

Verifying the Predictability of ^{13}C Chemical Shifts for a Series of Substituted-2-(4-Chlorophenyl)-3-Phenyl-1,3-Thiazolidin-4-Ones

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Abstract

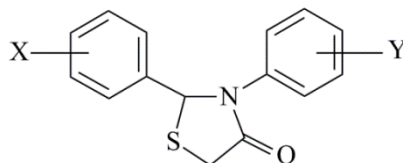
Previously, an “additivity” equation relating experimental ^{13}C chemical shift data for two *monosubstituted* diphenyl-1,3-thiazolidin-4-one series was developed to predict chemical shifts for a similarly substituted *bis*-disubstituted thiazolidinone series. The sites of interest in the 1,3-thiazolidin-4-one are at the C-2, C-4, and C-5 carbons. The empirically derived equation for predicting the chemical shifts is $\delta_{\text{XY}} = \delta_{\text{H}} + (\delta_{\text{X}} - \delta_{\text{H}}) + (\delta_{\text{Y}} - \delta_{\text{H}})$ where δ_{XY} is the predicted chemical shift for the disubstituted thiazolidinone, δ_{H} is the experimental chemical shift for the unsubstituted thiazolidinone, δ_{X} is the experimental chemical shift for substituent in the 2-phenyl ring, and δ_{Y} is the experimental chemical shift for substituent in the N-(3)-phenyl ring. This article discusses the application of the aforementioned equation with respect to a new series of 2-(*p*-chlorophenyl)-substituted-3-phenyl-1,3-thiazolidin-4-ones with a comparison of both experimental and predicted ^{13}C chemical shifts for the C-2, C4 and C-5 sites in the thiazolidinone ring. Utilization of the equation showed a level of chemical shift predictability with a degree of accuracy in concert with a previously reported series. The degree of predictability again showed a dependency on the particular substituent and the chemical shift for the site being predicted. This was ± 0.06 ppm for C-2, ± 0.2 ppm for C-4 and ± 0.09 ppm for C5. Finally, there was a correlation between Hammett σ values and the substituent chemical shifts using ^{13}C values at C-2. The r value was -0.86 indicating that the C-2 carbon preferred a positive charge.

Keywords: thiazolidin-4-ones, ^1H NMR, ^{13}C NMR, substituent effects

1. Introduction

Previous studies have reported Hammett correlations between the ^{13}C experimental chemical shift values (or substituent chemical shifts—SCS) for two series of monosubstituted 2,3-diphenyl-1,3-thiazolidin-4-ones (Woolston, Lee, Swinbourne, & Thomas, 1992; Woolston, Lee, & Swinbourne, 1993; Tierney et al., 1996a). These two groups used slightly different substituents on the two phenyl rings; however, the resulting correlations were very similar. The two monosubstituted chemical shift values were then used to predict the ^{13}C chemical shift values at the C-2, C-4 and C-5 sites values for a *bis*-(disubstituted)-2,3-diphenyl-1,3-thiazolidin-4-one series; where both substituents are the same and at the same location on both phenyl rings. The *bis*-(disubstituted)-2,3-diphenyl-1,3-thiazolidin-4-one series was also synthesized in order to compare observations to predicted values (Tierney et al., 2005). Correlations relating electronic effects from substituents in the phenyl rings to the observed chemical shifts for the monosubstituted and *bis*-disubstituted series utilized a form of the Hammett Equation, shown by Equation 1. The equation used to predict the chemical shift (δ) values for the *bis*-disubstituted series is shown by Equation 2. A reasonably good correlation was determined to exist between experimental and predicted values for the ^{13}C chemical shifts when applying Equation 2 relating the chemical shift values for the two monosubstituted series (Series 1 and 2) to the disubstituted series (Series 3) (Tierney et al.,

2005). The substituents used for all compounds in Series 1-3 that have been used to develop the relationship, represented by Equation 2, are shown in Figure 1.



