis ulmi*, the causative agent in Dutch Elm disease (14,15). One of the ligands used to form the tin complex was 2-trichloromethyl-3-phenyl-1,3-thiazolidin-4-one 1a. The activity of this ligand gave good cause for the synthesis of substituted derivatives. However, the unpredictability, shown in the literature (*vide supra*), of the reaction of chloral with substituted anilines gave added interest to the investigation, particularly as this was our route of choice.

Results and Discussion. The synthesis of 1a had been achieved by reacting chloral with aniline, followed by thioglycolic acid. This reaction could take many potential pathways, with limited reports of imine formation (6,8). Therefore, we decided to test its generality by repeating the synthesis with substituted anilines 1b-j, **Scheme 1**. All products 1a-j are racemic mixtures. Even though the imines were not successfully isolated due to their instability (16), imine formation *in situ* was achieved. There was no obvious correlation between substituent size or electronic effect on the yields obtained, the iodo derivatives 1g and 1h giving the poorest yields.



1a-j

X = 1a = H, 1b = m-F, 1c = p-Cl, 1d = m-Cl, 1e = p-Br, 1f = m-Br, 1g = p-i, 1h= m-I, 1i = m-Me, 1j = p-MeO

Scheme 1

Investigations utilising Hammett (17) and related constants, i.e. σ, $\sigma+$ and $\sigma-$, which reflect the increase or loss of electron density, have extended beyond kinetic and equilibrium measurements to spectroscopic data. Use of NMR spectroscopy has been employed extensively to investigate the variation of electron density surrounding different nuclei (18,19,20). The chemical shifts for the methine and methylene protons and the carbons of the heterocyclic ring (C2,C4,C5) for 1a-j might appear to be sensitive to substituents on the N-phenyl group. Therefore, chemical shift correlations for these sites, using ^{1}H and ^{13}C NMR respectively, with Hammett's s constants and Swain-Lupton dual substituent parameters were attempted.

No obvious correlations of the substituent with the heterocyclic ring protons, using either the Hammett or Swain-Lupton approaches, were obtained with the ^{1}H NMR data. This could possibly be due to the overpowering electron withdrawing effect of the trichloromethyl group. However, the ^{13}C NMR chemical shift data did show substituent

correlations with the chiral carbon and the carbonyl sites when using the field (F) and resonance (R) constants of Swain and Lupton (Equation 1), where δ_o is the chemical shift for the unsubstituted thiazolidinone 1a and δ is the chemical shift

$$\delta - \delta_o = f F + r R \qquad \text{Equation 1}$$

for the substituted compounds 1b-i. The resulting solution to Equation 1 for carbon, C2, gave -0.81F - 0.82R - 0.04 (r=0.93; n=10) with a 50% resonance contribution. For the carbonyl carbon (C4) - 0.65F - 0.76R + 0.02 (r=0.88; n=10) is the solution to Equation 1 with 54% resonance.

The ^{1}H NMR data show that the methylene protons H_A and H_B (2 and 3) are distinctly non-equivalent, with coupling constants between 114 and 117 Hz, consistent with earlier observations for substituted 2,3-diphenyl-1,3-thiazolidin-4-ones (21, 22). The methine proton is coupled to H_A, with the more downfield chemical shift assigned to H_A. This coupling is clearly observed because on irradiation of the methine proton the long range coupling disappears for H_A. The non-equivalent nature of these methylene protons is more a function of the lone pairs of electrons on the larger sulfur atom than field effects from the carbonyl. The geometry of the thiazolidine ring has been confirmed by an X-ray crystal structure of a closely related 2,3-diphenyl substituted system (15).

2 3

Ab initio calculations for 1a at the 3-21G level using Spartan 3.0 (23) showed the minimised structures for both conformers, 2 and 3, were close in energy, as expected. Interestingly, however, HyperChem (24) MM+ calculations for these same structures showed that 2 was about 15 kcal mol^{-1} more stable than 3. This calculated difference would intuitively appear to result largely from a change in dihedral angles for these structures. However, only small differences (maximum of 1.5°) in the calculated bond angles cannot be significant in fostering these differences in stabilities. From the data one may conclude that a change of about one-half degree in the C(CCl_3)-C2-S1 angle is associated with a shift of the trichloromethyl group between axial and equatorial positions; this was the case for both the Spartan (23) and the Hyperchem (24) calculated angles. Therefore, analyses of the data strongly indicates that both conformers are energetically very close, in solution. However, in the solid state structure 2 and related systems have shown a preference for the large group at C2 to favor the axial position (15, 21).

Conclusions. A valuable synthetic procedure for preparation of 2-trichloromethyl-3-substituted phenyl-1,3-thiazolidin-4-ones has been discovered. The resulting product appears to form via the reaction of an imine from chloral and amine with thioglycolic acid. This occurs even though alkylideneimines are known to be relatively unstable (16, 25). In this case the intermediate, a substituted S-α'-aminomercaptocacetic acid derivative is formed from the imine and thioglycolic acid. Subsequent ring closure to the thiazolidin-4-one completes the process.