Series 1: X = *p*-NO₂, *m*-NO₂, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, H, *p*-CH₃, *m*-CH₃, *p*-OCH₃, *m*-OCH₃; Y=H

Series 2: X = H; Y = *p*-NO₂, *m*-NO₂, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, H, *p*-CH₃, *m*-CH₃, *p*-OCH₃, *m*-OCH₃;

Series 3: X = Y = *p*-NO₂, *m*-NO₂, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, *p*-CH₃, *m*-CH₃, *p*-OCH₃, *m*-OCH₃

Series 4: X = *p*-NO₂, *m*-NO₂, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, H, *p*-CH₃, *m*-CH₃, *p*-OCH₃, *m*-OCH₃; Y = *p*-OCH₃

Figure 1. The mono and disubstituted series of compounds prepared to date

$$\delta_X - \delta_H = \rho\sigma \text{ or } \delta_Y - \delta_H = \rho\sigma \quad (1)$$

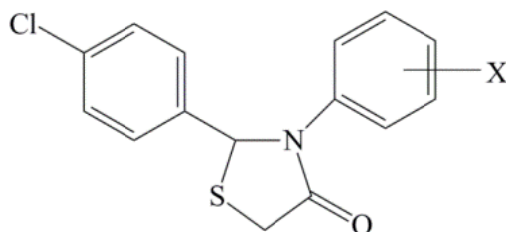
$$\delta_{XY} = \delta_H + (\delta_X - \delta_H) + (\delta_Y - \delta_H) \quad (2)$$

In Equation 1, δ_X (or δ_Y) is the chemical shift for the substituent under consideration, and δ_H is the chemical shift for the unsubstituted compound, *e.g.* where the substituent is hydrogen. In Equation 2, δ_H is the chemical shift value for the unsubstituted compound, δ_X is the chemical shift values observed for Series 1 compounds, δ_Y is the chemical shift values observed for Series 2 compounds, and δ_{XY} is the predicted chemical shift for the additivity effect shown by these shifts in the *bis*-disubstituted compounds in Series 3 (Figure 1). The components $\delta_X - \delta_H$ and $\delta_Y - \delta_H$ are relative substituent chemical shift (SCS) terms. In addition, predictions have been reported for a series of compounds, 3-(*p*-methoxyphenyl)-substituted-2-phenyl-1,3-thiazolidin-4-ones (Series 4, Figure 1), where the values predicted by δ_{XY} in Equation 1 yield the results from a fixed methoxy substituent in the C-2 phenyl ring and varying substituents on the phenyl ring at N-3 (Tierney et al., 2008). This was the first series reported in which the substituent, other than hydrogen, was fixed in one ring and the substituents were varied in the other ring. Effectively, the research already conducted allows for the predictions of the ¹³C chemical shifts at the C-2, C-4 and C-5 sites for the structure shown in Figure 1, for every possible substituent combination that would result from the 13 x 13 matrix shown in Table 1. The substituents shown in Table 1 are the same series of substituents used in the original studies where X represents the substituents on the C-2 phenyl ring and Y represents the substituents on the N-3-phenyl ring for the original Series 1 and 2. It is clear from Table 1 that there are a significant number of duplications between the columns and the rows and this allows for multiple reference points when determining a correlation within the data set.

The target molecules of interest for this study are labeled Series 5, in Table 1, and are shown in Figure 2. This series is the second series of disubstituted molecules prepared where the substituent in each phenyl ring was predominantly different. As previously indicated (Woolston, Lee, Swinbourne, & Thomas, 1992; Woolston, Lee, & Swinbourne, 1993; Tierney, Houghton et al., 1996a; Tierney, Koyfmann et al., 2008), experimental ¹³C chemical shifts data has been utilized to determine the degree of electronic effects at C-2, C-4 and C-5 due to the presence of substituents on the C-2 phenyl ring and the N-3 phenyl ring. A comparison of the correlation determined here with the previous studies will be further discussed.

Table 1. This shows the total possible substituent combinations for the substituted 2,3-dihenzylthiazolidin-4-one structure shown in Figure 1

$\begin{array}{c} \text{X} \\ \downarrow \\ \text{Y} \end{array} \longrightarrow$	$p\text{-NO}_2$	$m\text{-NO}_2$	$p\text{-F}$	$m\text{-F}$	$p\text{-Cl}$	$m\text{-Cl}$	$p\text{-Br}$	$m\text{-Br}$	H	$p\text{-CH}_3$	$m\text{-CH}_3$	$p\text{-OCH}_3$	$m\text{-OCH}_3$
$p\text{-NO}_2$	Series 3				Series 5				Series 2				
$m\text{-NO}_2$		Series 3			Series 5				Series 2				
$p\text{-F}$			Series 3		Series 5				Series 2				
$m\text{-F}$				Series 3	Series 5				Series 2				
$p\text{-Cl}$					Series 3 and 5				Series 2				
$m\text{-Cl}$					Series 5	Series 3			Series 2				
$p\text{-Br}$					Series 5		Series 3		Series 2				
$m\text{-Br}$					Series 5			Series 3	Series 2				
H	Series 1	Series 1	Series 1	Series 1	Series 1 and 5	Series 1	Series 1	Series 1	Series 1, 2 and 3	Series 1	Series 1	Series 1	Series 1
$p\text{-CH}_3$					Series 5				Series 2	Series 3			
$m\text{-CH}_3$					Series 5				Series 2		Series 3		
$p\text{-OCH}_3$	Series 4	Series 4	Series 4	Series 4	Series 4 and 5	Series 4	Series 4	Series 4	Series 2 and 4	Series 4	Series 4	Series 3 and 4	Series 4
$m\text{-OCH}_3$					Series 5				Series 2				Series 3



Series 5: X= *p*-NO₂, *m*-NO₂, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-Me, *m*-Me, *p*-MeO, *m*-MeO

Figure 2. The series of substituted thiazolidin-4-ones under investigation

2. Results and Discussion

The predicted and experimental ¹³C chemical shifts for the C-2, C-4 and C-5 sites for Series 5 are shown in Table 2. One result from this study is that unlike the *bis*-disubstituted compounds, which showed relatively good predictability with less than ±0.1 ppm in most cases at all three sites, C-4 chemical shift predictability is lower for this sequence of compounds (Series 5). The average deviation for predicted versus experimental chemical shifts for Series 5 are ±0.06 ppm at C-2, ±0.21 ppm at C-4 and ±0.09 ppm at C-5. As in prior studies, a reasonable correlation has been observed between Hammett σ values and substituent chemical shift values at C-2 (Woolston, Lee, Swinbourne, & Thomas, 1992; Woolston, Lee, & Swinbourne, 1993; Tierney, Houghton et al., 1996a; Tierney, Mascavage et al., 1996b; Tierney, Sheridan et al., 1996c; Tierney, Mascavage et al., 2005; Tierney, Koyfmann et al., 2008). Interestingly, in this present series the fixed *para*-chloro group on the C-2 phenyl ring has a constant additive effect on the chemical shift changes produced by varying the substituent on the N-3 phenyl ring. Hence a plot of the difference in the Hammett substituent values to the Hammett σ value (0.23) for the *para*-chloro group on the phenyl ring at C-2 yields the outcome shown in Figure 3.

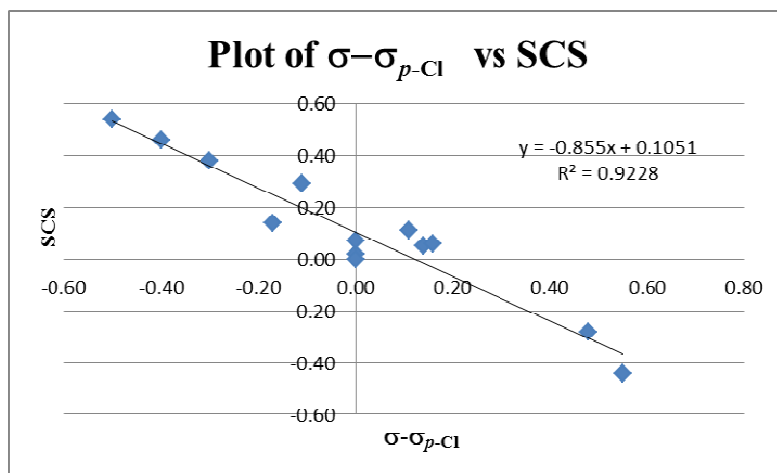


Figure 3. A plot of $\sigma-\sigma_{p-Cl}$ versus substituent chemical shift values at C-2 in the thiazolidinone ring