Experimental. The 2-trichloromethyl-3-phenyl substituted-1,3-thiazolidin-4-ones were prepared using the procedure previously described (25) to prepare 1a. The imine intermediates were not isolated, but were prepared *in situ* and thioglycolic acid was added to the same reaction vessel. Attempts to isolate the imine intermediate resulted in decomposition on work-up. No attempt was made to optimise the yields. Melting points were recorded either on a Thomas-Hoover or Mel-Temp apparatus and are uncorrected. Samples for both ^{1}H and ^{13}C were dissolved in deuterochloroform at a concentration of 40 mg/mL. Precision bore 5 mm NMR tubes supplied by Norrell, Inc. were used. ^{1}H NMR spectra were obtained on a General Electric QE 300 spectrometer at 300.67 MHz. ^{13}C spectra were obtained using a Varian VXRS400 spectrometer at 75.47 MHz with a 45° observed pulse using Waltz-16 decoulping. The operating temperature for both spectrometers was 298 K. Both spectrometers were locked to the deuterium resonance of the solvent ($CDCl_3$) and chemical shifts (ppm) were referenced to the solvent peaks at 7.26 and 77.0 ppm in the ^{1}H and ^{13}C spectra, respectively. Infrared spectra were obtained in KBr (Aldrich FT-IR grade) pellets on a Mattson Instruments Galaxy 4020 spectrometer at 2 cm^{-1} resolution. Elemental analyses were performed by Galbraith Laboratories, Inc., 2323 Sycamore Drive, Knoxville, TN 37921-1750. The mass spectrum for 1d was run on a Kratos 950 instrument using electron impact with a source temperature of 200°C

2-Trichloromethyl-3-phenyl-1,3-thiazolidin-4-one, 1a: Yield 43%, mp 174-175 °C; IR: 1687 cm^{-1}; ^{1}H NMR: δ 7.1-7.5 (m, 5H, aromatics), 5.72 (s, J=1.6 Hz, 1H), 3.77-3.96 (dd, J=1.6, 14.1 Hz, 2H); ^{13}C NMR: δ 171.65 (C=O), 138.45 (N-Ar), 129.17, 127.98, 126.98, 103.18 (CCl_3), 77.69 (C2), 33.08 (C5). Anal. Calcd. for $C_{10}H_8NOSCl_3$: C, 40.40; H, 2.72; N, 4.72; Cl, 35.86. Found: C, 40.60, H, 2.74; N, 4.60; Cl, 35.44.

2-Trichloromethyl-3-(3-fluorophenyl)-1,3-thiazolidin-4-one, 1b: Yield 46%; mp 186-187 °C; IR: 1687 cm^{-1}; 1688 cm^{-1}; ^{1}H NMR: δ 6.93-7.31 (m, 4H, aromatics), 6.04 (s, J=1.0 Hz, 1H), 3.85-4.02 (dd, J=1.0, 15.8 Hz, 2H); ^{13}C NMR: δ 171.52 (C=O), 139.83, 139.73 (N-Ar), 163.99, 161.52 (C-F), 130.38, 130.29, 122.14, 122.11, 115.27, 114.50, 115.06, 114.26, 103.10 (CCl_3), 77.53 (C2), 33.08 (C5). Anal. Calcd. for $C_{10}H_7NOSCl_3F$: C, 38.18; H, 2.24; N, 4.45. Found: C, 38.40; H, 2.29; N, 4.40.

2-Trichloromethyl-3-(4-chlorophenyl)-1,3-thiazolidin-4-one, 1c: Yield 20%; mp 183-185 °C; IR: 1685 cm^{-1}; ^{1}H NMR: δ 7.11-7.50 (m, 4H, aromatics), 6.04 (s, J=1.2 Hz, 1H), 3.80-3.92 (dd, J=1.2, 15.9 Hz, 2H); ^{13}C NMR: δ 171.61 (C=O), 136.96 (N-Ar), 133.78 (C-Cl), 129.46, 127.92, 103.06 (CCl_3), 77.51 (C2), 32.65 (C5). Anal. Calcd. for $C_{10}H7NOSCl_4$: C, 36.47; H, 2.13; N, 4.25. Found: C, 36.65; H, 2.12; N, 4.04.

2-Trichloromethyl-3-(3-chlorophenyl)-1,3-thiazolidin-4-one, 1d: Yield 20%; mp 170-171 °C; IR: 1687 cm^{-1}; 1H NMR: δ 7.05-7.65 (m, 4H, aromatics), 6.06 (s, J=1.5 Hz, 1H), 3.79-3.92 (dd, J=1.5, 15.8 Hz, 2H); ^{13}C NMR: δ 171.57 (C=O), 139.55 (N-Ar), 134.80 (C-Cl), 130.16, 128.31, 126.88, 124.99, 103.08 (CCl_3), 77.49 (C2), 33.04 (C5). Elemental analysis of this compound proved difficult because it was significantly more unstable than the other analogs. The molecular mass

determined to be correct, 329, using mass spectrometry. Also, the M+2, M+4, M+6, M+8 signals are consistent with molecule containing four chlorine atoms (26)