The ρ values for all series of compounds (Series 1-5) are shown in Table 3. Other workers have used similar correlation techniques in their studies of imine systems, norbornadienyl cations and benzamides (Echevarria et al., 1999; Park & Shin, 1999; DeRosa, 1997). The ρ value indicates the sensitivity towards a preferred charge buildup at a given site, a positive ρ showing a preference for a negative charge and a negative ρ showing a preference for a positive charge. To date, all of the series that have been investigated show a propensity for a positive charge buildup at the C-2 carbon irrespective of whether the substituent being varied is on the C-2 phenyl ring or the N-3 phenyl ring.

Table 2. Experimental and calculated (in parenthesis) ^{13}C chemical shift data for 2-(4-chlorophenyl)-substituted-3-phenyl-thiazolidin-4-ones in ppm relative to TMS

Compound	Substituent X	C(2)	C(4)	C(5)
5a	<i>p</i> -NO ₂	64.12 (63.69)	170.40 (170.78)	33.31 (33.28)
5b	<i>m</i> -NO ₂	64.28 (64.10)	170.90 (170.83)	33.29 (33.26)
5c	<i>p</i> -F	64.70 (64.75)	170.59 (171.71)	33.01 (33.14)
5d	<i>m</i> -F	64.67 (64.49)	170.63 (171.70)	33.16 (33.29)
5e	<i>p</i> -Cl	64.58 (64.47)	170.70 (170.63)	33.23 (33.26)
5f	<i>m</i> -Cl	64.61 (64.50)	170.74 (170.71)	33.27 (33.26)
5g	<i>p</i> -Br	64.63 (64.40)	170.72 (170.61)	33.30 (33.26)
5h	<i>m</i> -Br	64.62 (64.32)	170.72 (170.51)	33.25 (33.15)
5i	H	64.56 (64.73)	170.54 (170.65)	33.14 (33.32)
5j	<i>p</i> -CH ₃	65.02 (64.84)	170.79 (170.71)	33.35 (33.32)
4k	<i>m</i> -CH ₃	64.94 (64.84)	170.81 (170.66)	33.34 (33.32)
5l	<i>p</i> -OCH ₃	65.10(65.07)	170.75 (170.83)	33.18 (33.27)
5m	<i>m</i> -OCH ₃	64.85 (65.45)	170.75 (171.43)	33.33 (34.05)

Table 3. The ρ values observed for ^{13}C chemical shifts at the C-2 carbon for Series 1-5 derived from the application of the Hammett Equation

Series	ρ
1	-1.48
2	-1.33
3	-2.16
4	-1.11
5	-0.86

Attempts to determine substituent effects transmitted to the C-4 and C-5 sites proved fruitless with Series 5. As in prior instances, the substituent effects have readily been seen because of the proximity of the C-2 site to both the substituents on the C-2 phenyl and the N-3 phenyl rings. The electronegative oxygen atom comprising the carbonyl at C-4 has too large an impact on the ability to measure any transmission of electronic effects from substituents on either of the phenyl rings. The lack of a discernible chemical shift correlation at C-5 is most likely due to distance from the substituent to site. The *para*-chloro group at C-2, as might be expected from its proximity to the C-2 carbon, has a constant electronic effect on the C-2 carbon of the thiazolidinone ring and an additive interaction with all the substituents placed on the phenyl ring at N-3. The results shown in Table 2 show a significant additive effect with respect the sensitivity to the chemical shift values at the C-2 carbon when both rings are substituted with the same substituents at the same sites in both ring (either both *para* or both *meta*). This is manifested by an absolute ρ value of 2.16 (Tierney et al., 2005). In the cases where there is only one substituent in one ring (Series 1 and 2), these exhibit the next highest sensitivity to substituent changes with

absolute ρ values of 1.48 and 1.33 for Series 1 and 2, respectively. The higher ρ value for Series 1 compared to Series 2 is most likely due to the fact that the substituents that are being varied are in closer proximity to the site being observed for an effect, C-2. In the case of Series 4, the correlation using Equation 1 was one of the weakest ($R^2 = 0.82$) for all the substituents. Further, the correlation did go through zero and did not need a correction factor as indicated for the Hammett correlation for the *para*-chloro series (Series 5). The fixed *para*-methoxy group (Series 4) was on N-3 phenyl whereas the fixed *para*-chloro series (Series 5) is located on the phenyl group attached to the C-2 carbon. It would appear that the mode of transmission of electronic effects to the C-2 atom by varying the substituents on the C-2 phenyl group with a fixed *para*-methoxy group at N-3, in Series 5, is different from the mode of transmission of effects in Series 5. It is evident that because of the correction that had to be made in order to bring the correlation through zero, within experimental error for Series 5, the *para*-chloro group at C-2 is exerting a relatively constant effect encapsulated by the inductive and resonance effects at C-2 relative to the substituent changes on the N-3 phenyl. A comparison can be made between the correlations found between Series 1 with 3 (rows in Table 1) and Series 2 with 5 (columns in Table 1). By substituting the hydrogen in Series 1 with a methoxy group in Series 3, the methoxy group lowers the sensitivity observed by substituent changes on the phenyl group at C-2 when observing the ^{13}C chemical shift changes at C-2. Similarly, the sensitivity to substituent changes for ^{13}C chemical shift variations at C-2 for Series 5 versus Series 2 is significant; the *para*-chloro group appears to be coupled in a constant manner both inductively and through resonance effects in concert with their ratio encapsulated in the Hammett σ value of +0.78, thereby decreasing the previously observed attenuation usually effected through the N-3 nitrogen atom from the substituent to the C-2 site being observed.

3. Conclusion

Equation 1, which was previously formulated from the linear combination of two monosubstituted series of thiazolidinone chemical shift values, appears to have a reasonable sensitivity toward predicting the ^{13}C chemical shifts at C-2, C-4 and C-5 for the present series of substituted thiazolidin-4-ones, Series 5. In addition, there was a reasonable correlation for the transmission of substituent effects from the groups on the N-3 through the nitrogen to the C-2 site if a correction is made for the presence of the *para*-chloro group situated on the phenyl group at C-2. For Series 5, the C-2 carbon prefers a positive charge buildup as recognized by the ρ value of -0.86 that is in concert with the other series already investigated.

4. Experimental

4.1 General

The thiazolidin-4-ones were prepared using the procedure previously described by adapting a method originally utilized by Surrey (1947). Melting points are uncorrected; a Uni-Melt capillary melting point apparatus was used. All spectra were recorded on a Bruker DRX 500 at 300 K observing ^1H and ^{13}C at 500 and 126 MHz, respectively. All samples were dissolved in CDCl_3 at a concentration of 50 mg/mL using precision bore 5 mm NMR tubes supplied by Norell, Inc. ^1H spectra were collected over a spectral width of 6009.6 Hz using a 30° flip angle pulse; acquisition time, 5.45 s; relaxation delay, 2.0 s; number of scans, 32. ^{13}C spectra were collected over a spectral width of 30030 Hz with a 30° flip angle pulse; acquisition time 1.091 s; relaxation delay, 2.0 s; number of scans, 2560. The spectrometer was locked to the deuterium resonance of the solvent (CDCl_3) and all chemical shifts were referenced to residual CHCl_3 .

Infrared spectra were obtained as an evaporated thin film on a sodium chloride plate (Janos Technology, Inc.) on a Nicolet Nexus 670 spectrometer using 32 scans at a 2 cm^{-1} resolution. Mass spectra were recorded on a Varian 2100 G ion trap mass spectrometer, fitted with a Varian 3900 gas chromatograph: column—Factor 4 VF-5 ms 0.25 mm id, 30 m, $0.25\text{ }\mu\text{m}$ film thickness, He carrier gas, 1.0 ml/min flow, $80\text{ }^\circ\text{C}$ for 1 minute then isothermal $15\text{ }^\circ\text{C/min}$ to $275\text{ }^\circ\text{C}$ then $275\text{ }^\circ\text{C}$ for 3 minutes isothermal, injector temp $250\text{ }^\circ\text{C}$, 0 min, 1:50 split. Isolated yields are based on starting amounts for the imines (amine is the limiting reactant) and it was assumed that 100% of the imine was produced *in situ*. No attempt was made to maximize the product yields. Hammett correlations were obtained using Excel in Microsoft Office.