2-Trichloromethyl-3-(4-bromophenyl)-1,3-thiazolidin-4-one, 1e: Yield 45%; mp 174-176 °C; IR: 1680 cm^{-1}; ^1H NMR: δ 7.12-7.45 (m, 4H, aromatics), 6.10 (s, J=1.5 Hz, 1H), 3.82-4.01 (dd, J=1.5, 15.8 Hz, 2H); ^{13}C NMR: δ 171.57 (C=O), 137.50 (N-Ar), 121.78 (C-Br), 132.46, 128.22, 103.07 (CCl_3), 77.47 (C2), 33.01 (C5). Anal. Calcd. for $C_{10}H_7NOSBrCl_3$: C, 31.99; H, 1.88; N, 3.73. Found: C, 31.96; H, 1.86; N, 3.62.

2-Trichloromethyl-3-(3-bromophenyl)-1,3-thiazolidin-4-one, 1f: Yield 12%; mp 169-70 °C; IR: 1688 cm^{-1}; ^1H NMR: δ 7.07-7.41 (m, 4H, aromatics), 6.08 (s, J1.2 Hz, 1H), 3.80-4.00 (dd, J=1.2, 15.9 Hz, 2H); ^{13}C NMR: δ 171.56 (C=O), 122.50 (N-Ar), 131.21 (C-Br), 131.21, 130.41, 129.64, 125.49, 103.06 (CCl3), 77.47 (C2), 33.02 (C5). Anal. Calcd. for $C_{10}H_7NOSBrCl_3$: C, 31.99; H, 1.88; N, 3.73. Found: C, 31.85; H, 1.83; N, 3.64.

2-Trichloromethyl-3-(4-iodophenyl)-1,3-thiazolidin-4-one, 1g: Yield 7%; mp 212-213 °C; IR: 1683 cm^{-1}; ^1H NMR: δ 6.94-7.61 (m, 4H, aromatics), 6.08 (s, J=1.5 Hz, 1H), 3.83-4.01 (dd, J=1.5, 15.8 Hz, 2H); ^{13}C NMR: δ 171.54 (C=O), 139.09 (N-Ar), 93.19 (C-Cl), 138.45, 138.26, 128.39, 128.11, 103.10 (CCl_3), 77.43 (C2), 33.04 (C5). Anal. Calcd. for $C_{10}H_7NOSICl_3$: C, 28.43; H, 1.67; N, 3.32. Found: C, 28.58; H, 1.71; N, 3.23.

2-Trichloromethyl-3-(3-iodophenyl)-1,3-thiazolidin-4-one, 1h: Yield 6%; mp 170-171 °C; IR: 1687 cm^{-1}; ^1H NMR: δ 7.04-7.28 (m, 4H, aromatics), 6.03 (s, J=1.5 Hz, 1H), 3.80-3.95 (dd, J=1.5, 15.8 Hz, 2H); ^{13}C NMR: δ 171.61 (C=O), 139.56 (N-Ar), 93.69 (C-Cl), 137.19, 135.31, 130.59, 126.33, 103.09 (CCl_3), 77.52 (C2), 33.04 (C5). Anal. Calcd. for $C_{10}H_7NOSICl_3$: C, 28.43; H, 1.67; N, 3.32. Found: C, 28.61; H, 1.60; N, 3.30.

2-Trichloromethyl-3-(3-methylphenyl)-1,3-thiazolidin-4-one, 1i: Yield 74%; mp 166-167 °C; IR: 1696 cm^{-1}; ^1H NMR: δ 6.90-7.50 (m, 4H, aromatics), 6.08 (s, J=1.8 Hz, 1H), 3.90-4.05 (dd, J=1.8, 15.7 Hz, 2H); 2.27 (s, 3H, Ar-CH_3); ^{13}C NMR: δ 171.77 (C=O), 139.10 (N-Ar), 138.24 (Ar-CH_3), 128.85, 128.76, 127.02, 123.54, 103.12 (CCl_3), 77.70(C2), 33.03 (C5); 21.20 (CH_3). Anal. Calcd. for $C_{11}H_{10}NOSCl_3$: C, 42.72; H, 3.24; N, 4.53. Found: C, 42.38; H, 3.46; N, 4.34.

2-Trichloromethyl-3-(4-methoxylphenyl)-1,3-thiazolidin-4-one, 1i: Yield 62%; mp >340 °C; IR: 1688 cm^{-1}; 1H NMR: δ 6.80-7.34 (m, 4H, aromatics), 6.01 (s, J=1.8 Hz, 1H), 3.84-4.03 (dd, J=1.8, 15.7 Hz, 2H); 3.70 (s, 3H, OCH_3); ^{13}C NMR: δ 171.99 (C=O), 131.15 (N-Ar), 159.13 (Ar-OCH_3), 127.97, 114.51; 103.14 (CCl_3), 77.95 (C2), 32.96 (C5); 55.46 (OCH_3). Anal. Calcd. for $C_{10}H_{10}NO_2SCl_3$: C, 40.45; H, 3.09; N, 4.29. Found: C, 40.93; H, 3.17; N, 4.28.

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