4.2 Synthesis and Characterization of Compounds

2-(4-chlorophenyl)-3-(4-nitrophenyl)-1,3-thiazolidin-4-one (5a) (60.2 %); m.p. $139\text{--}141^\circ\text{C}$; $\nu\text{ cm}^{-1}$ 1695 (C=O); ^1H NMR (CDCl_3): 8.18–7.23 (8H, m, aromatics), 6.23 (1H, br s, C2), 3.97 (1H, dd, C5, $J = 1.2\text{ Hz}$ and $J = 16.1\text{ Hz}$), 3.89 (1H, dd, C5, $J = 0.6\text{ Hz}$ and $J = 16.1\text{ Hz}$); ^{13}C NMR: 170.99 (C4), 145.33, 143.11, 137.09, 135.30, 129.56, 127.88, 124.47, 124.22 (Ar), 64.12 (C2), 33.31 (C5); (m/z) 334, (M^+ , found 100%, calc. 100%), $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{SO}_3$ (334.78).

2-(4-chlorophenyl)-3-(3-nitrophenyl)-1,3-thiazolidin-4-one (5b) (81.5 %); m.p. 107-109 °C; ν cm^{-1} 1689 (C=O); ^1H NMR (CDCl_3): 8.20-7.21 (8H, m, aromatics), 6.22 (1H, br d, C2, $J = 2.8$ Hz), 3.99 (1H, ddd, C5, $J = 1.4$ Hz, $J = 3.8$ Hz, and $J = 16.1$ Hz), 3.91 (1H, ddd, C5, $J = 0.7$ Hz, $J = 3.7$ Hz, and $J = 16.1$ Hz); ^{13}C NMR: 170.90 (C4), 148.56, 138.54, 136.92, 135.30, 130.75, 129.84, 129.48, 128.28, 121.46, 119.70 (Ar), 64.28 (C2), 33.29 (C5); (m/z) 334, (M^+ , found 100%, calc. 100%), $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{SO}_3$ (334.78).

2-(4-chlorophenyl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one (5c) (82.6 %); m.p. 79-81 °C; ν cm^{-1} 1690 (C=O); ^1H NMR (CDCl_3): 7.22-6.93 (8H, m, aromatics), 6.02 (1H, br s, C2), 3.94 (1H, dd, C5, $J = 1.5$ Hz and $J = 15.8$ Hz), 3.85 (1H, d, C5, $J = 15.9$); ^{13}C NMR: 170.59 (C4), 161.90, 159.93, 137.58, 134.63, 133.03, 133.04, 128.92, 128.34, 127.47, 127.40, 116.01, 115.83 (Ar), 64.70 (C2), 33.01 (C5); (m/z) 307 (M^+ , found 100%, calc. 100%), $\text{C}_{15}\text{H}_{11}\text{FNOS}$ (307.45).

2-(4-chlorophenyl)-3-(3-fluorophenyl)-1,3-thiazolidin-4-one (5d) (52.1 %); m.p. 119-120 °C; ν cm^{-1} 1681 (C=O); ^1H NMR (CDCl_3): 7.28-6.86 (8H, m, aromatics), 6.10 (1H, br s, C2), 3.95 (1H, br d, C5, $J = 15.9$ Hz), 3.85 (1H, br d, C5, $J = 15.9$ Hz); ^{13}C NMR: 170.63 (C4), 163.52, 161.56, 138.74, 138.66, 137.60, 130.10, 130.02, 129.10, 128.06, 120.45, 120.43, 113.90, 113.73, 112.61, 112.42 (Ar), 65.39 (C2), 33.16 (C5); (m/z) 307 (M^+ , found 100%, calc. 100%), $\text{C}_{15}\text{H}_{11}\text{FNOS}$ (307.45).

2-(4-chlorophenyl)-3-(4-chlorophenyl)-1,3-thiazolidin-4-one (1e) (66.3%); m.p. 143-145 °C, (lit. m.p. 143-144 °C); ν cm^{-1} 1671 (C=O); ^1H NMR (CDCl_3): 7.29-7.10 (8H, m, aromatics), 6.06 (1H, br s, C2), 3.96 (1H, dd, C5, $J = 1.4$ Hz and $J = 16.0$ Hz), 3.87 (1H, d, $J = 16.0$ Hz); ^{13}C NMR: 170.70 (C4), 137.57, 135.79, 134.89, 132.70, 129.28, 129.17, 128.30, 126.62 (Ar), 64.58 (C2), 33.23 (C5). (m/z) 323, (M^+ , found 100%, calc. 100%) $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{NOS}$ (323.90) (Tierney, 2005).

2-(4-chlorophenyl)-3-(3-chlorophenyl)-1,3-thiazolidin-4-one (1f) (81.7 %); m.p. 121-122 °C; ν cm^{-1} 1683 (C=O); ^1H NMR (CDCl_3): 7.35-7.04 (8H, m, aromatics), 6.08 (1H, br s, C2), 3.97 (1H, dd, C5, $J = 1.5$ Hz and $J = 16.0$ Hz), 3.87 (1H, br d, C5, $J = 16.0$ Hz); ^{13}C NMR: 170.74 (C4), 138.58, 137.65, 135.01, 134.81, 130.01, 129.29, 128.25, 127.26, 125.53, 123.35 (Ar), 64.61 (C2), 32.27 (C5). (m/z) 323 (M^+ , found 100%, calc. 100%), $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{NOS}$ (323.90).

2-(4-chlorophenyl)-3-(4-bromophenyl)-1,3-thiazolidin-4-one (1g) (78.5 %); m.p. 164-165 °C; IR: ν cm^{-1} 1695 (C=O); ^1H NMR (CDCl_3): 7.47-7.04 (8H, m, aromatics), 6.06 (1H, br s, C2), 3.97 (1H, dd, C5, $J = 1.6$ Hz and $J = 15.9$ Hz), 3.88 (1H, dd, C5, $J = 0.7$ Hz and $J = 15.9$ Hz); ^{13}C NMR: 170.72 (C4), 137.68, 136.45, 135.04, 132.04, 132.34, 132.03, 129.28, 128.32, 126.93 (Ar), 64.63 (C2), 33.30 (C5); (m/z) 368 (M^+ , found 12.9%, calc. 14.3%), $\text{C}_{15}\text{H}_{11}\text{BrClNOS}$ (368.45).

2-(4-chlorophenyl)-3-(3-bromophenyl)-1,3-thiazolidin-4-one (1h) (88.2 %); m.p. 117-118 °C; IR: ν cm^{-1} 1685 (C=O); ^1H NMR (CDCl_3): 7.43-7.07 (8H, m, aromatics), 6.08 (1H, br s, C2), 3.96 (1H, dd, C5, $J = 1.5$ Hz and $J = 15.9$ Hz), 3.87 (1H, dd, C5, $J = 0.7$ Hz and $J = 15.9$ Hz); ^{13}C NMR: 170.72 (C4), 138.71, 137.63, 135.03, 130.27, 130.18, 129.28, 128.41, 128.27, 123.89, 122.61 (Ar), 64.62 (C2), 33.25 (C5); (m/z) 368 (M^+ , found 14.8%, calc. 12.9%), $\text{C}_{15}\text{H}_{11}\text{BrClNOS}$ (368.45).

2-(4-chlorophenyl)-3-phenyl-1,3-thiazolidin-4-one (1i) (75.8%); m.p. 139-140 °C, (lit. m.p. 139-140 °C). ν cm^{-1} 1692 (C=O); ^1H NMR (CDCl_3): 7.29-7.15 (8H, m, aromatics), 6.10 (1H, br s, C2), 3.96 (1H, dd, C5, $J = 1.4$ Hz and $J = 15.9$ Hz), 3.86 (1H, d, C5, $J = 15.8$ Hz). ^{13}C NMR: 170.54 (C4), 137.88, 137.13, 134.38, 128.90, 128.82, 128.19, 126.89, 125.32, (Ar), 64.56 (C2), 33.14 (C5); (m/z) 289 (M^+ , found 100%, calc. 100%), $\text{C}_{15}\text{H}_{12}\text{ClNOS}$ (289.78) (Tierney, 1996a).

2-(4-chlorophenyl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one (1j) (79.8 %); m.p. 168-169 °C; ν cm^{-1} 1668 (C=O); ^1H NMR (CDCl_3): 7.29-7.01 (8H, m, aromatics), 6.04 (1H, br d, C2, $J = 1.4$ Hz), 3.98 (1H, dd, C5, $J = 1.7$ Hz and $J = 15.8$ Hz), 3.88 (1H, d, C5, $J = 15.7$ Hz), 2.28 (3H, CH_3). ^{13}C NMR: 170.79 (C4), 138.24, 137.25, 134.73, 134.70, 129.87, 129.08, 128.48, 125.63 (Ar), 65.02 (C2), 33.35 (C5), 20.96 (Ar- CH_3); (m/z) 303 (M^+ , found 100%, calc. 100%), $\text{C}_{16}\text{H}_{14}\text{ClNOS}$ (303.45).

2-(4-chlorophenyl)-3-(3-methylphenyl)-1,3-thiazolidin-4-one (1k) (6.0%); m.p. 98-100 °C; ν cm^{-1} 1688 (C=O); ^1H NMR (CDCl_3): 7.44-6.90 (8H, m, aromatics), 6.07 (1H, s, C2), 3.98 (1H, d, C5, $J = 15.8$ Hz), 3.88 (1H, d, C5, $J = 15.8$ Hz), 2.28 (3H, CH_3). ^{13}C NMR: 170.81 (C4), 139.14, 138.08, 137.12, 134.62, 128.98, 128.93, 128.36, 128.13, 126.38, 122.65 (Ar), 64.94 (C2), 33.34 (C5), 21.24 (Ar- CH_3); (m/z) 303 (M^+ , found 100%, calc. 100%), $\text{C}_{16}\text{H}_{14}\text{ClNOS}$ (303.45).

2-(4-chlorophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (1l) (58.1%); m.p. 167-169 °C; ν cm^{-1} 1666 (C=O); ^1H NMR (CDCl_3): 7.29-6.80 (8H, m, aromatics), 5.98 (1H, br d, C2, $J = 1.1$ Hz), 3.98 (1H, dd, C5, $J = 1.6$ Hz and $J = 15.8$ Hz), 3.89 (1H, d, C5, $J = 15.8$ Hz), 3.75 (3H, s, Ar- OCH_3); ^{13}C NMR: 170.75 (C4), 158.49,

138.15, 134.63, 129.83, 128.95, 128.55, 127.29, 114.47, (Ar), 65.10 (C2), 55.25 (Ar-OCH₃), 33.18 (C5); (m/z) 319 (M⁺, found 100%, calc. 100%), C₁₆H₁₄ClNO₂S (319.45).

2-(4-chlorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one (1m) (50.2%); m.p. 149-150 °C; ν cm⁻¹ 1667 (C=O); ¹H NMR (CDCl₃): 7.29-6.72 (8H, m, aromatics), 6.07 (1H, br d, C2, J = 1.1 Hz), 3.97 (1H, dd, C5, J = 1.6 Hz and J = 15.8 Hz), 3.89 (1H, dd, C5, J = 0.5 Hz and J = 15.8 Hz), 3.73 (3H, s, Ar-OCH₃); ¹³C NMR: 170.75 (C4), 160.05, 138.36, 138.12, 134.67, 129.76, 129.04, 128.59, 114.51 (Ar), 64.85 (C2), 55.25 (Ar-OCH₃), 33.33 (C5); (m/z) 319 (M⁺, found 100%, calc. 100%), C₁₆H₁₄ClNO₂S (319.45).

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